ENDOCRINE AND METABOLIC DISEASES

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PREFACE

Dear Healthcare Professionals;

Hormones secreted from glands in the endocrine system transmit important messages to every cell in the body through the blood. Nerves react within seconds, but their effects soon fade. However, the effects of hormones are longer and can last for hours, days or even weeks. Endocrine glands are located in different parts of the body. However, it has a functional integrity and is in close relationship with the nervous system and works in a coordinated manner. Because of this integrity, these processes are evaluated under the name of the endocrine system.

The body, which has to adapt to the changes in the external environment and maintain its own balance, must have a proper functioning of the endocrine system in order to cope with this situation. This system regulates many functions related to metabolism such as nutrition, salt-fluid balance, reproduction, growth and development.

Hormones only affect target cells and are controlled in two ways; chemical and neurological control. While the chemical control of the endocrine system is provided according to the changing blood hormone order, the neurological control is provided according to the stimuli coming from the central and autonomic nervous system.

Diagnosis and treatment of endocrine and metabolic diseases have gained importance due to the increase in this disease group in the society. For example, diabetes has become a huge problem globally. The International Diabetes Federation (IDF) estimates that 382 million adults worldwide have diabetes. The prevalence of diabetes has reached epidemic proportions and is expected to reach 592 million by 2035. And the prevalence of metabolic syndrome is estimated at more than 30% in the United States.

There are also a wide variety of diagnosis and treatment methods for endocrine and metabolic diseases. These range from drug therapy to surgical intervention. It is inevitable for every physician to encounter endocrine and metabolic diseases in their working lives.

Our book aims to enable all physicians to recognize endocrinological and metabolic diseases, and to better determine their approach with the information given in the diagnosis and treatment approaches.

Our esteemed physicians, who have written articles in our book, have done their best to make our book a source of information in terms of approach to endocrine and metabolic diseases by compiling up-to-date information and adding their knowledge and experience. I express my deepest gratitude to them.

Kind regards
MD., Prof. Zahide DOĞANAY

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PART 1:

ENDOCRINE HYPERTENSION

Gülşah BOZ

1. INTRODUCTION

Although the exact frequency of seconder hypertension is not known exactly, it is estimated to constitute 5-10% of all hypertensive patients [1,2]. In the presence of resistant hypertension, secondary hypertension should be considered. Resistant hypertension; it is the inability to reach the target blood pressure level despite using at least three different antihypertensive drugs at appropriate doses, one of which is a diuretic. Resistant hypertension is considered in cases where the target can only be achieved using four or more classes of antihypertensive drugs [3]. Secondary causes of hypertension include primary kidney disease, use of oral contraceptive, sleep apnea syndrome, congenital or acquired cardiovascular disease and excess hormonal secretion. The most common causes of secondary hypertension, endocrine, renovascular, renal parenchymal diseas [3,4]. One of the causes of secondary hypertension is endocrine pathologies. The insidence is higher in patients with resistant hypertension. Causes of endocrine hypertension; includes parathyroid, thyroid, adrenal, disorders and renin-secreting tumors. Primary hyperaldosteronizm is the most common cause of endocrine hypertension. Other endocrinological pathologies are less common.

2. CAUSES OF ENDOCRINE HYPERTENSION

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Secondary hypertension while primary hyperaldosteronism is common among the causes, other endocrine causes are rare [5].

2.1. Adrenal-dependent causes

Pheochromocytoma and sympathetic paraganglioma

Pheochromocytoma and paragangliomas; rare neuroendocrine tumors are composed of chromaffin tissue containing neurosecretory granules [6]. Annual incidence 2-8 cases per million [7]. Epinephrine, norepinephrine, or both are usually benign tumors. Pheochromocytomas are more common in the fourth and fifth decades but it can occur at any age. It occurs equal for men and women. Most pheochromocytomas are sporadic. In about 10%, it is hereditary causes can be identified. These hereditary causes are multiple endocrine neoplasia type 2A or 2B (MEN-2A or MEN2B), Von Hippel-Lindau (VHL) and neurofibromatosis type 1 (NF-1) syndromes. Classic triad of symptoms includes headache, profuse sweating, and palpitations [8].

The diagnosis of pheochromocytoma is made by detecting high free catecholamine excretion or high metabolite (such as metanephrine) levels in free plasma or urine. Twenty-four hour urine fractionated catecholamine (epinephrine, norepinephrine, dopamine) and metanephrine (methanephrine, normetanephrine) levels are the most effective in identifying catecholamine-secreting tumors of all tests (sensitivity 98% and specificity 98%) [9]. Localization of lesions or lesions imaging techniques must be used for. The gland can be visualized by CT (computed tomography), MRI (magnetic resonance imaging), and sodium iodine I131-methyliodobenzylguanidine (MIBG) scintigraphy.

Surgical excision of the accessible tumor, if possible, or maximal reduction is the recommended treatment of pheochromocytoma. In preoperative preparations (regulation of hormone release, prevent cardiovascular complications, along with normalization of blood pressure as well as heart rate) alpha-adrenergic blockade followed by a β-adrenergic blockade is recommended.

Primary aldosteronism

Primary aldosteronism is characterized by excessive secretion of aldosterone from the adrenal gland and suppression of plasma renin activity. Secondary hypertension is the most common cause of endocrine hypertension. There are studies showing an overall prevalence of >5% and possibly >10% in the hypertensive population [10,11]. It is stated that this rate exceeds 20% in patients with resistant hypertension [12].

The cause of the majority of patients with primary aldosteronism is bilateral idiopathic hyperaldosteronism. Conn syndrome is the second most common cause. Very rarely, primary aldosteronism can be caused by an adrenal carcinoma, or unilateral adrenal cortex hyperplasia, familial aldosteronism type 1, type 2, type 3, and type 4 [13,14].

Clinical presentation; myopathy, weakness, polyuria/polydipsia, cardiac dysrhythmias, may occur in cases of severe hypokalemia. Patients recommended to be investigated; resistant hypertension, stage 2 or stage 3 hypertension, adrenal incidentaloma with hypertension, spontaneous hypokalemia.

The basic screening test to be used in the suspicion of primary aldosteronism is the ratio of serum aldosterone to plasma renin activity (SA/PRA). Suppressed PRA, increased aldosterone and low potassium are detected.

The various types of primary aldosteronism need to be distinguished, as disease management may differ in clinical practice. Surgical resection is the first line of treatment for unilateral adenoma. Medical therapy is indicated in patients with adenoma, bilateral adrenal hyperplasia and in those patients with adenomas in whom there exists a high surgery risk. Spironolactone, an aldosterone receptor antagonist, is used in medical treatment.

Cushing syndrome

Chronic glucocorticoid excess due to different causes is called Cushing's syndrome. Cushing’s syndrome separated into ACTH-dependent and ACTH-independent causes.

ACTH-dependent causes:

- Cushing's disease (%60-80)
- Nonpituitary ectopic sources of ACTH

ACTH-independent causes:

- Adrenal adenoma
- Adrenal carcinoma
- Macronodular hyperplasia
- Micronodular hyperplasia
- McCune-Albright syndrome

The peak incidence of Cushing's syndrome, whether due to an pituitary or adrenal adenoma, occurs from age 25 to 40 [15]. The typical clinical presentation of Cushing's syndrome is that of truncal obesity including a buffalo hump, hypertension, hyperglycemia, plethoric moon facies, proximal muscle weakness, hirsutism, depression, insomia, fatigue, skin abnormalities (acne, purple skin striae, bruising). The hypertension of Cushing's syndrome can be explained by the oversupply of cortisol [16]. Screening is recommended in cases of suspected Cushing's syndrome.

Cushing's syndrome can be difficult to diagnose. Screening tests for Cushing's syndrome include measuring:

- Free cortisol excretion in the 24-hour urine at least 2 times
- 1 mg dexamethasone suppression test
- Checking a midnight salivary cortisol
- Diurnal rhythm of cortisol secretion

Pituitary magnetic resonance imaging (MRI) is recommended in all ACTH-dependent CS cases. MRI alone is diagnostic in most cases (especially those with adenomas larger than 6 mm) [17] . Thin section CT of the adrenal gland can be used as the first choice in ACTH-independent CS. MRI is another alternative.

The 5-year survival of untreated Cushing's syndrome is only 50% and relates primarily to the effects of excess glucocorticoid hormone. The preferred approach in Cushing's syndrome is selective excision of the pituitary adenoma by transsphenoidal surgery with preservation of as much pituitary function as is possible [5] . Treatment in ACTH-independent CS is almost always a surgical approach to the side of pathological hormone production (adrenal adenomas, micronodular or macronodular hyperplasia, carcinoma).

Hyperdeoxycorticosteronism

Deoxycoticosterone (DOC) is caused by a deficiency of 11 β-hydroxylase, the second most common cause of congenital adrenal hyperplasia. Deoxycoticosterone is caused by a deficiency of 11 β-hydroxylase, the second most common cause of congenital adrenal hyperplasia [18].

Diagnosis is made by, clinical features, basal or ACTH-stimulated DOC, 24-hour urinary 17-ketosteroid levels and 11-deoxycortisol level. Treatment includes glucocorticoid replacement. ACTH suppression is achieved with replacement therapy.

11β-Hydroxylase deficiency

It is a rare enzyme deficiency. This enzyme inactivates cortisol in the kidney to prevent its binding to mineralocorticoid receptors. Mineralocorticoid excess is seen in enzyme deficiency.

Diagnosis tools, increased 17 OH PRG, DOC, 11-deoxycortisol, androstenedione, testosterone, DHEA-S levels are checked.

Treatment includes glucocorticoid replacement.

17α-Hydroxylase deficiency

This enzyme deficiency is rare. Leads to diminished production of sex steroids and cortisol.

Deoxycorticosterone-producing tumor

Deoxycorticosterone secreting tumors are rare adrenal tumors that mostly occur as malignant and large [19].

2.2. Thyroid-dependent causes

Hyperthyroidism

Hyperthyroidism is often associated with elevated systolic blood pressure. In thyrotoxicosis, patients usually are systolic hypertension, tachycardic, atrial fibrillation have high cardiac output with an increased stroke volüme [20].

Hypothyroidism

Hypothyroidism is often associated with elevated diastolic blood pressure. Blood pressure often falls with correction of hypothyroidism.

2.3. Parathyroid-dependent causes

Hyperparathyroidism

In patients with primary hyperparathyroidism, hypertension is observed in approximately 40% of cases. The mechanism of hypertension has not been

clearly determined. Hypertension is usually not treated or better controlled after parathyroidectomy [21].

2.4. Pituitary-dependent causes

Acromegaly

Acromegaly, excessive amounts of growth hormone (GH) it is a disease that develops due to secretion. In the vast majority of patients, the cause of acromegaly is anterior pituitary adenomas. Growth hormone has antinatriuretic actions and may lead to sodium retention and volume expansion. In addition, the RAAS system seems to play a role in the pathogenesis of hypertension in patients with growth hormone excess [22] .

The first-line test for diagnosis is serum IGF-1 (insülin like growth factor) measurement. Measuring GH values during the OGTT (oral glucose tolerance test) is the standard test for the diagnosis of acromegaly.

The most common treatments for acromegaly are surgery, medication and radiation therapy. The first choice in treatment is surgery.

2.5. Other endocrine causes

Renin-secreting tumors

This tumor, which is usually seen at a young age, is quite rare.

The major clinical and chemical findings revealed the association of severe hypertension with hypokalemia and increased plasma aldosterone and plasma renin activity. The treatment option is surgical excision.

Liddle syndrom

Liddle syndrom is a rare autosomal dominant disease. This condition is characterized by severe hypertension that begins uncommon early in life, often in childhood, although some affected individuals are not diagnosed until adulthood. Symptoms are of hypertension, fluid retention, and metabolic alkalosis.

Vitamin D deficiency

There is evidence that vitamin D deficiency may be linked to an increased hypertension and cardiovascular risk [23] .

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PART 2:

BETHESDA III (AUS/FLUS) SUB-GROUPS IN THYROID CYTOLOGY AND THE RISK OF MALIGNANCY

Aytül BUĞRA
Gizem AYAZ

1. INTRODUCTION

Thyroid gland diseases are a common condition affecting 3-5% of the population worldwide. Thyroid diseases have an important place in daily practice because neoplasms can arise from thyroid gland nodules. Thyroid nodules are detected by ultrasonography (USG) in 20-76% of the population, but they are easy to detect with physical examination. The incidence of thyroid nodules has increased significantly due to the widespread use and development of imaging techniques. Although the frequency of nodule diagnosis increases, thyroid carcinoma is less than 5% of the diagnosis. In addition to USG, methods such as thyroid hormone levels and fine needle aspiration cytology (FNAC) are used in the evaluation of thyroid nodules. FNAC cytology is a minimally invasive, inexpensive, and highly reliable gold standard first-line diagnostic test.[1,2]

2. THROID GLAND HISTOLOGY

The main structure of the thyroid is round or oval shaped follicles with an average diameter of 200 microns, consisting of a single layer of epithelial cells sitting on a basement membrane. Follicles are separated from each other by capsule extensions, which are composed of loose connective tissue and allow the formation of lobulations by entering into the thyroid. The lumen of the follicle contains a viscous material called colloid, mostly composed of protein. The cells lining the follicles differ in shape and size according to the functional state of the gland. There are 3 major types of these cells. Squamous cells line the inactive gland. While cuboidal cells, which constitute the main majority, are responsible for colloid synthesis, columnar cells are responsible for the release of hormones bound with thyroglobulin in the follicle lumen into the

bloodstream .[3,4] The second cell type found in the thyroid tissue is parafollicular or C cells, which constitute the minor component of the thyroid gland (<0.1%). C cells are polygonal shaped, larger and pale than follicular cells, with weak eosinophilic granular cytoplasm. They contain a round or oval shaped, centrally located nucleus with prominent nucleoli. They are located at the periphery (parafollicular) of the follicle wall.[3-5]

3. THE BETHESDA CLASSIFICATION USED IN THYROID CYTOLOGY AND REPORTING

The Bethesda classification was first created in 2007 and is divided into 6 standard, diagnostic categories: nondiagnostic/unsatisfactory (I), benign (II), atypia of undetermined significance/follicular lesion of undetermined significance (III) (AUS/FLUS), follicular neoplasia/suspected follicular neoplasia (IV) (FN/FNS), suspected malignancy (V), malignant (VI) (Table 1).

There are separate expected malignancy risk ratios for each category and each group has its own clinical management (Table 2).

Table 1. The Bethesda 2007 Classification of Thyroid Cytopathology[6]

I) Nondiagnostic or Unsatisfactory	III) Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	VI) Malignant
Cyst fluid only	**IV) Follicular Neoplasm or Suspicious for a Follicular Neoplasm**	Papillary thyroid carcinoma
Virtually acellular specimen	Specify if oncocytic (Hürthle cell) type	Poorly differentiated carcinoma
Other (obscuring blood, clotting artifact, drying artifact, etc.)	**V) Suspicious for Malignancy**	Medullary thyroid carcinoma
II) Benign	Suspicious for papillary thyroid carcinoma	Undifferentiated (anaplastic) carcinoma
Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.)	Suspicious for medullary thyroid carcinoma	Squamous cell carcinoma
Consistent with chronic lymphocytic (Hashimoto) thyroiditis in the proper clinical context	Suspicious for metastatic carcinoma	Carcinoma with mixed features (specify)

Consistent with granulomatous (subacute) thyroiditis	Suspicious for lymphoma	Metastatic malignancy
Other	Other	Non-Hodgkin lymphoma

Table 2. Malignancy risks and clinical approach of the categories in the Bethesda classification[6]

Category	Risk of Malignancy	Clinical Management
I	1-4%	Repeat FNA with ultrasound guidance
II	0-3%	Clinical and sonographic follow-up
III	5-15%	Repeat FNA
IV	15-30%	Lobectomy
V	60-75%	Near-total thyroidectomy or lobectomy
VI	97-99%	Near-total thyroidectomy

The purpose of the Bethesda system is to standardize the reporting of fine needle aspiration (FNA) findings, to increase cohesion among pathologists, and to assist clinicians in the management of treatment. Since 2007, the reporting quality of FNAs has increased, uncertain diagnoses have decreased considerably, and the surgical rates of benign lesions have decreased.[2] Evaluation of the adequacy of thyroid FNACs is very important in correct interpretation of smears. In order for FNAC to be sufficient, it is recommended to have at least 6 follicular cell groups, each of which contains at least 10 cells, and at least 200 cells for liquid-based cytology smears.[6]

Despite all the benefits of the Bethesda System and FNA, there are still points that cause uncertainty and confusion today. The most important of these is the atypia of Indeterminate/Unsignificant follicular lesion in Bethesda Category III.[2]

4. ATYPIA OF UNDETERMINED SIGNIFICANCE OR FOLLICULAR LESION OF UNDETERMINED SIGNIFICANCE AND SUB-GROUPS

By definition, AUS/FLUS includes samples consisting of cells that contain structural and/or nuclear atypia but cannot be classified as suspicious for follicular neoplasia, suspicious for malignancy, or malignant (follicular, lymphoid, other).[1] AUS/FLUS diagnosis rates vary among pathologists, but should be approximately 7%. This category should not be used haphazardly and should be the last category.[3]

In terms of malignancy-risk, AUS/FLUS is a well-defined heterogeneous subgroup that does not have standard diagnostic criteria, with 5-15% according to Bethesda system 2007 and significantly different (15-81%) according to studies. There is a need to define the diagnostic criteria of the AUS/FLUS category more clearly, and to redefine the Bethesda category III by reviewing the cytological features that make up this category and cause the malignancy rates to reach 80%.[1,2,7,8]

Some criteria have been defined for the diagnosis of AUS/FLUS in the Bethesda 2007 classification system. These criteria are[6]:

1. Samples that predominantly consist of microfollicles but do not fully meet the FN/FNS criteria: this occurs when microfollicles are predominant in cellular and colloid-poor smears, or when the number of microfollicles is above normal in cellular smears but not sufficient for the diagnosis of FN/FNS.

2. Cell and colloid-poor specimens containing predominantly Hürthle cells or specimens of moderate/pronounced cellular but only Hürthle cells but clinically evaluated as lymphocytic thyroiditis or multinodular goiter

3. Specimens containing generally benign nuclear clefts, pale chromatin, large, oval, irregularly shaped nuclei suggestive of papillary carcinoma in the focal area.

4. Samples where atypia in follicle cells cannot be evaluated due to smear artifacts

5. Examples of atypical but generally benign-appearing cyst-laying epithelium due to nuclear clefts, elongated nuclei, prominent nucleoli

6. Specimens with atypical lymphoid infiltration (requires repeat aspiration for flow cytometry) but in which the degree of atypia is insufficient for the suspected malignancy category.

One of the difficulties of this category is to determine the risk of malignancy.[2] Inter-center malignancy rates reported in many studies are quite variable, and the rates determined in cases with resection vary between 14.5% and 81%, and the rates determined in cases with follow-up vary between 5% and 37%.[1,2,8-15] There are studies stating that the results are biased when only the cases with resection are evaluated while determining the risks of malignancy. Because these cases are resected for various reasons (nodule size, suspicious USG features, patient preference, 2nd FNA result, etc.), high rates of malignancy are expected.[9,13] For this reason, while the malignancy risk of all cases diagnosed with AUS/FLUS has been determined in some studies, other

rates have been reported other than the value calculated among the cases with resection.[9,11,13-15]

A subclassification of this category was proposed at the international panel held in Yokohama in 2016. In the classification, attention was drawn to the title of nuclear atypia and it was recommended to go for subgrouping based on this group.[16]

The criteria for the diagnosis of AUS/FLUS have been updated in the second edition of the Bethesda thyroid cytology classification in 2018. The last defined criteria are given below:[17]

1. Cytological atypia

a. Focal cytological atypia

b. Diffuse but mild cytological atypia

c. Atypical cyst lining cells

d. Histiocytoid cells

2. Architectural atypia

a. A smear of low cellularity with rare follicular cell clumps almost entirely in microfollicles or in crowded three-dimensional groups and scanty colloid

b. Focally prominent microfollicles with minimal nuclear atypia on a cellular smear

3. Cytological and architectural atypia

4. Hürthle cell aspirates

a. Aspirate consisting only of Hürthle cells with minimal colloid

b. Moderate or prominent cellular pattern consisting only of Hürthle cells

5. Atypia, not otherwise classified

a. A small population of follicular cells shows nuclear enlargement, often accompanied by prominent nucleoli.

b. Psammomatous calcifications in the absence of nuclear features of papillary carcinoma

c.Rare examples of atypia not elsewhere defined requiring the definition of AUS/FLUS

6. Atypical lymphoid cells from which lymphoma is excluded

Atypical lymphoid infiltration showing insufficient atypia to suspect malignancy

In the 2007 Bethesda classification, malignancy risks and clinical management are listed in Table 2. The malignancy risk and clinical management were also updated in the last edition published in 2018 (Table 3).[17]

Table 3. Current malignancy risks and clinical approach of the categories in the Bethesda classification[17]

Category	Risk of Malignancy	Clinical Management
I	5–10%	Repeat FNA with ultrasound guidance
II	0-3%	Clinical and sonographic follow-up
III	10-30%	Repeat FNA, molecular testing, or Lobectomy
IV	25-40%	Molecular testing, lobectomy
V	50-75%	Near-total thyroidectomy or lobectomy
VI	97-99%	Near-total thyroidectomy or lobectomy

In many studies, it has been suggested that subdividing the AUS/FLUS category would be beneficial in predicting malignancy.[7,8,9,18]

In the study of Erdoğan-Durmuş et al., this category was divided into two subgroups. In their study, which they divided into two subgroups as cytological and architectural atypia, they found the malignancy rate to be 28.8% in the cytological atypia category and 7.1% in the architectural atypia category.[18]

Another issue considered unclear for the AUS/FLUS category is to determine the most appropriate clinical management. Bethesda 2007 classification recommends re-aspiration after an appropriate time with clinical correlation.[6] In addition, molecular testing and lobectomy has been added in 2018.[17]Repeat FNA often gives more accurate results, and approximately 20-25% of nodules are diagnosed with AUS/FLUS.[6,15] Resection is recommended in cases of suspected or malignant diagnosis of AUS/FLUS, FN/FNS, or malignancy as a result of re-aspiration 3-6 months after the initial diagnosis of AUS/FLUS.[6]

Although molecular tests are also recommended for cases in the AUS/FLUS group in the current approach, their use is limited in many centers due to their high cost. As a result, the clinical management method, which is still common today, is correlation with clinical information, USG and cytopathological findings.[19]

5. CONCLUSION

Subgrouping is important in predicting malignancy when diagnosing AUS/FLUS.

Molecular tests can be used to determine the risk of malignancy.

Along with cytological findings, laboratory and ultrasonographic findings are also important in predicting malignancy.

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PART 3:

ACUTE PANCREATITIS

Filiz KOÇ

Introduction

Pancreatitis is a non-infectious inflammation even though it is called pancreatic infection that occurs for various reasons. While the infection is rare in primary etiology, its addition to the picture as a secondary infection is more common.

Pancreatitis is the self-harm of the organ with its enzymes. Normally, these enzymes do not come into contact with the pancreatic cells, they are carried directly into the intestinal system through ducts and canaliculi, where they become active by mixing with bile or other enzymes. Being a problem in the ducts and the activation of these enzymes in the pancreatic duct starts the inflammation. This inflammation is roughly classified as acute and chronic.

Acute Pancreatitis

It can be described as the sudden onset inflammation of the pancreas, which is indicated by abdominal pain and pancreatic enzyme levels rise in the blood. Acute pancreatitis is one of the diseases that should be treated under surveillance in parallel with the severity of the disease. In addition, it is the most common gastrointestinal cause in hospitalizations. Although the etiology of pancreatitis is different in various societies, gallstones and alcohol are the most common factors[1].

Epidemiology

The disease, which is seen in different etiologies and rates in all societies, is reported with a frequency of 0.035 percent in the United States[2]. The increase in obesity and consequently the increase in gallstones increases the incidence of pancreatitis[3]. Likewise, smoking, which is widely used, is effective in the pathogenesis by contributing to the development of pancreatitis both alone and due to gallstone and alcohol use[4].

While systemic inflammatory response syndrome and organ failure are the most common causes of death in acute pancreatitis in the first two weeks, sepsis and its aftermaths are the most common reasons after two weeks.

Systematic analyzes have shown that mortality is around 5 percent, and it can reach up to 17 percent in necrotizing pancreatitis, and this high mortality rate can be reduced to 6-9 percent in specialized centers[5].

Etiology

Gallstones

Gallstones block the bile ducts and the ampulla, making it the most common (40-70%) cause of pancreatitis.

A small proportion (3-7%) of patients with gallstones develop pancreatitis and the risk decreases as the size of the gallstone increases, with stones up to 5mm at the highest risk for pancreatitis[6,7,8].

It is accepted that pancreatitis occurs due to reflux of bile, which causes obstruction of the duct of gallstones. Cholecystectomy and clearing of stones in the common bile duct prevent recurrence and confirm the cause-effect relationship[6]. While gallstones are more common in the etiology of acute pancreatitis in men, the more frequent occurrence of gallstones in women increases the role of gallstones in the etiology in women[7].

Alcohol

Alcohol is the second main reason in etiology with a rate of 25-35%[9]. The risk of pancreatitis increases as the duration and amount of alcohol use increases. When the risk factors of smoking, obesity, hypertriglyceridemia, which are easily added to people who use alcohol, come together with genetic factors, it increases the incidence of acute pancreatitis. The incidence of acute pancreatitis in these people increases to 10 %[9].

Alcohol may function by boosting the production of digestive and lysosomal enzymes by pancreatic acinar cells that is assumed to be resulting acinar cell hypersensitivity to cholecystokinin. However, the exact mechanism of pancreatic damage, environmental and genetic factors affecting the development of alcoholic-related pancreatitis have not been fully determined[9].

While explaining the role of alcohol in the etiology, there are arguments that the acute attack occurs on the basis of the underlying chronic pancreatitis rather than acute pancreatitis.

This suggests that some patients with alcohol use disorder may have pancreatitis without acute attacks. However, the fact that patients who had

acute attacks did not turn into chronic pancreatitis in long-term follow-up despite continued alcohol use shows that this theory is not valid in all cases[10].

It is known that smoking is associated with acute pancreatitis, both by itself and with alcohol[11]. These results suggest that tobacco use has a greater risk of developing or conversion of acute and chronic pancreatitis and that there is a positive correlation between the number of cigarette consumption and pancreatitis risk result of dose-response relationship[11].

Hypertriglyceridemia

Acute pancreatitis can be triggered by serum triglyceride values above 1000 mg/dL (11 mmol/L), but lower levels can exacerbate the condition. Acute pancreatitis is caused by hypertriglyceridemia in 1 to 14 percent of cases [12]. Hypertriglyceridemia-induced pancreatitis is linked to both main (genetic) and secondary (acquired) lipoprotein metabolism problems. Obesity, hypothyroidism, diabetes, pregnancy, and medicines are all acquired causes of hypertriglyceridemia (e.g., estrogen or tamoxifen therapy, beta-blockers).

Endoscopic Retrograde Cholangiopancreatography (ERCP)

The role of ERCP in the etiology of acute pancreatitis has been proven. Although the rates vary according to the reason for ERCP, it has been shown that pancreatitis develops in 3 percent for diagnosis, 5 percent for treatment, and 25 percent for sphincter processes[13].

The risk of ERCP is due to the structure of the anatomical region as well as the operation itself.

Genetic Risk

Patients at genetic risk for pancreatitis may present as recurrent acute pancreatitis or childhood pancreatitis with no known cause and eventually progress to chronic pancreatitis. The majority of idiopathic cases under the age of 35 appear to carry a genetic risk.

Medicines

Many drugs used for different treatments cause acute pancreatitis, although not frequently. This group constitutes a small portion of about 5 percent in the etiology of acute pancreatitis14. These pancreatitides usually regress easily and do not leave sequelae[14]. The mechanisms by which some drugs cause acute pancreatitis have been determined.

Immunological reactions (e.g., 6-mercaptopurine, aminosalicylates, sulfonamides), with direct toxic effect (e.g., diuretics, sulfonamides), toxic metabolite accumulation (e.g., valproic acid, didanosine, pentamidine, tetracycline), with ischemic effect (e.g., diuretics, azathioprine), by

intravascular thrombosis (e.g., estrogen) and by increasing the viscosity of pancreatic secretions (e.g. diuretics and steroids)[14].

Pancreatic Duct Injury

The sheltered location of the pancreas in the abdomen protects it from trauma. Although traumas that cause severe damage are rare, they can be damaged by blunt or penetrating trauma[15].

A traumatic injury might bring a minor bruise or serious crush damage or transection of the pancreas gland where it crosses the spine. Acute duct rupture and pancreatic acid can result from pancreatic injury. Scarring can occur as a result of pancreatic duct injury healing.

Other Rare Causes

Bile sludge and Microlithiasis: Bile sludge is the feature of decreasing the flow of bile and can contain 5mm small stones. This viscous suspension and small stones easily clog the bile ducts, the bulb. In the analysis of bile sludge, cholesterol monohydrate crystals or calcium bilirubinate granules are detected. The presence of functional or mechanical bile stasis due to long-term fasting, distal bile duct obstruction, or exposure to long-term total parenteral nutrition leads to the formation of biliary sludge[16]. Bile sludge is often detected incidentally in the patient and most of the patients are asymptomatic. However, 20 to 40 percent of patients with acute pancreatitis have biliary sludge for no obvious reason. In patients with acute pancreatitis with transient elevation in liver tests, biliary sludge should be suspected as the cause in the absence of any other etiology.

Biliary Obstruction: Conditions that cause ampullary obstruction linked to pancreatitis include periampullary diverticulum, biliary ascariasis, and pancreatic and periampullary tumors[17,18].

Autoimmune pancreatitis: Acute pancreatitis is rarely caused by autoimmune pancreatitis, which can lead to weight loss, jaundice, and pancreatic enlargement that mimics a neoplasm on imaging. In rare cases, duodenal inflammation and papillary stenosis secondary to celiac disease can cause recurrent episodes of acute pancreatitis Celiac disease and recurrent pancreatitis.

Hypercalcemia: Hypercalcemia, which may develop due to various pathologies, is one of the rare causes in the etiology of acute pancreatitis[19].

Infections and Toxins: Pancreatitis has been linked with the following infections[20]:

Viruses: Mumps, coxsackievirus, hepatitis B, cytomegalovirus, varicella-zoster, herpes simplex, human immunodeficiency virus (HIV)

Bacteria: Mycoplasma, Legionella, Leptospira, Salmonella

Fungus: Aspergillus

Parasites: Toxoplasma, Cryptosporidium, Ascaris.

There are limited data on the frequency of these infections causing pancreatitis. It is reported that 4.7% of 939 hospitalized patients who were seropositive for HIV developed acute pancreatitis. Studies reports that pancreatitis developing during HIV infection is primarily due to the virus or more likely due to drugs used to treat the virus or opportunistic infections (such as Pneumocystis Carinii, Mycobacterium avium-intracellular)[21].

Vascular Disease: Organ ischemia is a rare cause in the etiology of acute pancreatitis. Ischemia resulting in pancreatitis has been reported in association with vasculitis, atheroembolism, intraoperative hypotension, and hemorrhagic shock. Pancreatitis due to vasculitis has also been confirmed by the demonstration of cardiogenic shock induced by experimental pericardial tamponade in animals and the demonstration of ischemic vasospasm in the pancreas[22].

Anatomical or Physiological Pancreatic Anomalies: Biliary cysts, some types of choledochal cysts, anomalies that possibly cause pressure, and obstruction to the pancreatic duct have been associated with acute pancreatitis due to mechanical obstruction.

Idiopathic: In 25 to 30 percent of patients with acute pancreatitis, a clear etiology cannot be identified after history, laboratory tests, and gallbladder ultrasound, and extensive investigations. The majority of patients with idiopathic acute and recurrent acute pancreatitis have been shown to have complex underlying genetic risk profiles[23].

Clinical Features

Most patients with acute pancreatitis have persistent, severe epigastric abdominal pain of acute onset. In some patients, the pain can confine to the right upper quadrant and in some rare instances to the left side. In cases caused by gallstones, the pain is well localized and the pain occurs suddenly, reaching maximum intensity within 10 to 20 minutes. In contrast, patients with inherited or metabolic, or alcohol-induced pancreatitis may have a slower onset of pain and the localization of pain is unclear. Pain radiates to the back in about 50

percent of patients[5]. The pain persists for several hours to days, and the patient can be partially relieved by sitting or leaning forward.

In the vast majority of patients, nausea and vomiting are observed, which can last for several hours[5].

Dyspnea owing to pancreatitis, pleural effusions, or diaphragmatic inflammation secondary to acute respiratory distress syndrome can occur in patients with severe cases. Severe acute pancreatitis cases such as postoperative and critically ill patients, dialysis patients, organophosphate poisoning, and Legionnaires' disease, may experience painless clinical and inexplicable hypotension.[24].

Acute pancreatitis clinic divides the Revised Atlanta classification system into two main categories[25]:

Acute pancreatitis with interstitial edema and acute inflammation without necrosis in the pancreatic parenchyma and peripancreatic tissues

Necrotizing acute pancreatitis; Presence of necrosis as well as inflammation in the pancreatic parenchyma and/or peripancreatic tissues

Acute pancreatitis is divided into three according to its clinical severity[25]:

1-Mild acute pancreatitis: Clinical manifestation characterized by organ failure and the absence of local or systemic complications.

2-Moderate acute pancreatitis: Transient organ failure (resolves within 48 hours) and/or local or systemic complications (more than 48 hours) without permanent organ failure

3-Severe acute pancreatitis: Clinical manifestation with permanent organ failure that may involve one or more organs.

Physical Examination

Physical findings may differ according to the severity of acute pancreatitis. For instance, the epigastrium can be less sensitive to palpation among patients with mild cases, while among patients with severe pancreatitis, palpation tenderness can be found more commonly in the epigastrium or over the abdomen. Due to an ileus caused by inflammation, abdominal distention and hypoactive bowel noises may develop among some patients. Patients may experience scleral icterus as a result of obstructive jaundice caused by choledocholithiasis or edema of the pancreas head.

Fever, tachypnea, hypoxemia, and hypotension are common symptoms of acute pancreatitis. In 3% of patients who have acute pancreatitis, echymotic coloring can be detected in the periumbilical area (Cullen sign) or along the

flank (Grey Turner sign) [26]. The presence of retroperitoneal bleeding in the event of pancreatic necrosis is suggested by these signs, which are nonspecific.

Patients may develop subcutaneous nodular fat necrosis or panniculitis in rare circumstances[27], which are tender red nodules typically occur on the distal extremities while can be found elsewhere.

Patients may have findings that point to an underlying cause such as xanthomas in hyperlipidemic pancreatitis patients, hepatomegaly in alcoholic pancreatitis patients, and parotid edema in mumps patients.

Laboratory Findings

Pancreatic Enzymes and Their Products: In the first period of acute pancreatitis, the typical functioning of the pancreas is obstructed and the synthesis-secretion coupling of pancreatic digestive enzymes is disrupted. While synthesis still functions, secretion is blocked leading to leakage of digestive enzymes from the acinar cells through the basolateral membrane into the interstitial space, which ends up in the systemic circulation.

Serum Amylase: Serum levels rise within 6 to 12 hours, and amylase, which has a short half-life of approximately 10 hours, returns to normal levels within three to five days in an uncomplicated attack. An increase in serum amylase more than three times the normal level is reported to have a sensitivity of 67-83 percent and a specificity of 85-98 percent for the diagnosis of acute pancreatitis[28]. Although elevated serum amylase is the main finding in the diagnosis, the increase in serum amylase cannot reach threefold in approximately 20 percent of these patients during an attack due to impaired amylase secretion in alcoholic pancreatitis. Likewise, high amylase levels may not be present in half of the pancreatitis attacks associated with hypertriglyceridemia. Pancreatitis interferes with the detection of amylase as triglycerides. Again, the short half-life of amylase may cause the diagnosis of acute pancreatitis to be missed in patients who are controlled 24 hours after the onset of pancreatitis[28].

Serum Lipase: Since lipase rises rapidly in the systemic circulation and has a long residence time, it is considered a stronger diagnostic criterion than amylase. Serum lipase elevation has a sensitivity ranging from 82 to 100 percent in cases of acute pancreatitis28. Serum lipase levels begin to rise in the first 4-8 hours following the onset of symptoms, peak at 24 hours and return to normal values after 8-14 days[28].

Elevated serum lipase is diagnostic in cases that do not present or cannot be diagnosed in the first 24 hours. Serum lipase is considered to be more sensitive than amylase in patients with alcohol-induced pancreatitis. On the other hand, serum lipase elevations are detected without pancreatitis[28].

Other Enzymes and Products: Trypsinogen activation peptide (TAP), a peptide with five amino acids that cleaves from trypsinogen to produce active trypsin, increases in acute pancreatitis in parallel with its severity from the early period and is used in the diagnosis[29].

Urinary and serum trypsinogen-2 levels are elevated in early acute pancreatitis. However, further investigations are required to understand their role in the diagnosis of acute pancreatitis[29].

Trypsin, phospholipase, carboxypeptidase, lipase, serum amyloid protein are other pancreatic enzymes that can be used in diagnosis by passing into the bloodstream[29].

Immune Activation Markers: Activation of granulocytes and macrophages in acute pancreatitis causes the release of a number of cytokines and inflammatory mediators. Acute pancreatitis is associated with elevations in C-reactive protein (CRP), procalcitonin, interleukin (IL)-6, IL-8, IL-10, tumor necrosis factor (TNF), and polymorphonuclear elastase30. A CRP level above 150 mg/L over 48 hours is associated with severe pancreatitis. Although procalcitonin is a general acute phase reactant, it has been shown to confirm acute pancreatitis with 86% in the study conducted with the strip test[30].

Other Laboratory Findings: Hemoconcentration from intravascular fluid extravasation into the third spaces might cause leukocytosis and an increased hematocrit in pancreatitis patients. High blood urea nitrogen (BUN), hypocalcemia, hyperglycemia, and hypoglycemia are all possible metabolic abnormalities.

Imaging

Various features can be seen on imaging in patients with acute pancreatitis.

Abdominal and Chest Radiographs: On direct X-ray in acute pancreatitis, it ranges from unremarkable findings in mild disease to localized ileus of the small intestine segment (protective ring) or to a colon cut-off mark in more severe disease. The colon apostrophe reflects the functional spasm of the descending colon due to pancreatitis and the lack of air in the colon at the distal

end of the splenic flexure. The ground glass appearance may indicate the presence of an acute collection of peripancreatic fluid[31].

Chest radiographs show hemidiaphragm elevation, pleural effusions, basal atelectasis, pulmonary infiltrates, or acute respiratory distress syndrome in approximately one-third of patients[31].

Abdominal Ultrasound: On abdominal ultrasound of patients with acute pancreatitis, the pancreas appears enlarged and hypoechoic. Ultrasound is useful for detecting gallstones, the most common cause of pancreatitis[31].

A collection of peripancreatic fluid is visible on abdominal ultrasound. These collections may show internal echoes in the setting of pancreatic necrosis.

However, in approximately 25 to 35 percent of patients with acute pancreatitis, intestinal gas due to ileus precludes evaluation of the pancreas or bile duct[29]. In addition, ultrasound cannot clearly identify the extrapancreatic spread of pancreatic inflammation or identify necrosis within the pancreas[31].

Abdominal Computed Tomography: Contrast-enhanced abdominal computed tomography (CT) shows a focal or diffuse enlargement of the pancreas with heterogeneous enhancement by intravenous contrast of acute interstitial edematous pancreatitis[32].

Necrosis of pancreatic tissue appears as a lack of contrast enhancement after intravenous contrast administration.

The presence of pancreatic necrosis, the severity and extent of the disease, and local complications can be more reliably determined if a contrast-enhanced CT scan is performed within 72 hours of the onset of symptoms. An enhanced CT scan of the abdominal can also determine the cause[32].

Magnetic Resonance Imaging: MR T1-weighted images in patients with acute pancreatitis shows fat suppression, diffuse or focal enlargement of the pancreas and pancreas borders of the pancreas may be blurred. Due to pancreatic edema, relative to the liver, the signal intensity of the pancreatic parenchyma shows hypointense on T1-weighted images and hyperintense on T2-weighted images. In contrast-enhanced magnetic resonance imaging (MRI), undeveloped pancreatic parenchyma indicates pancreatic necrosis[32].

While MRI shows acute pancreatitis in the early stage, it shows pathology in the bile ducts or tissue changes due to pancreatitis with higher sensitivity than contrast-enhanced abdominal CT scan32.

Magnetic resonance cholangiopancreatogram (MRCP) can be compared to ERCP for the detection of choledocholithiasis. MRI has the advantage of not requiring radiation, and gadolinium has a lower risk of nephrotoxicity

compared to iodinated contrast. In addition, in patients with renal insufficiency, an unenhanced MRI can detect pancreatic necrosis.

However, MRI has the disadvantage of being operator-dependent which can lead to scattered metrics in quality and technique, and local expertise and accessibility make its usage limited. In addition, MRI has a longer scanning time compared to CT scanning, making it difficult to study in critically ill patients.

Diagnosis

Acute pancreatitis should be kept in mind in patients with sudden onset pain and tenderness in the epigastrium. The severe and continuous pain, epigastric sensitivity of the patient during the examination, and the patient's preference for a forward-leaning position to reduce pain should alert the physician in terms of acute pancreatitis.

According to the acute pancreatitis guidelines, the diagnosis can be made by the presence of two of the following three criteria[33].

- Acute onset, usually radiating to the back, persistent, severe epigastric pain,

- Increase in serum lipase or amylase three times or more above the upper limit of normal

- Characteristic imaging findings of acute pancreatitis (with contrast-enhanced computed tomography, magnetic resonance imaging, or transabdominal ultrasonography).

Radiological imaging is not recommended to confirm the diagnosis in patients who meet the first two criteria.

A contrast-enhanced abdominal CT scan is preferred to confirm acute pancreatitis. Contrast-enhanced abdominal CT is diagnostic by excluding the differential diagnosis in patients with uncharacteristic abdominal pain in the diagnosis of acute pancreatitis, or whose serum amylase and lipase levels rise less than three times the upper limit of normal, or whose diagnosis cannot be confirmed. Non-contrast abdominal MRI is recommended in patients with severe contrast allergy or renal impairment33.

Differential Diagnosis

All diseases that cause epigastric pain should be considered in the differential diagnosis. It is possible to distinguish acute pancreatitis from other pain etiologies by laboratory findings such as pain style, the elevation of pancreatic enzymes. Peptic ulcer, choledocholithiasis, cholangitis, cholecystitis, abdominal organ perforations, intestinal bowel obstructions, mesenteric

ischemia, and hepatitis should be kept in mind in the differential diagnosis of acute pancreatitis.

Treatment

Fluid resuscitation, pain control, nutritional support, and supportive care are all part of the treatment plan for a patient with acute pancreatitis. 5 to 10 mL/kg of isotonic crystalloid solution per hour is used to hydrate the patient. For patients with severe volume insufficiency with evidence of hypotension, tachycardia, 20 mL/kg of intravenous infusion should be quickly supplemented within 30 minutes, 3ml/kg/h for 8 to 12 hours. Unless cardiovascular, renal, or other comorbid problems prevent intensive fluid replacement, severe fluid replacement should be performed in all patients with acute pancreatitis. Depending on the severity of the attack, fluid passing into the third spaces may impair systemic circulation and tissue blood supply. Analyzes have linked early fluid replacement within the first 12 to 24 hours of the onset of acute pancreatitis with reduced morbidity and mortality[33].

Abdominal pain is the main symptom that brings patients with acute pancreatitis to the hospital and severe pain should be treated with analgesics. Uncontrolled pain aggravates the clinic by causing hemodynamic instability.

Adequate fluid replacement should be used to treat abdominal pain, as hypovolemia from vascular leakage and hemoconcentration can lead to ischemic pain followed by lactic acidosis.

Opioids can safely and effectively control pain in patients with acute pancreatitis[34]. Intravenous opiates are used to provide a suitable pain control which is regulated with a patient-controlled analgesia pump.

Initial phases especially the first 24 to 48 hours of patients should be closely monitored. Patients in need of intensive care should be identified and necessary follow-up should be provided. Patients with organ failure should be followed up continuously for other complications that may occur.

Nutrition: Patients with mild pancreatitis can usually be treated with intravenous hydration alone, and recovery occurs quickly with hydration. Patients with mild acute pancreatitis clinically tolerate an oral diet within one week.

If patients with acute pancreatitis cannot start oral intake after the first 5-7 days, nutritional support is required. Nasogastric or naso-enteral tube feeding is preferred to total parenteral nutrition (TPN). The timing of resumption of oral feeding depends on the severity of pancreatitis. When ileus, vomiting, or nausea

are not monitored, the pain subsides and inflammatory markers improve and oral feeding can be started early (within 24 hours) if the patient can tolerate it. These patients are started on a low-fiber, low-fat, soft diet. The diet is then carefully advanced according to the patient's tolerance. In some patients with moderate to severe pancreatitis, satiety causes nausea, vomiting, and pain due to gastroduodenal inflammation or fluid collections leading to obstruction of the gastric outlet, and oral feeding may not be tolerated. If the duration is prolonged in such patients, enteral nutrition is needed. Since the use of parenteral nutrition may be harmful, it is recommended as short-term support in patients who cannot tolerate enteral[35].

Antibiotics: Infection is rarely seen in the primary etiology of patients with acute pancreatitis. Appropriate treatment is initiated when these etiologies are detected. About 20 percent of patients with acute pancreatitis develop an infection in the later days of the disease. These infections are usually nosocomial infections, often associated with the invasive tools used and are outside the pancreas. While pneumonia, urinary and central catheter infections are frequently detected, extra pancreatic infections are also associated with increased mortality. When infection is suspected, the source of infection should be determined and antibiotics should be started. Antibiotics should be discontinued if negative culture and source of infection are not identified. Prophylactic antibiotics are not recommended regardless of the clinical category (interstitial or necrotizing) or severity (mild, moderate, or severe) of acute pancreatitis[36].

The patient should be checked for complications that may develop during an attack after acute treatment. In order to prevent pancreatitis from recurring, necessary support should be provided for the problems that can be corrected in the etiology. Supports such as removal of gallstones or tissues that block the bile ducts, discontinuation of alcohol use, regulation of triglycerides prevents acute pancreatitis attacks and prevent the progression of the pathology of the pancreas to the chronic pancreatitis form.

When infection is suspected, the source of infection should be determined and antibiotics should be started. In the case of negative culture and lack of an identification of the infection source, antibiotics should be discontinued. Prophylactic antibiotics are not recommended irrespective of the clinical category (interstitial or necrotizing) or degree of its severity (mild, moderate, or severe) of acute pancreatitis[36]

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PART 4:

CHRONIC PANCREATITIS

Filiz KOÇ

Introduction

Chronic pancreatitis is a chronic inflammation of the pancreas most commonly seen in patients with multiple recurrent episodes of acute pancreatitis and may result from episodes of acute pancreatitis of any cause. While acute pancreatitis can be considered an event, chronic pancreatitis is an ongoing pathological response to pancreatic injury. Acute and chronic pancreatitis cannot be thought of as two completely separate conditions, but as two parts of a continuum and the same disease spectrum. Chronic pancreatitis syndrome results from exposure to risk factors (genetic and environmental) and is characterized by irregularities in pancreatic function (digestive function or insulin secretion) and structural changes in the pancreas that can be seen on imaging or endoscopic studies. However, many of the clinical features take time to appear and may not be present in the early stages of chronic pancreatitis[1]. While chronic pancreatitis can be easily diagnosed when end-stage features develop, the clinical challenge is to make an accurate diagnosis early in the clinical course where interventions to prevent progression can be most effective.

Because the diagnostic criteria for chronic pancreatitis are so variable, population-based reliable estimates of the epidemiology of chronic pancreatitis are not widely available. However, limited evidence suggests that the incidence of chronic pancreatitis ranges from 5 to 12/100,000 and the prevalence is about 50/100,000 people.

Regional differences are seen in the prevalence of chronic pancreatitis according to the etiology. Alcohol-induced pancreatitis is more common in the West and Japan compared to other Asian countries. Alcohol is also associated with about half of all chronic pancreatitis cases in the United States[2]. There is wide variation in the prevalence of a form of chronic pancreatitis that is endemic in tropical countries. Idiopathic chronic pancreatitis accounts for about 10 to 30

percent of all cases. The number of patients labeled as idiopathic is largely dependent on how detailed and comprehensive the etiology research is.

Most patients with chronic pancreatitis have more than one underlying etiology. Causes of chronic pancreatitis are classified using a system commonly referred to as "TIGAR-O"[3]. This means toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, and obstructive. In etiology, similar to acute pancreatitis, alcohol, smoking, hyperglyceridemia, genetic, autoimmune causes, and mass trauma, etc. can be counted.

The clinic of chronic pancreatitis is roughly classified into three forms;

Early-Onset

The median age of onset of the early-onset form is 20 and has an equal sex distribution. Pain is the predominant feature (>90 percent) and evidence of advanced pancreatic damage (eg, pancreatic calcifications) or exocrine or endocrine insufficiency is rare and, if present, takes several decades to develop. The early-onset form can be difficult to diagnose, as imaging and laboratory features of chronic pancreatitis may be absent for years.

Late-Onset

The median age of the late-onset form is 56 years, it is relatively painless. Pain occurs in about 50 percent of cases and is more commonly associated with pancreatic calcifications or endocrine or exocrine insufficiency.

Fibrocalcific or Tropical Pancreatitis

Classically, it is defined as chronic pancreatitis, the age of onset most commonly childhood, in which patients typically develop fibrocalculous pancreatic diabetes and malnutrition, often resulting in premature death. Fibrocalcific or tropical pancreatitis, a disease largely confined to south India, is becoming less common even there. The demographics of tropical pancreatitis appear to be changing, and some experts say it represents complex genetic etiologies as seen in Western countries and the term should be dropped.

Pathogenesis

The pathophysiology of chronic pancreatitis is not fully understood. However, there seems to be a common pathway that comes with an attempt to heal through injury followed by fibrosis and regeneration. All causes of chronic pancreatitis ultimately show similar features, including loss and injury of acinar, islet, and ductal cells, fibrosis, and loss of pancreatic function.

The mechanisms of chronic pancreatitis vary depending on the underlying etiology, genetic background, and environmental exposures. The

mechanisms by which the most common causes (alcohol and tobacco) cause chronic pancreatitis are also complex and not fully understood. Alcohol can cause damage through toxic alcohol metabolites, upregulation of various genes associated with cell death, direct activation of pancreatic stellate cells (which produce fibrosis), and other mechanisms. The interactions of alcohol and cigarettes may be mainly through increased endoplasmic reticulum stress[4].

Many patients have underlying genetic mutations and polymorphisms that increase the risk of disease progression. These polymorphisms may primarily affect the acinar cell (for example, the serine protease inhibitor accidental-1 or the cationic trypsinogen gene), the ductal cell (the cystic fibrosis transmembrane conductivity regulator), or both.

Clinical Findings

Abdominal Pain: Abdominal pain is the most common clinical symptom in chronic pancreatitis. Pain is most commonly felt in the epigastric region and often radiates to the back. It may be worse at bedtime and patients may experience postprandial flare-ups. Pain is most common in patients with chronic pancreatitis due to alcohol or tobacco use and in those with idiopathic pancreatitis that occurs at a young age. Nausea, vomiting, and loss of appetite are often associated with pain.

The pattern of abdominal pain differs between patients. Some patients may experience constant pain of varying intensity with periodic exacerbations, while others have unrelenting and severe pain that continues. Many patients may present with episodes of pain and remain pain-free for a long time between exacerbations. At this stage, patients may be labeled with recurrent acute pancreatitis. Pain patterns can change over time, most commonly changing from episodic pain to more continuous pain. In rare patients, pain may actually subside after years of illness. However, a change in pain pattern or sudden worsening of pain should also warrant investigation for complications of chronic pancreatitis, such as pseudocyst, duodenal or biliary obstruction, or secondary pancreatic carcinoma.

The presence or severity of pain is not related to the severity of pancreatic damage in imaging studies (eg, computed tomography [CT] or magnetic resonance cholangiopancreatography [MRCP])[5]. An important clinical consequence of this lack of correlation is that patients have severe pain on CT with only minimal evidence of pancreatic damage or are pain-free despite

having dramatic damage on CT. Pain is the most common reason for hospitalization or endoscopic or surgical intervention.

In these patients, the cause of the pain may be increased pressure in the pancreas, ischemia, and inflammation, which may be due to damage and changes in the pain signaling of nociceptive neurons or complications of chronic pancreatitis. These mechanisms may overlap. Damage and alteration in pain signaling in these patients may cause central nervous system neural signaling and structural reorganization to function centrally, producing ongoing pain regardless of local pancreatic events. These patients develop hyperalgesia (pain that normally increases in response to painful stimuli) and allodynia (pain in response to non-pathological stimuli)[6]. This explains why therapeutic approaches to pain often fail.

Steatorrhea: This is when patients report oily or floating stools due to impaired fat digestion but may not have frequent or watery diarrhea. About 90 percent of the pancreatic exocrine secretory capacity must be lost before a digestive disorder develops due to exocrine pancreatic insufficiency (steatorrhea). This degree of damage takes time to build up. Steatorrhea is usually the result of long-standing chronic pancreatitis (usually >5 to 10 years) but may also occur in lesions that obstruct the pancreatic duct and prevent enzymes from reaching the duodenum, and after severe episodes of acute pancreatitis. Weight loss may occur, especially if pain also limits oral intake. Weight loss, particularly sarcopenia, is associated with an increased risk of mortality in patients with chronic pancreatitis[7].

Asymptomatic: Although most patients with chronic pancreatitis have significant symptoms, a small group of patients does not have symptoms or identifiable clinical signs. In such patients, the diagnosis of chronic pancreatitis can be made incidentally by CT scan.

Laboratory Findings

Low serum amylase or lipase levels are frequently seen in patients with advanced chronic pancreatitis but have no diagnostic value. In patients with an attack of acute pancreatitis, serum amylase or lipase levels are elevated to more than three times the upper limit of normal. However, in patients with recurrent attacks and progressing to chronic pancreatitis, the peak levels of amylase and lipase tend to decrease with each exacerbation. In those with established chronic pancreatitis, severe painful exacerbations cause only minimal or no

elevation in amylase or lipase. This change is probably the result of the gradual destruction of the acinar cells, which are the source of the enzymes, over time.

Elevations of serum bilirubin and alkaline phosphatase may suggest that the intrapancreatic portion of the bile duct is compressed by pancreatic edema or fibrosis. Jaundice or significant cholestasis can also occur from a co-existing pancreatic cancer.

Deficiencies of fat-soluble vitamins, especially vitamin D, often develop, increasing the risk of metabolic bone disease. Deficiencies of water-soluble vitamins and trace elements are less common but can occur when oral intake is limited or inadequate.

In those with chronic pancreatitis due to hypertriglyceridemia, serum triglyceride levels are elevated. Although triglyceride levels above 1000 mcg/mL are typically needed to produce the first episode of acute pancreatitis in these patients, relapses can occur at levels as low as 500 mcg/mL.

Elevations in serum immunoglobulin G4 (IgG4) levels can be observed in patients with type 1 autoimmune pancreatitis (AIP), and these elevations are part of the diagnostic criteria. In addition, other autoimmune markers may occasionally be elevated (rheumatoid factor, antinuclear antibody, and anti-smooth muscle antibody titer)[8].

Radiological Findings

Direct abdominal radiograph: The presence of diffuse pancreatic calcifications can be seen. While the presence of pancreatic calcification is specific to chronic pancreatitis, it is not present in the same way and can take decades to develop. Nearby vascular calcifications may also mistakenly appear as pancreatic calcifications.

Abdominal ultrasonography: An increase in echogenicity is detected on ultrasound images of chronic pancreatitis. Ultrasonography provides limited diagnostic utility in the diagnosis of chronic pancreatitis because the pancreas may not be seen due to intestinal gas covering it. The sensitivity of abdominal ultrasound for chronic pancreatitis is about 60 percent[9]. However, changes in pancreatic echotexture similar to chronic pancreatitis can be seen in older individuals and people with long-standing type 1 or type 2 diabetes.

Cross-sectional imaging: Cross-sectional imaging with high-quality CT scan using multi-detector technology and pancreatic protocol or magnetic resonance imaging (MRI) with MRCP can diagnose chronic pancreatitis.

Chronic Pancreatitis Complications

Chronic pancreatitis is associated with various complications. The most common complications include osteopenia and osteoporosis due to exocrine insufficiency, pancreatogenic (type 3c) diabetes, and metabolic consequences of opioid dependence due to pain management[10]. Two-thirds of patients with chronic pancreatitis develop osteoporosis or osteopenia, and patients are also at risk for bone fractures. Other less common complications include pseudocyst formation, bile duct or duodenal obstruction, pancreatic acid or pancreatic pleural effusion, splenic vein thrombosis, arterial pseudoaneurysms, small intestinal bacterial overgrowth, gastroparesis, and pancreatic ductal adenocarcinoma.

Diagnosis

Chronic pancreatitis should be suspected in patients with chronic abdominal pain and/or a history of recurrent acute pancreatitis, symptoms of pancreatic exocrine insufficiency (diarrhea, steatorrhea, or weight loss), or pancreatogenic diabetes. Rarely, patients with chronic pancreatitis are asymptomatic and the diagnosis is suspected incidentally on imaging. Cross-sectional imaging with high-quality computed tomography (CT) scanning using multi-detector technology and pancreatic protocol or magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) are the best diagnostic tests for chronic pancreatitis. Patients who have a routine Abdomen CT (usually through an emergency department) but do not have a high-quality CT (or MRI with MRCP) have repeat imaging of the pancreas. In patients without advanced chronic pancreatitis, especially early in the clinical course, CT or MRI may not show conclusive evidence for chronic pancreatitis[9]. As chronic pancreatitis progresses over time, the damage visible on cross-sectional imaging will accumulate with the risk of exocrine insufficiency and/or diabetes. Most current diagnostic tests easily detect advanced chronic pancreatitis.

Direct pancreatic function test with secretin or endoscopic ultrasound (EUS) is recommended, if available, in patients with suspected chronic pancreatitis but with doubtful cross-sectional imaging. However, no test should be used as the sole diagnostic criterion for chronic pancreatitis and the results of these tests should be interpreted in the context of the patient's history (recurrent acute pancreatitis), symptoms, and possible risk of chronic

pancreatitis. If the diagnosis remains questionable, follow-up over time with periodic reassessment is the best approach.

Computed tomography (CT):CT has become the most commonly used test to diagnose chronic pancreatitis. It is commonly found and can view the entire pancreas and pancreatic duct. Features of chronic pancreatitis on CT include pancreatic atrophy, ductal dilatation, and multiple parenchymal and intraductal calcifications. The overall sensitivity of CT for chronic pancreatitis ranges from 80 to 90 percent, and the specificity is about 85 percent. However, like all diagnostic tests for chronic pancreatitis, sensitivity and specificity increase with disease duration, and patients with early chronic pancreatitis have lower sensitivity, who may have a normal or near-normal CT of the pancreas[9].

MRI, including MRCP: It gives more detailed images of the pancreatic duct. It appears to hold promise for earlier diagnosis than is possible with CT. Secretin can be administered during MRCP both to improve visualization of the pancreatic duct and to predict the secretion of fluid from the pancreatic duct in response to secretin. MRCP, especially with secretin infusion, has replaced diagnostic endoscopic retrograde cholangiopancreatography (ERCP) in these patients and is more accurate and much safer.

Endoscopic ultrasound (EUS): It provides an extremely detailed examination of the pancreatic parenchyma and duct. However, the EUS features of chronic pancreatitis are not specific. Similar changes in the pancreas can be detected in patients without chronic pancreatitis, including elderly individuals, chronic alcoholics, social drinkers, smokers, diabetics, and those with chronic renal failure.

Direct pancreatic function test: The function of the pancreas can be evaluated by administering a stimulating hormone (to cause acinar cell secretion of cholecystokinin, digestive enzymes, or secretin). The secreted fluid is collected by an oroduodenal tube or an upper endoscope.

Indirect pancreatic function test - Measurement of pancreatic enzymes in the stool is not commonly used to diagnose chronic pancreatitis, but rather to document possible exocrine pancreatic insufficiency in a patient with known pancreatic disease. Pancreatic enzymes can be measured in stool, and tests for chymotrypsin and elastase are commercially available.

ERCP: Although it gives the most detailed images of the pancreatic duct, it is no longer used in the diagnosis of chronic pancreatitis due to the availability of alternative imaging methods and the associated risk of complications.

Differential Diagnosis

Other conditions that can mimic chronic pancreatitis include diseases that cause pancreatic ductal obstruction, for example, pancreatic ductal adenocarcinoma, intraductal papillary mucinous neoplasms, and cystic neoplasms. Differential diagnosis is made with cross-sectional imaging.

Treatment

In the treatment of chronic pancreatitis, as pancreatic damage continues, steatorrhea, digestive disorder, and diabetes may develop due to pancreatic insufficiency. Likewise, pancreatic pseudocyst, bile duct or duodenal obstruction, visceral artery pseudoaneurysm, pancreatic acid, and pancreatic pleural effusions, gastric varicose due to splenic vein thrombosis and pancreatic malignancy may develop as a complication of chronic pancreatitis.

Patients with chronic pancreatitis are questioned in terms of smoking and alcohol use and it is recommended to quit. It is recommended that patients consume low-fat meals, small meals and avoid dehydration.

Most patients with chronic pancreatitis-related pain require analgesics. A phased approach to treatment should be followed to avoid high-dose opioids for pain control. For the initial treatment of abdominal pain associated with chronic pancreatitis, acetaminophen and/or nonsteroidal anti-inflammatory drugs (NSAIDs) are started. Tricyclic antidepressants, serotonin reuptake inhibitors (SSRIs), and combined serotonin and norepinephrine reuptake inhibitors or gabapentoids can be used in patients whose pain requires opioid therapy to minimize the use of opioid analgesia[11].

In patients with chronic pancreatitis-related pain who do not respond to initial medical therapy alone, subsequent therapy is planned to expand the pancreatic ductal anatomy.

Endoscopic drainage is preferred in patients with occluded pancreatic duct with refractory pain. Emerging data suggest that surgical treatment is more effective and more durable than endoscopic approaches[12]. In practice, however, many patients still choose endoscopic therapy because of their reluctance to undergo surgery, and many surgeons opt for surgery when endoscopic approaches to pancreatic drainage have been exhausted or have failed.

Pancreatic enzyme supplementation is required in patients with exocrine pancreatic insufficiency. The efficacy of enzyme supplementation is generally measured clinically by improvement in stool consistency, apparent loss of stool

fat, improvement in fat-soluble vitamin levels, and increase in muscle strength and body weight.

Patients with chronic pancreatitis may suffer from type 2 diabetes mellitus but are also predisposed to diabetes from the destruction of pancreatic islets from chronic pancreatitis (type 3c diabetes). This can produce fragile diabetes with a high risk of treatment-induced hypoglycemia. Metformin may reduce the risk of secondary pancreatic carcinoma in these patients[13]. However, insulin is often needed to control diabetes.

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PART 5:

ADRENAL GLAND DISEASES AND TUMORS

Kubilay SARIKAYA
Fahri Erkan SADİOĞLU

Introduction

Although they are very small in size, the adrenal glands which sit atop the kidneys produce a wide range of endocrine products which have potent effects on numerous body systems. Diseases characterized by either excessive or insufficient adrenal hormones may lead to serious chronic illness and even fatality. It is very difficult to differentiate benign and malignant adrenal tumors. Benign or malignant adrenal tumors appear as some hypersecretory syndromes as oversecretion of aldosterone (Conn syndrome), cortisol (Cushing syndrome) or androgens (androgenital syndrome) and adrenaline or noradrenaline (pheochromocytoma). Although it is difficult to differentiate from benign to malignant, benign adrenal kortex tumors are generally smaller in size. Benign tumours tend to be homogeneousin cross-section compared with heterogeneous malignant tumours [1]. Open or laparoscopic adrenalectomy is currently the gold standard treatment for adrenal tumors [2]. The success and complication rates of open and laparoscopic adrenalectomy are similar. Adrenalectomy is curative, especially in small localized tumors [3]. Adjuvant treatment regimes for more advanced adrenocortical carcinoma involves the chemotherapeutic agent mitotane [4].

Adrenal Physiology and Anatomy

Both adrenal glands consist of two parts, cortex and medulla. These two parts of the adrenal gland have completely different functions, morphologically and functionally [5]. Adrenal cortex is divided into three parts as zona glomerulosa, zona fasciculata and zona reticularis. Themain products of the peripheral zone ofthe cortex, the zona glomerulosa, are mineralocorticoids (mainlyaldosterone), while secretion of glucorticoids (mainlycortisol)

predominates in the zona fasciculata and the sex steroids (androgens, progesterone and oestrogens) are secreted bytheinnermostzone, the zonareticularis.The function of the zona glomerulosa is under the control of the rennin-aldosterone system, whereas glucorticoid and androgen production is controlled mainlyby hypophyseal adrenocorticotropic hor-mone (ACTH). ACTH secretion exhibits a diurnal rhythm, with highest levels at 6 levels at10 pm, which correlates with the oscillating pattern of cortisol plasma levels. A common precursor of steroidal hormones of the adrenal cortex is cholesterol; these hormones are metabolised by the liver and the metabolites are secreted by the kidneys [6]. Arterial blood supply to the adrenal gland is provided by the superior adrenal artery, medial adrenal artery and inferior adrenal artery. The right adrenal vein is shorter and empties into the right vena cava, while the left adrenal vein is thinner and longer and empties into the left renal vein.

Hormonal secretion:

Mineralocorticoids regulate extracellular and intracellular fluid volume and fluid-electrolyte balance. Aldosterone stimulates reabsorption of sodium and increases secretion of K into urine. An excess of aldosterone causes arise of the extracellular fluid, hypertension, hypokaliaemia and metabolic alkalosis. While glucocorticoids increase gluconeogenesis, they have a catabolic effect on protein metabolism. Glucocorticoids influence the immune system and have anti-inflammatory and immunosuppressive effects. Due to the effect of cortisol, the blood inflow and glomerular filtration increase in the kidneys. Unlike glucocorticoids, adrenal androgens have anabolic effects. the adrenal glands contribute to the daily production of testosterone byabout 100 μg per day, while the testicles produce about 7000 μg of testosterone aday in males. On the other hand, adrenal glands produce roughly 50% of circulating testosterone in females [7].

Hypersecretion Syndromes:

Syndromes of hypersecretion of the adrenal gland occur in several variants:

Bilateral hyperplasia of the adrenalcortex, adrenocortical adenoma, or adrenocortical carcinoma.

1. Pimary Hyperaldestoronism (Conn syndrome):

It develops as a result of excessive secretion of aldosterone from the zona glomerulosa. Female/male ratio is 2/1. It causes from benign adrenocortical adenoma and in 20% of cases by bilateral hyperplasia of the adrenal cortex; very rarely the syndrome is due to anadrenocortical carcinoma [8]. The most common symptoms of Conn syndrome are muscular weakness, headache, polydipsia and polyuria, arterial hypertension, hypocalaemia, metabolic alkalosis and low plasma rennin levels [9].

2. Cushing syndrome:

Cushing's syndrome is a condition that develops as a result of excessive cortisol secretion and includes a wide variety of symptoms and clinical findings as: Trunk obesity, plethora and moon-shaped face, purple striae on the belly, breasts and thighs, hirsutism, acne, sexual malfunction, arterial hypertension, hyperglycaemia andosteoporosis. Cushing's syndrome can be divided into five main subgroups:

- 1.Central type: Characterized by bilateral diffuse hyperplasia of the adrenal cortex and hyperproduction of cortisol due to permanently increased ACTH secretion.
- 2.Paraneoplastic: It has the same clinical-pathological findings as the central type. Difference is that ACTH is produced by ACTH-producing tumors and not by the hypophysis.
- 3.Macronodular hyperplasia: This type is independent of ACTH and characterized by the presence of large nodules in the adrenal cortex and concomitant bilateral hyperplasia of the adrenal cortex.
- 4.Peripheral type: This type is caused by a benign or malignant tumour of the adrenal cortex. It is seen in especially in pubertal girls.
- 5.Iatrogenic type: This type is typically seen in patients receiving large doses of corticosteroids as in organ transplantation.

3. Adrenogenital syndrome:

Adrenogenital syndrome is nearly always caused by a tumor with in the zona reticularis, which produce sexcessive amounts of androgens or oestrogens and sometimes also cortisol. Approximately 50% of cases are in children and adolescents [10]. Overproduction of androgens in women leads to virilisation manifesting itself through hirsutism, breast atrophy, oligomenorrhagia and clitoridomegalia. In boys, overproduction of androgens results in pubertas praecox, while in adult men the adrenogenital syndrome virtually cannot be

detected. Overproduction of estrogens causes feminization of adult men, which may manifests itself through gynaecomasty, atrophy of the testicles and decreased libido. The first subjective symptom of adrenocortical carcinoma is pain, which may be of the blunt persistent type caused by the pressure of the tumour on the neighbouring organs or by of iniltration into the nevre bundles [11] . Another, less frequent type of pain is severe abdominal pain due to acute bleeding into the tumour or from a rupture of the adrenocortical carcinoma.

A relatively large group of adrenocortical tumours (around 15%) comprises the so-called adrenal gland incidentalomas. These are asymptomatic and hormonally inactive tumours, which are found incidentally by sonographic or radiological examination of the abdominal organs [12].

4. Myelipoma:

It can to be identified as metaplasia of adrenal gland which may originate from the adrenal medulla or the cortex. It is completely benign and clinically asymptomatic. It is usually detected incidentally or when it reaches excessive size, causing pain [13].

Adrenal medullar tumors

The adrenal medulla is a part of sympathico-adrenal system. It includes chromoinic cells, which are in principle neurons without efferent fibres. In this area catecolamines (adrenaline, noradrenaline) are produced that influence the regulation of numerous physiological and metabolic functions. The most common tumor of the adrenal medulla is pheochromocytoma and produces catecholamines.). If the tumour arises from extraadrenal chromafine cells, it is referred to as an extraadrenal pheochromocytoma or paraganglioma [14]. In 80-90 % of cases, the pheochromocytoma occurs as a solitary tumour and is considered to be anacquired disease. In 10% of cases, it occurs extraadrenally, in10% of cases, bilaterally (sometimes as part of familial multiple endocrine neoplasia syndrome MEN2A and MEN2B), and in10% of cases, it has histological features of malignancy. A pathognomic sign of the pheochromocytoma is paroxysmal hypertension appearing in approximately 50% of the patients [15].

Diagnosis and Laborotory of adrenal masses:

Detailed medical history and physical examination should be performed primarily in the diagnosis of adrenal lesions. Laboratory tests aimed at proving over production of hormones of the adrenal cortex and hypophysis, their metabolites and main stimulators of their biosynthesis. In the diagnosis of corticoid-secreting lesions, plasma cortisol level measurement is performed. It

changes in a broad physiological range (100-650 nmol/l). Free cortisol in urine is a sensitive indicator of the concentration of free cortisol in plasma; values range between 70 and170 nmol per day and rise markedly with Cushing syndrome. Further examinations are stimulation tests (ACTH tests, metopirone test, corticoliberin test) and inhibition tests (dexamethason test). In order to determine the mineralocorticoid level, plasma renin activity and concentration of angiotensin are used in plasma and urine. androstendione and dehydroandrostendione, free testosterone and 17-ketosteroid in urine are used to evaluate the androgens levels. The detection of >100 nmol per 24h adrenaline and >500 nmol per 24 h noradrenaline in urine is diagnostic for pheochromocytoma.

Imaging techniques:

Computed tomography (CT), especially spiral CT and Magnetic resonance imaging (MR) are likeliy adequate for visualizing the adrenal masses. Anjiograph may be performed as it provides information onthe vascular supply of the tumour as well as information useful for surgical decisions [16].

Surgical approach:

Adrenalectomy is indicated for syndromes of hyperfunction of either the adrenal cortex or the medulla caused by a tumour or cortical hypertrophy (with the exception of congenital adrenal hyperplasia), or for adrenal tumours 4 >cm in diameter with no hormonal activity where malignancy is suspected. The choice of incision site is made dependent on: the size of the lesion; the type of disease; patient habitus; and the experience and preference of the surgeon. The lateral approach is used with smaller tumours (<5 cm). The posterior approach goes direct to the adrenal gland, but does not allow widening of the field in case of complications; this approach through the 10th intercostals space isused infrequently. The thoraco-abdominal approach is used for very large tumours, particularly those on the right side, and isthrough the eighth intercostal space. The transperitoneal incision is used for large tumours, especially malignancies or pheochromocytomas due to the possibility of multifocality (10% of cases). This approach can be used in bilateral hyperplasias and in some patients with Cushing's syndrome who have extreme osteoporosis with multiple fractures, this is the only one possible. Sufficient time must be allowed with this technique because the approach to the adrenal glands is not direct. There are several transperitoneal approaches, including middle laparotomy, subcostal incision (suited to large tumours), the transabdominal or Chevron incision. This is a bilateral subcostal incision, which gives wide Access to both adrenal glands; it

is not necessary to extend the incision of the contralateral side in the case of unilateral disease.

Laparoscopic adrenelectomy:

Retroperitoneal or transperitoneal techniques are used in laparoscopic adrenalectomy. Laproscopic adrenalectomy is indicatedfor hormone-inactive mass, hormone-active solid mass, recurrent central forms of Cushing'ssyndrome. Contraindications of the procedure are: Hernias following abdominal operations, severe obesity, concurrent significant intraperitoneal tumours, coagulopathy, serious ischaemich eart or broncho-pneumonic disease and advanced pregnancy. The major advantage of the laparoscopic technique is comfortable recovery with as shorter period of hospitalisation; transfusion requirements are less and there are fewer perioperative complications with trained staff. Adrenal sparing technique can be applied to patients with vonHippel-Lindau disease who have developed multiple bilateral adrenal pheochromocytoma [17].

Preoperative and postoperative preperation:

Pre and post operative preparation of the patient is important. For those patients treated for hypercortisolism and patients undergoing bilateral adrenalectomy cortisol substitution should be applied consisting of 100 mg during surgery and100 mg at 6 h intervals for the first day. Parenteral administration of cortisol is followed by peroral substitution in descending dosage from 50 to 0 mg per day divided in two dosages (morning 0-20 mg; midday 20-10 mg). For patients with pheochromocytoma or conditions involving overproduction of catecholamine the situation is more complicated. There is a potential danger from flooding of the system with catecholamines during tumour manipulation, resultingin a very rapid increase in blood pressure. Consequently, attempts should be made to dissect and ligate the central suprarenal vein; fentolamine (Regitine) should be applied in the case of a rapid blood pressure rise. Dispensarization after surgery for pheochromocytoma is necessary, with measurement of urinary metabolites of catecholamines. Anaesthesia in these patients also has to be modified; the use of atropine in the pre-medication is not advised. Halothane and curare should not be used, whereas methoxyflurane, succinylcholine and nitrous oxide are considered suitable. Lidocaine may be applied in the event of arrhythmias during surgery.

Adrenocortical carcinoma:

Adrenocortical tumors are rarely seen clinically and their incidence is higher in women. Autopsies indicate adenomatous changes of the adrenal glands 2% up to 8% of patients with primary extraadrenal malignancies have adrenal metastases at the time of autopsy [18]. Only a small proportion of adrenocortical tumours cause endocrine diseases such as primary hyperaldosteronism, hypercortizism, hyperandrogenism and/or hyperoestrogenism. Adrenocortical carcinoma is a rare tumour with an incidence of 0. 5-2% of adenomas of the adrenal gland. The incidence of left adrenal tumours was 52. 8% and bilateral tumours occurred in 2. 4% of patients and female patients developed functional tumours more often than male patients. Patients with untreated adrenocortical carcinoma have a very poor prognosis; the mean survival time is only months. Overall, 5-year survival in treated patients ranges from 16 to 4% [19].

The aetiology of adrenocortical carcinoma is unknown and it carises from adrenal cortex. According to an another opinion, the carcinomas develop from hyperplastic nodules in the adrenal gland. Neoplastic transformation of the tissue of the adrenal cortex may also be caused by chronic excessive stimulation of ACTH. Genetic aberrations and chromosomal abnormalities, including several chromosomal loci (loss of heterozygosityon chromosomes l1p, 1 q and 17p) and the genes coding for p5, p57 and insulin-like growth factor, have been reported in adrenal tumours and may be important in pathogenesis [20].

Adrenocortical carcinoma is divided into two forms as either functional (75%) or non-functional (25%) tumours. Functional carcinomas are classified according to whether they produce an excess of corticosteriod, sex hormone (s), or mineralocorticoid. In contrast to adult tumours, over 95% of paediatric tumours are functional and are frequently associated with congenital abnormalities and secondary tumours [21].

Staging (European Network for The Study of Adrenal Tumors):

T staging:

T1: tumor <5cm

T2: tumor > 5 cm

T3: Tumor infiltrates into surrounding adipose tissue

T4: Tumor infiltrates surrounding organs and tissue

N staging:

N0: Lymph node metastases(-)

N1: At least one lymph node metastases (+)

M staging:

M0: Distant metastases(-)
M1: Distant metastases(+)
TNM stage:
Stage 1: T1N0M0
Stage 2: T2N0M0
Stage 3: T1–2N1M0/ T3–4N0–1M0
Stage 4: T1–4N0–1M1

Identification of malignant adrenocortical tumours:

It is very dificult to distinguish benign and malignant adrenocortical tumours. However, a number of criteria can be applied, including size; benign tumours of the adrenal cortex are generally smaller than malignant tumours. Benign tumours tend to be homogeneous in cross-section compared with heterogeneous malignant tumors. Benign adrenocortical adenomas are a uniformly yellow, darkred or even black colour on cross-section, depending on fatand lipofuscin content of the cells on CT imaging. In contrast, adrenocortical carcinomas, which on cross-section have a lobarnature, are non-uniform with regions of necroses and bleeding [(1)]. Nevertheless, the presence of distant metastases are the absolute indication of malignancy.

Treatment:

The treatment protocol for adrenocortical tumors includes surgery including adrenalectomy and chemotherapy. The most commonly used chemotherapeutic agent for this purpose is mitotane. The specific cytotoxic activity of mitotane on the adrenal glands has lead to its use in both primary and adjuvant therapy settings. Studies indicate that the response to mitotana varies in the range of 14-35%. Survival rates of 1 % after 2 years have been reported by Venkatesh et al. [(22)], however, signiicantly longer survival beneits were possible when mitotane serum blood levels were maintained above 14 mg/l. Most common side effects of mitotane therapy, nausea, anorexia, lethargy, dizziness, somnolence and depression. Almost all patients on this mitotane therapy will experience adrenal insuficiency and steroid replacement should be routinely used. Fludrocortisone acetate is the most common agent that should be given at an initial dose of 0. 1 mg three times per week, adjusted to 0.1mg per day according to serum electrolytes and weight gain. Combination of cisplatin and etosposide may also been used for chemotherapy, but an effect close to the efficacy of mitotane cannot be obtained.

Follow-up: Approximately 85% of adrenocortical carcinomas develop recurrence or metastasis. In follow-up period, CT of theabdomen and chest x-

ray should be performed four times each year for the first 2 years and thereafter twice each year. Patients with an elevated serum level of dehydroepiandrosterone can be followed with this marker. Patients with a tumour producing elevated levels of urinary corticosteroids should have their urine checked every 6 months.

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PART 6:

DYSLIPIDEMIA

Tuba UYANIK

Atherosclerotic cardiovascular diseases (ASKVD) are the leading cause of premature death in developed and developing countries[1]. Dyslipidemia is the most important preventable risk factor that increases the risk of atherosclerotic cardiovascular disease[2]. Studies conducted in Turkey have shown that approximately 80% of the adult population has dyslipidemia[3]. The increasing prevalence of obesity and Type 2 Diabetes causes the frequency of dyslipidemia to increase gradually.

The most common autosomal dominant single gene disease in the world is Familial Hypercholesterolemia (AD). AH cases progress with high cholesterol levels and early ASPVH that occur independently of their lifestyle. The frequency of heterozygous AH (HeAH) has been reported between 1/100 and 1/500 in different populations[4]. However, unfortunately, there is no data on the frequency of AD in our country.

We usually evaluate the concept of dyslipidemia with the risk of ASPVD. But it is also useful to remember that there is an increased risk of pancreatitis at very high TG levels.

Relationship between Dyslipidemia and Cardiovascular Disease

Cholesterol is a very important lipid for our body. It is involved in the structure of the cell membrane, in the formation of bile acids, and is used in the synthesis of steroid hormones. The cholesterol needed by the tissues is carried by lipoproteins labeled with Apolipoprotein B (ApoB). ApoB-labeled lipoproteins continuously enter and leave the vascular intima to meet the cholesterol needs of the tissues. Inflammation, oxidative stress, endothelial dysfunction, or the presence of excess circulating ApoB-labeled lipoproteins result in greater entry of these lipoproteins into the intima, where they are phagocytosed by macrophages[5]. These macrophages calcify, necrosis and begin

to accumulate in the vascular intima. These deposits are called oily streaks. This lesion, which has not yet narrowed the lumen, is the initial stage of atherosclerosis. Fatty streaking begins to be seen from childhood in those with high-risk lifestyles. Low-density lipoprotein (LDL) constitutes the majority (>90%) of circulating ApoB-containing lipoproteins. Therefore, in clinical practice, we determine the amount of circulating LDL by measuring the amount of cholesterol in LDL (LDL-C). That is, we use LDL levels to represent all ApoB-containing lipoproteins.

However, in atherogenic dyslipidemia, which is common in patients with diabetes mellitus (DM) and metabolic syndrome (MS), it may be misleading to determine the amount of LDL by measuring LDL-C. In these cases, LDL particles are small and dense, and the amount of cholesterol they contain does not accurately indicate LDL numbers. In atherogenic dyslipidemia, besides LDL, the amount of very low-density lipoprotein (VLDL) and medium-density lipoproteins (IDL) and their residues also increases.

Normal Lipid Values

Epidemiological studies show that serum lipids increase or decrease the risk of ASPVD from a certain limit. Based on these data, it is possible to classify serum lipid levels as optimal, borderline high and high-risk levels in terms of ASPVD risk.

TOTAL CHOLESTEROL (MG/DL)	
<200	Ideal
200-239	Lımıted Hıgh
≥240	Hıgh
HDL-CHOLESTEROL (MG/DL)	
<40	Low (Rısk Factor)
≥60	Hıgh (Rısk Factor)
TRIGLYCERIDE (MG/DL)	
<150	Normal
150-199	Lımıted Hıgh
200-499	Hıgh
≥500	Very Hıgh
LDL-KOLESTEROL (MG/DL)	
<100	Ideal
100-129	Close to the ıdeal
130-159	Lımıted hıgh
160-189	Hıgh
≥190	Very hıgh

Necessity of Dyslipidemia Screening

In order to screen for a disease, the disease should be widely seen in the community, its treatment should be possible, and an easy-to-apply and inexpensive screening test should be available. These criteria reveal why dyslipidemia is a disease that should be screened. Dyslipidemia is almost always asymptomatic and leads to early atherosclerosis. It is possible to reduce the risk of developing ASPVD by early recognition and timely measures. Today, blood lipids can be measured easily, quickly, cheaply and reliably. With dyslipidemia screening, it is possible to reliably estimate the risk of future cardiovascular disease (CVD).

Screening Frequency and Patient Selection

The atherosclerotic process begins to develop many years before its clinical consequences appear[6,7]. Dyslipidemia is one of the most important causes of atherosclerosis. It is asymptomatic. It is very common. Even people with no comorbidities or cardiovascular risk factors should be screened appropriately for dyslipidemia. The factors that determine the frequency of screening are the patient's age, gender, and the presence of other risk factors. Screening is recommended every 5 years in young adults, every 1-2 years in men over 40, and every 1-2 years in women over 50 (or after menopause).

Table 2. Dyslipidemia Screening Frequency

People who are asymptomatic, without ASPVD or risk factors for ASPVD • Every 5 years from the age of twenty • Every 1-2 years in men from the age of 40 • Once every 1-2 years in women from the age of 50 (or after menopause) • After the age of sixty-five, once a year
Diseases and risk factors that require annual screening for dyslipidemia • Clinical findings suggestive of atherosclerotic disease • Type 1 or Type 2 diabetes • Early history of ASPVD in first degree relatives (<55 years in men, <65 years in women) History of dyslipidemia in first degree relatives • Hypertension (including gestational hypertension) • Obesity • smoking • Chronic kidney disease (CKD) • Chronic inflammatory diseases (rheumatoid arthritis, systemic lupus erythematosus and psoriasis etc.) • Clinical findings of genetic dyslipidemias (Xanthoma, xanthelasma and arcus cornea etc.) • HIV infection

History and Physical Examination Features in a Dyslipidemic Case

In a patient with dyslipidemia, possible causes of secondary dyslipidemia, familial dyslipidemias, complications of dyslipidemia, other diseases frequently accompanying dyslipidemia, and risk factors for ASPVD should be investigated. It is necessary to systematically approach each patient in order to decide on the appropriate treatment. Therefore, in the evaluation of cases with dyslipidemia, it is very important to take a good anamnesis and perform a detailed systemic physical examination.

Anamnesis

Dyslipidemia cases are mostly asymptomatic. It is often detected during investigations performed for other reasons or while being evaluated for ASPVH. The age and gender of the patients are important in the anamnesis because these factors influence the overall risk score that determines the treatment decision in primary prevention. In the patient's history, ASPVD, DM, hypertension, inflammatory diseases (rheumatoid arthritis, systemic lupus erythematosis, psoriasis, etc.), kidney and liver diseases and other endocrinological diseases should be questioned. In addition, in cases with very high TG levels, since there is a risk of acute pancreatitis, it would be appropriate to question from this aspect. Clinical features of secondary causes that may cause dyslipidemia should also be questioned during the history and system examination. The patient's diet and exercise habits, as well as smoking and alcohol consumption, medications and lifestyle should be reviewed. When evaluating your family history; Whether there is dyslipidemia in first-degree relatives, a history of ASPVH at a young age (<60 years in women, <50 years in men), tendon xanthomas should be questioned. This questioning is important in terms of revealing familial dyslipidemias.

Table 6. Diseases and Drugs Causing Dyslipidemia

	LDL-K ↑	TG ↑, HDL-K ↓
Hypothyroidism	+	+
Nephrotic Syndrome	+	
Chronic Kidney Disease		+
Cholestatic Diseases	+	
Obesity		+
Pregnancy		+
Type 2 Diabetes		+

Excessive Alcohol Consumption		+
Anabolic Steroids	+	
Corticosteroids		+
Oral Contraceptives, Estrogens		+
HIV Treatment (Protease İnhibitors)	+	+
Thiazide Diuretics, Beta Blockers		+

Physical Examination

The aim of physical examination in cases of dyslipidemia is to reveal complications that may develop due to dyslipidemia, secondary causes that may cause dyslipidemia, and additional ASPVD risk factors. Physical examination may be completely normal in dyslipidemic cases. Especially in familial dyslipidemia cases, some specific system findings can be detected. More common clinical findings are clinical findings related to atherosclerosis caused by dyslipidemia. In the physical examination, the patient's weight, height and waist circumference (WC) should be evaluated and BMI should be calculated. In a sitting position, arterial blood pressure (ABP) should be measured in both arms after at least 5 minutes of rest. Out-of-office follow-ups of cases with high ABP should be requested and ABP measurements should be repeated at the next visit they come with.

Thyroid examination of the patients should be performed, and clinical signs and symptoms of thyroid diseases should be reviewed. Findings related to endocrinological diseases such as Cushing's Syndrome and acromegaly should be investigated. Physical examination findings of chronic liver and kidney diseases and rheumatological diseases should be evaluated.

Skin: In some cases of AH, xanthomas may occur in the Achilles tendon, wrist and elbow tendons, and metacarpophalangeal joints due to high LDL-C. These xanthomas may be planar or tuberous. Planar xanthomas are flat or slightly raised, yellowish plaques. Tuberous xanthomas are painless, solitary lesions that often appear on the extensor surfaces of the joints. In patients with severe TG elevation, yellowish eruptive xanthomas may occur on the trunk, back, hands, feet, knees, and elbows with multiple millimeters of raised skin.

Eye: Due to the high LDL-C level, a ring-like white lipid deposit occurs around the cornea. This finding, called arcus cornea, is considered significant in terms of dyslipidemia in people under the age of 45. On the other hand, subcutaneous lipid accumulations in gray-yellow color with unclear borders in and around the eyelids are called xanthelasma. Again, due to the reflection of

light by high TG levels, the pink-cream appearance of retinal arteries and veins is called lipemia retinalis.

Cardiovascular System: Peripheral pulses may be weak or absent due to atherosclerosis. It may be a listening finding due to aortic atherosclerosis or carotid stenosis. Findings consistent with coronary artery disease (CAD) can be detected in the ECG.

Gastrointestinal System: As a result of prolonged lipid accumulation in tissues, fatty liver disease and related hepatosplenomegaly may be detected. Patients with acute pancreatitis due to severe TG elevation may apply to the emergency department with severe abdominal pain.

Total Cardıovascular Rısk

a. Total Cardiovascular Risk Definition

Total cardiovascular risk is the probability that an adult person will experience ASKVO in the near future. There are many unavoidable (age, gender, genetic predisposition) and preventable (smoking, dyslipidemia, hypertension, obesity, etc.) risk factors in the development of ASPVD. The amount and severity of these risk factors vary in each person. Therefore, it is possible to determine the individual risk of ASKVO and/or death by calculating the total cardiovascular risk. Total cardiovascular risk is now generally calculated for adults over 40 years of age, over a 10-year period. This calculation includes all ASKVOs in some calculators, while in others it calculates only fatal ASKVOs.

b. Importance of Total Cardiovascular Risk Calculation

Unhealthy living habits play an active role in the emergence of many chronic diseases today. Therefore, the basic rule in the treatment of hypertension, obesity, Type 2 diabetes, dyslipidemia and similar diseases is primarily to review the lifestyle and eliminate risk factors. But if the severity of these risk factors is above a certain limit, lifestyle changes will not be enough and medical treatment options will come to the fore. Knowing the total cardiovascular risk level is helpful in making healthy lifestyle recommendations, deciding when to start medical treatment, and determining the intensity of treatment in a dyslipidemia patient evaluated for primary prevention. Thus, it will be possible to apply more effective treatment to those with higher risk. All guidelines aimed at reducing the risk of ASPVD recommend calculating the total cardiovascular risk. Calculation of total cardiovascular risk

mainly determines the risk of future ASPVD-related events and deaths in patients who appear healthy and have no clinical problems. Therefore, the total cardiovascular risk is not calculated in patients with clinically detected ASPVD or in people with AKVD risk equivalents such as diabetes, chronic kidney disease, or people with AD or very high individual risk factors. Such people are already at high risk and need intensive treatment and lifestyle changes related to their risk factors.

c. The Most Appropriate Total Cardiovascular Risk Calculator for Our Country

Ideal for a total cardiovascular risk calculator to be used in our country, it should be created by taking into account the characteristics of our own people. In this respect, it would be the most appropriate approach to use the SCORE calculation model specified in the ESC/EAS guideline for cardiovascular risk estimation in our country8. The SCORE calculation model was calculated from 12 different European cohorts with different levels of CVD risk, covering a wide geographical area.

The SCORE system calculates the risk of death due to the first atherosclerotic event (myocardial infarction, stroke, other conditions with atherosclerosis, sudden cardiac death) to occur within 10 years in a person with no known cardiovascular disease. Estimating absolute risk in this way provides an advantage for the SCORE risk calculation system used in the ESC/EAS guide. If it is desired to estimate the total event risk based on the risk of death measured by SCORE, it is necessary to obtain 3 times this risk score for men. This coefficient is slightly higher for women and slightly lower for the elderly. That is, if the risk calculated by SCORE in a man is 5%, the total CVO rate rises to approximately 15%.

d. Calculating Total Cardiovascular Risk with the SCORE Risk Calculator

For a person over 40 years of age, the number seen on the SCORE risk calculator at the intersection of sex, age, smoking status, Total-K, and systolic blood pressure gives the risk of cardiovascular death in ten years[8].

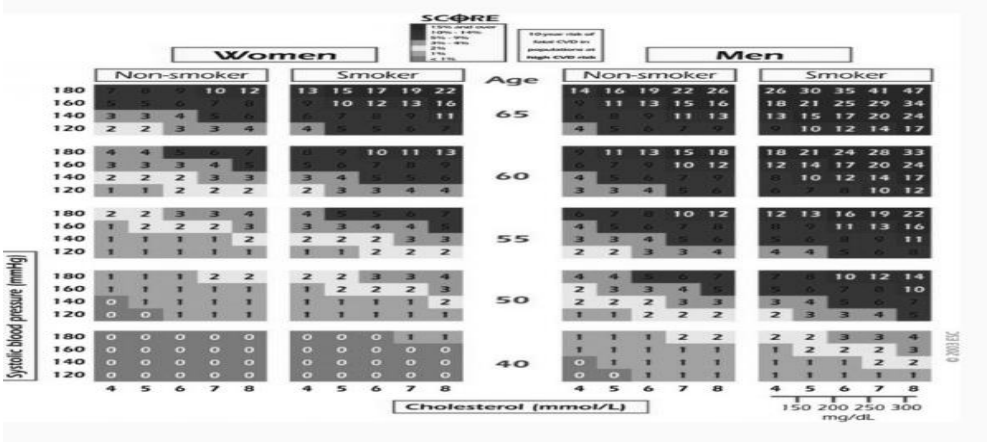


Figure 2. SCORE, 10-year Fatal Cardiovascular Risk Calculation Chart*.

* Only the 10-year risk of death is calculated with this table prepared in accordance with the populations with high cardiovascular risk. If event and death risk are to be seen together, multiply the number obtained in the table by 3 for men and 4 for women. The 10-year risk of cardiovascular death calculated with SCORE is considered low risk if it is less than 1%, moderate risk if it is between 1-5%, high risk if it is more than 5%, and very high risk if it is more than 10% (Table 8).

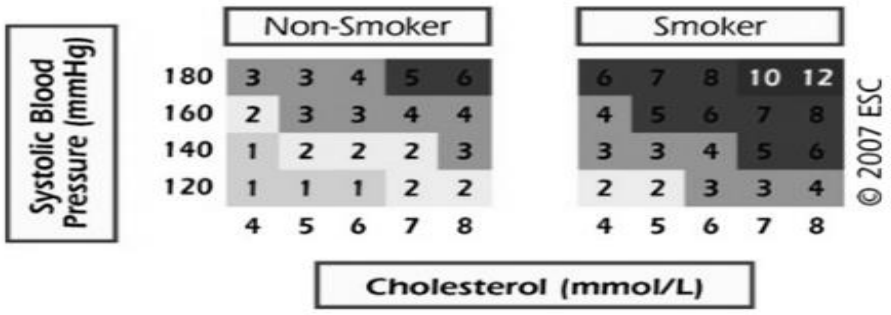
Table 8. 10-year Fatal ASKVD Risk Categories by SCORE Risk Calculator

Very High Risk	• Clinically Recorded Cvd. For Example, Previous Mı, Acute Coronary Syndrome (Acs), Coronary Revascularization (Percutaneous Coronary İntervention), Cabg Surgery, Other Arterial Revascularization Procedures, Stroke, Transient İschemic Attack And Peripheral Arterial Disease (Pah). • Cvd Recorded By İmaging Methods. For Example, Showing Plaque On Coronary Angiography Or Carotid Ultrasound. • Dm Cases With Target Organ Damage Such As Proteinuria Or An İmportant Risk Factor Such As Smoking, Hypertension Or Dyslipidemia. • Severe Ckd (Egfr<30 Ml/Min/1.73 M2). • 10-Year Cvd Risk Of Death Score≥10%
High Risk	• Significant Elevation Of A Single Risk Factor, Particularly Total-K >310 Mg/Dl (Ah) Or Blood Pressure ≥180/110 Mmhg • Other Diabetics (Some Young People With Type 1 Diabetes May Be Considered Low Or Moderate Risk). • Moderate Ckd (Gfr 30-59 Ml/Min/1.73 M2). • 10-Year Cvd Mortality Risk Score 5-10%
Medium Risk	•10-Year Cvd Mortality Risk Score 1% And <5%
Low Risk	•10-Year Cvd Death Risk Score<1%

Only age, gender, smoking, Total-K and systolic blood pressure parameters are used in the SCORE calculator, not all risk factors. Therefore, the patient has atherogenic dyslipidemia, obesity, sedentary life, etc. If other risk factors are present, it should be noted that the risk will be higher than calculated. Indeed, studies in the SCORE database have shown that HDL-C can have a significant impact on risk estimation. When HDL-C values are entered, it is seen that the risk varies in all risk levels, age and gender in SCORE tables. This is especially important for people below the 5% threshold for high risk. This is important in people with low HDL-C. In order to increase the accuracy of risk assessment, the use of HDL-C levels is particularly recommended in individuals with high risk and low HDL-C levels.

e. Calculation of Cardiovascular Risk in Young People

Total cardiovascular risk calculation is mostly planned for people over 40 years of age. Therefore, their use in young people is problematic. Even if the risk among young people is high compared to their peers, their absolute risk will be low due to their life expectancy. However, these people are at relatively high risk when compared to people of their own age. This situation may delay the taking of necessary precautions by causing false relief and the continuation of the wrong lifestyle in risky people. To address this problem and to calculate the cardiovascular risk in young people, the ESC/EAS guideline has proposed a table that compares the cardiovascular risk status of young people by their age group. Thus, it is possible to compare a young person with a low absolute risk of 10 years in terms of ASPVD with a person of his/her own age and reveal their relative risk. When this relative risk table is carefully examined, it is seen that the risk score is 1 in a young person who does not smoke and has normal blood pressure and Total-K levels. As the risk factors increase, the risk coefficient of the person also increases. For example, a risk score reported as 12 in the top right of the figure would mean that person's risk of CVD is 12 times greater than that of a healthy person of their age.



f. Considerations for Cardiovascular Risk Calculation in the Elderly

The estimated risk according to the SCORE table is higher than it should be for the elderly. It should be noted that, excluding women who do not smoke, almost all people over the age of 65 are in the intermediate and high risk category (SCORE score (5-10). Therefore, almost all of these people seem to deserve statin therapy, even if their risk factors for ASPVD are very low. In the version of the SCORE calculator developed for Turkey, the risk scores are much higher, so the problem is much more obvious. Therefore, it would be misleading to estimate the risk based on the SCORE risk score alone in the elderly. Also, there are no data showing that statin therapy reduces mortality in primary prevention, especially for people over 70 years of age. Therefore, the treatment decision in such individuals should be individualized and based on the severity of the accompanying risk factors and the number of other drugs being used.

Treatment And Follow-Up

Dyslipidemia treatment; It includes lifestyle change, diet, treatment of secondary causes, and medical treatment. Exercise causes a decrease in TG and LDL levels, while increasing HDL levels. At least 4 times a week, at least 30 minutes of brisk walking or, according to the patient's medical capacity, activities such as swimming, cycling, jogging can be recommended regularly and continuously. Diet is always the first approach in the treatment of dyslipidemia. The dietary content to be applied depends on the type of hyperlipidemia. Saturated fatty acid intake is restricted in those with hypercholesterolemia. Alcohol intake is restricted in those with high TG. Although fish oil causes high LDL, it can be recommended up to 6 grams per day for those with high TG. In the studies conducted, it is recommended to start medical treatment in the presence of CAD or at a high risk of developing CAD, if the desired lipid levels

cannot be achieved with 3-6 months of diet therapy and regular exercise. Patients with hyperlipidemia, who are divided into 5 different risk categories, taking into account the presence of CAD or equivalent conditions and 10-year CAD risk percentages, as well as major risk factors; It is followed with a treatment approach aimed at target lipid levels[9].

Presence of atherosclerotic diseases such as symptomatic carotid artery disease, peripheral artery disease or abdominal aortic aneurysm or presence of diabetes mellitus is considered as CAD equivalent9. Treatment response is assessed after 6 and 12 weeks. Subsequently, patients are followed up every 4-6 months. The goal of lipid-lowering therapy is to slow or even reverse the progression of cardiovascular disease. This is why treatment should be continued for life[10].

Statins act by inhibiting the enzyme 3-hydroxy 3-methyl glutaryl-CoA reductase, reducing cholesterol synthesis and inhibiting liver LDL uptake. They reduce the risk of CAD and mortality. Fibric acid derivatives reduce both triglycerides and cholesterol by increasing lipoprotein lipase activity, decreasing VLDL synthesis in the liver and increasing LDL uptake. Resins (bile acid binders) bind bile acids in the small intestine, disrupting the reabsorption step of the enterohepatic circulation. They activate LDL receptors in the liver, causing LDL to drop. Nicotinic acid reduces both LDL and triglyceride levels by reducing the synthesis of VLDL in the liver.

It has been shown that if women who have entered the menopausal period have high cholesterol levels, a decrease in LDL level and an increase in HDL level can be achieved with oral estrogen replacement therapy. It is stated that the experimental studies carried out on gene transplantation therapy, which is considered to be applied to those with LDL receptor gene defects, are promising. Metformin, which is mainly used to treat insulin resistance in patients with type 2 diabetes, has a significant TG-lowering effect[9].

Degree Of Risk		Diet And Lifestyle Change	Medication	Ldl Target
Very High	Acute Myocardial İnfarction, Cad/Peripheral Artery Disease + Diabetes/Smoking/Metabolic Syndrome/Chronic Kidney Disease	Ldl ≥ 70 Mg/Dl	Ldl ≥ 70	Ldl < 70
High	Hr Or Hr Equivalents	Ldl ≥ 100 Mg/Dl	Ldl ≥ 100	Ldl < 100
High Medium	No Cad, Cad Risk Factor ≥ 2 10-Year Risk Of Cad 10-20%	Ldl ≥ 130 Mg/Dl	Ldl ≥ 130	Ldl < 130
Middle	No Cad Cad Risk Factor ≥ 2 10-Year Risk Of Cad < 10%	Ldl ≥ 130 Mg/Dl	Ldl ≥ 160	Ldl < 130
Düşük	No Cad, Cad Risk Factor ≤ 1	Ldl ≥ 160 Mg/Dl	Ldl ≥ 190	Ldl < 160

Drugs with selective action on lipids

Drug groups	Drugs	LDL decrease	HDL increase	TG decrease	Initial /Dose	Side effect
Statins	Fluvastatin Pravastatin Lovastatin Atorvastatin Simvastatin Rosuvastatin	%20-30 %25-40 %25-40 %25-40 %25-40 %40-50	%5-10 %5-10 %5-10 % 5-10 %5-10 %10-15	%20 %20 %20 %40 %40 %40	20 /40 mg once a day 20 /40 mg once a day 10 /80 mg once a day 10 /80 mg once a day 5 /80 mg once a day 10 /40 mg once a day	Myopathy, rhabdomyolysis liver enzyme elevation
Fibric acid derivatives	Gemfibrozil clofibrate	%10-15 %10-15	%15-20 %15-20	%40-60 %40-60	1x600/2x600 mg 1x500/2x500 mg	Rhabdomyolysis, constipation, hair loss, impotence, increased risk of gallstones
Nicotinic acid	Niacin colesevelam	%15-25 %10-20	%25-35 %10	%30-50 ±	1x100mg/4 g bölerek 625 /625mg bir kez	Impaired glucose tolerance, peptic ulcer, rash, itching, uric acid elevation
Resins	colestipol Cholestyramine	%15-25 %15-25	%5 %5	± ±	2x2,5/30 gr bölerek 2x2/24 gr bölerek	Constipation, bloating, gas, lack of fat-soluble vitamins AD-E-K
Azetidione	Ezetimibe	%20	%5	±	10/10 mg bir kez	No significant side effects

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Part 7:

DIABETIC KETOACIDOSIS AND HYPERGLYCEMIC HYPEROSMOLAR STATE

Necla DERELİ

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS), the acute complications of decompensated diabetes mellitus, can occur in patients with both type 1 and type 2 diabetes mellitus. In these clinical pictures, which occur due to insulin deficiency, patients deteriorate rapidly, but most patients recover rapidly with aggressive treatment. The presence of a history of diabetes in patients presenting with coma or mixed acid-base disorder should suggest the presence of DKA or HHS. After excluding other causes of coma and metabolic disorders, the diagnosis of DKA and HHS is confirmed by clinical and laboratory examination. In order for the treatment to be a successful, rapid and accurate diagnosis, immediate initiation of treatment, and close monitoring of the patients are required. The main treatment for DKA and HHS is fluid replacement, insulin therapy, and correction of electrolyte disorders. Identifying the precipitating causes during treatment may be helpful in preventing hyperglycemic crises that may occur later[1].

Despite the availability of well-established diagnostic criteria and treatment protocols, DKA and HHS are the important causes of mortality and morbidity among diabetic patients[2]. DKA is seen at a higher rate than HHS in patients admitted to the hospital with a hyperglycemic crisis. While DKA is more common in patients with type 1 DM, HHS is more common in patients with type 2 DM. Contrary to popular belief, DKA is more common in adults than children[3]. There may also be cases where DKA and HHS cases overlap[4]. While mortality rates are around 2-5% in DKA, it is around 15% in HHS[3,5]. DKA is the most common cause of death in children and adolescents with type 1 DM[6].The cause of death in DKA or HHS is not related to metabolic complications of hyperglycemia or metabolic acidosis, is related to underlying diseases. Since

these diseases precipitate metabolic decompensation, careful investigation of these causes affects the success of treatment[7]. In this article, the clinical presentation, pathogenesis, treatment, and complications of DKA and HHS will be reviewed.

Definitions

DKA consists of the triad of hyperglycemia, ketonemia, and high anion gap metabolic acidosis[8], while HHS is defined as hyperglycemia with varying degrees of ketosis and altered consciousness (usually without coma). Insulin deficiency (insulinopenia) is present in DKA and HHS. While insulin deficiency in DKA is almost complete, there is enough insulin in HHS to prevent lipolysis and ketosis formation. While DKA and HHS are distinguished according to severity of dehydration, ketosis, and metabolic acidosis, DKA is also classified as mild, moderate, and severe DKA according to these criteria[9-12]. The classification made by the American Diabetes Association (ADA) is given in Table 1[1].

In DKA, where the major finding is metabolic acidosis, blood glucose is usually below 800 mg/dl (often between 350-500 mg/dl). However, it may exceed 900 mg/dl in some comatose patients [10-13]. Euglycemia may occur in patients with poor oral intake, pregnant women, patients treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors, and patients treated with insulin prior to hospital admission (blood glucose <250 mg/dl).

Typical laboratory characteristics of DKA and HHS*

	DKA			HHS
	Mild	Moderate	Severe	
Plasma glucose (mg/dL)	>250	>250	>250	>600
Plasma glucose (mmol/L)	>13.9	>13.9	>13.9	>33.3
Arterial pH	7.25 to 7.30	7.00 to 7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15 to 18	10 to <15	<10	>18
Urine ketones¶	Positive	Positive	Positive	Small
Serum ketones - Nitroprusside reaction	Positive	Positive	Positive	≤ Small
Serum ketones - Enzymatic assay of beta hydroxybutyrate (normal range <0.6 mmol/L)Δ	3 to 4 mmol/L	4 to 8 mmol/L	>8 mmol/L	<0.6 mmol/L
Effective serum osmolality (mOsm/kg)◇	Variable	Variable	Variable	>320
Anion gap§	>10	>12	>12	Variable
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

DKA: diabetic ketoacidosis; HHS: hyperosmolar hyperglycemic state.
* There may be considerable diagnostic overlap between DKA and HHS.
¶ Nitroprusside reaction method.
Δ Many assays for beta hydroxybutyrate can only report markedly elevated values as >6.0 mmol/L.
◇ Calculation: 2[measured Na (mEq/L)] + glucose (mg/dL)/18.
§ Calculation: (Na+) – (Cl– + HCO3–) (mEq/L).

There is little or no ketoacid accumulation in HHS, so patients may not have overt acidosis. Serum glucose concentrations are higher than DKA, often above 1000 mg/dl. Patients with plasma osmolality above 380 mOsmol/kg often have neurologic deficits (coma in 25-50%)[10,11,14,15].

Pathogenesis

While there is a decrease in insulin secretion in DKA, insulin released in HHS is ineffective. Insulin deficiency causes an increase in gluconeogenesis, glycogenolysis, ketogenesis, and lipolysis and a decrease in glycolysis. The increase in the release of counterregulatory hormones such as glucagon,

cortisol, catecholamin, and growth hormone decreases glucose utilization in the periphery and increases glucose production in the liver. The osmotic diuresis caused by glucosuria causes dehydration and electrolyte imbalance[16,17].

Depending on the major catabolic process in DKA, glycogen stores are destroyed, triglycerides from adipose tissue are broken down, and amino acids are released from muscles. While insulinopenia and an increase in cortisol level convert protein metabolism from synthesis to destruction, insulinopenia and an increase in catecholamines cause lipolysis. Triglycerides liberated from adipose tissue are converted to glycerol and free fatty acids. While glycerol is used in gluconeogenesis, free fatty acids are used in ketone bodies. Carnitine palmitoyltransferase 1 (CPT1) plays a key role in fatty acid oxidation[17]. CPT1 is inhibited by malonyl CoA. The increase in glucagon and other counterregulatory hormones inhibits hepatic malonyl CoA. The reduction in malonyl CoA removes the inhibition of CPT 1 (CPT 1 allows them to enter the mitochondria where FFA is oxidized). Fatty acids that cannot be oxidized are converted to ketone bodies. The increase in the production of ketone bodies causes ketonemia. Decreased hepatic clearance of ketone bodies contributes to ketonemia. The hydrogen ions formed by the hydrolysis of ketoacids are neutralized by intracellular and extracellular buffers. High anion gap metabolic acidosis occurs when ketoacid production exceeds its buffering capacity. Ketoacidosis is milder in the absence of intravascular volume loss and intervening disease.

Insulinopenia increases glycogenolysis in muscle tissue. Glycogen is converted to lactic acid then lactic acid is transported to the liver. The carbon skeleton of lactic acid enters the CORI cycle which means; it is used in gluconeogenesis. The increase in glucagon, catecholamine, and cortisol with insulinopenia stimulates gluconeogenetic enzymes such as phosphoenolpyruvate carboxykinase[18]. The increase in circulating catecholamines and free fatty acids further reduces glucose utilization[16].

Precipitating Causes

DKA is the first manifestation of the disease in 20% of adult patients with type 1 diabetes and in 30-40% of pediatric patients[19]. Infection and non-compliance with insulin therapy are the two most important factors that precipitate the development of DKA and HHS in patients with diabetes for many years[20,21]. Urinary tract infections and pneumonia are the most common infections. SVO, alcohol/drug abuse, pancreatitis, pulmonary embolism, myocardial infarction, and various drugs that disrupt carbohydrate metabolism

may cause DKA. Various drugs that cause the release of counterregulatory hormones or impaired access to water cause severe volume loss and can cause HHS[20]. Corticosteroids, thiazide diuretics, sympathomimetic agents, beta-blockers, and 2nd generation antipsychotics, cocaine use may precipitate DKA or HHS[9]. Sodium-glucose cotransporter 2 inhibitors and anticarcinogens such as Ipilimumab, Nivolumab, Pembrolizumab may also cause DKA.

In young T1D patients, skipping insulin doses for fear of weight gain or hypoglycemia, presence of chronic disease or eating disorders cause recurrent DKA cases[22]. Mechanical problems in patients using subcutaneous insulin pumps may precipitate DKA[23]. DKA is seen in up to 50% of newly diagnosed African/American or Hispanic diabetic patients. It is noteworthy that these patients have high obesity rates, family history, measurable insulin reserves, and low autoimmune markers against beta cells[24]. Because of insulin secretion and effect suddenly decrease, these patients are suitable for the development of ketosis[25]. Metabolic diseases such as glucose-6-phosphate dehydrogenase deficiency[26], low socioeconomic status, adolescent age and female gender, psychiatric comorbidities, and history of DKA may precipitate DKA[27]. It has been understood that COVID-19 infection triggers DKA in diabetic patients, although there are no other risk factors for the development of ketosis during the newly occurring COVID-19 pandemic[28]. HbA1c ≥ 9% in adult T1Ds increases the incidence of DKA[29].

Diagnosis

Symptoms and Signs

The clinical course of DKA usually develops in less than 24 hours. Polyuria, polydipsia, and weight loss may occur a few days before ketoacidosis occurs and vomiting and abdominal pain are common. Abdominal pain in DKA can be severe enough to mimic an acute abdomen[30]. Abdominal pain usually goes away after the metabolic disorder disappears. On physical examination, there may be signs of dehydration such as decreased skin turgor, tachycardia, and hypotension. Mental status can vary between full alertness and deep lethargy. However, 20% of patients have a loss of consciousness[5,31]. Most patients are normothermic and some may even be hypothermic. The breath of patients with severe metabolic acidosis smells like acetone and Kussmaul breathing may develop in these patients.

Patients with HHS are often between the ages of 55 and 75, undiagnosed, and mostly in nursing homes. After days, weeks of polyuria, and polydipsia, a

change in consciousness occurs. The most common reason for admission in these patients is the change in the level of consciousness[32]. Only patients with serum osmolality >320 mOsm/kg are blunt or coma. If there is a change in the level of consciousness in a patient with <320 mOsm/kg, other events such as SVO and MI should be investigated. In the presence of focal neurologic findings such as hemiparesis, hemianopsia, and seizures (partial motor seizures are more common than generalized seizures), the diagnosis of a stroke may be misdiagnosed[31]. Physical examination shows volume depletion. Infection-related fever is common, but there is no acetone odor and Kussmaul respiration. Unlike DKA, there are no gastrointestinal symptoms such as abdominal pain and vomiting. Abdominal pain (in the absence of metabolic acidosis) should be investigated in detail.

Laboratory Findings

Diagnosis of DKA and HHS suspected based on clinical findings is confirmed by laboratory tests. In the past, blood glucose of 250 mg/dl, moderate ketonemia, serum bicarbonate level of 15 mEq/L, and arterial pH<7.3 were used as diagnostic criteria for DKA, which consists of the triad of hyperglycemia, hyperketonemia, and metabolic acidosis. The definition of DKA has recently been modified, as these criteria have significant limitations in clinical practice (such as hyperglycemia and mild metabolic acidosis despite increased beta-hydroxybutyrate concentrations). The ADA classifies DKA as mild, moderate, and severe, based on the severity of metabolic acid and changes in mental status. More than 30% of patients may have signs of both DKA and HHS[33].

Typically, patients with HHS have a pH >7.30 and bicarbonate level >20 mEq/L. No ketone bodies are found in plasma or urine. However, the presence of ketoacidosis and/or hyperlactatemia in approximately 50% of patients causes high anion gap metabolic acidosis. Several studies show a linear relationship between plasma osmolality, pH, and altered consciousness[34].

The method of measurement of ketonemia is important. With nitroprusside, it measures only acetoacetate and acetate. It cannot measure beta-hydroxybutyrate, the main ketoacid of DKA. For these reasons, the direct measurement method may be a more accurate indicator for the evaluation of ketoacidosis. β-hydroxybutyrate (β-OHB) ≥3.8mmol/Loma is highly specific and sensitive for DKA[35].

The presence of a chronic metabolic acidosis or mixed type acid-base imbalance in patients with stage 4-5 chronic kidney disease may complicate the

diagnosis of DKA. Anion gap >20 mEq/L in these patients supports the diagnosis of DKA[36].

The main cause of water deficiency in DKA and HHS is glucose-mediated osmotic diuresis[37]. Despite excessive water loss, serum sodium tends to decrease. Glucose cannot enter the cell due to insulinopenia in DKA and HHS. Because of osmotic effect, glucose causes water to pass from the intracellular space to the extracellular space. The result is dilutional hyponatremia. Osmotic diuresis and ketonemia increase urinary loss of sodium, while gastrointestinal losses such as diarrhea and vomiting also contribute to hyponatremia. If dilutional hyponatremia is suspected, the corrected serum sodium concentration should be calculated. If the corrected sodium level is still low, secondary hypertriglyceridemia, which may be present in uncontrolled diabetics, should be considered. In patients with hypertriglyceridemia, plasma is milky and physical examination may reveal lipemia retinalis[38].

The transition of potassium from the intracellular to the extracellular space due to insulinopenia, volume loss, and acidosis may cause hyperkalemia. However, osmotic diuresis and ketonemia cause potassium loss as well as sodium loss. Thus, total body potassium may decrease. It is dangerous if the first measured potassium level is normal or low. With the initiation of insulin therapy, potassium enters the cell and fatal hypokalemia may occur if potassium replacement is not performed in the early period. Phosphorus, like potassium, is deficient however, at the time of application, it can be normal, low, or high, just like potassium[39].

In DKA and HHS, in addition to basic laboratory evaluations such as plasma glucose, BUN, serum Cre, serum ketone level, electrolytes, osmolality, urine ketone, and arterial blood gas measurements (including anion gap calculation), ECG should be taken, sputum and urine cultures should be taken. If there is any indication, chest film should be taken. Measuring the level of HbA1c allows distinguishing between controlled and uncontrolled cases[9].

Common Laboratory Pitfalls

Most laboratories measure ketone bodies with the nitroprusside method. While this method measures acetoacetate, it cannot measure β-hydroxybutyrate (β-OHB). Since β-hydroxybutyrate is converted to acetoacetate during treatment, serum ketone is still measured positive, which can be interpreted as worsening ketonemia[40]. Therefore, it is not recommended to use the nitroprusside method in treatment follow-up. With the new glucometers measuring β-hydroxybutyrate, this problem is eliminated[41,42].

Although there is no infection in patients with DKA, leukocytosis may be present. However, a bacterial infection should be considered in the presence of a leukocyte count over 25,000 mm3 and a neutrophil band over 10%[43].

The shift of water into the extracellular space due to hyperglycemia causes dilutional hyponatremia. The corrected sodium amount is calculated by adding 2.4 mmol/L to sodium for every 100 mg/dl increase in glucose (formerly 1.6 mg/dl was added)[44]. The presence of hypernatremia in the presence of hyperglycemia indicates too much water deficiency.

Decreased lipoprotein lipase activity in DKA may cause lipemic serum. However, despite this obvious hypertriglyceridemia, pseudo hyponatremia and pseudo normoglycemia can be detected if the volumetric method in which samples are diluted with ion-specific electrodes is used in the laboratory[45,46].

High potassium levels at presentation in patients with DKA are due to insulin deficiency, hypertonicity, and the shift of potassium from the intracellular to the extracellular space due to acidemia. High phosphate level is also due to metabolic acidosis. Dehydration may cause increased concentrations of total serum protein, albumin, amylase, and creatine phosphokinase in patients with DKA.

Clinicians should not assume that all patients with ketoacidosis have DKA. In patients with chronic alcohol consumption, alcoholic ketoacidosis may develop due to the development of nausea, vomiting, and acute hunger following recent alcohol consumption. The development of ketoacidosis without hyperglycemia is diagnostic in these patients. Fasting ketosis can be seen in those who have a daily food intake of less than 500 kcal for a few days. A healthy individual adapts to prolonged starvation by increasing ketone clearance from peripheral tissues and increasing renal ammonia excretion to compensate for increased acid production. Therefore, bicarbonate concentration is rarely <18mEq/L in fasting ketosis[7].

Differential Diagnosis

In DKA and HHS, patients may present to the hospital in a similar metabolic state. In alcoholic ketoacidosis (AKA), the total ketone amount is greater than DKA, and the β-OHB/acetoacetate ratios are also different. While this ratio is 3/1 in DKA, it is 7/1 in AKA[5]. Hyperglycemia is mild in AKA[48]. Hyperglycemia and serum bicarbonate levels <18mEq/L are rare in fasting ketosis.

DKA should be distinguished from other causes of high anion gap metabolic acidosis. In the advanced stages of CKD patients, high anion gap

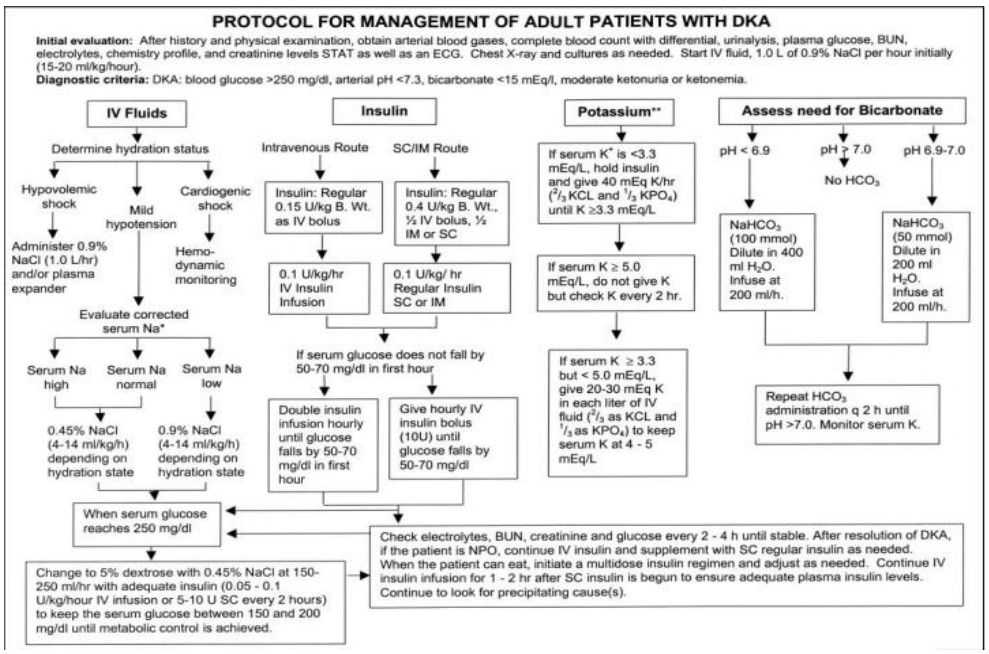
metabolic acidosis occurs. While in the intake of salicylate, methanol, and ethylene glycol high anion gap metabolic acidosis occurs, intake of isopropyl alcohol results in an increase in serum osmolality without metabolic acidosis. Diabetes incipidus can be confused with HHS. When these patients present with severe polyuria and dehydration, hyper glycemia may occur if they are treated with dextrose solution[49].

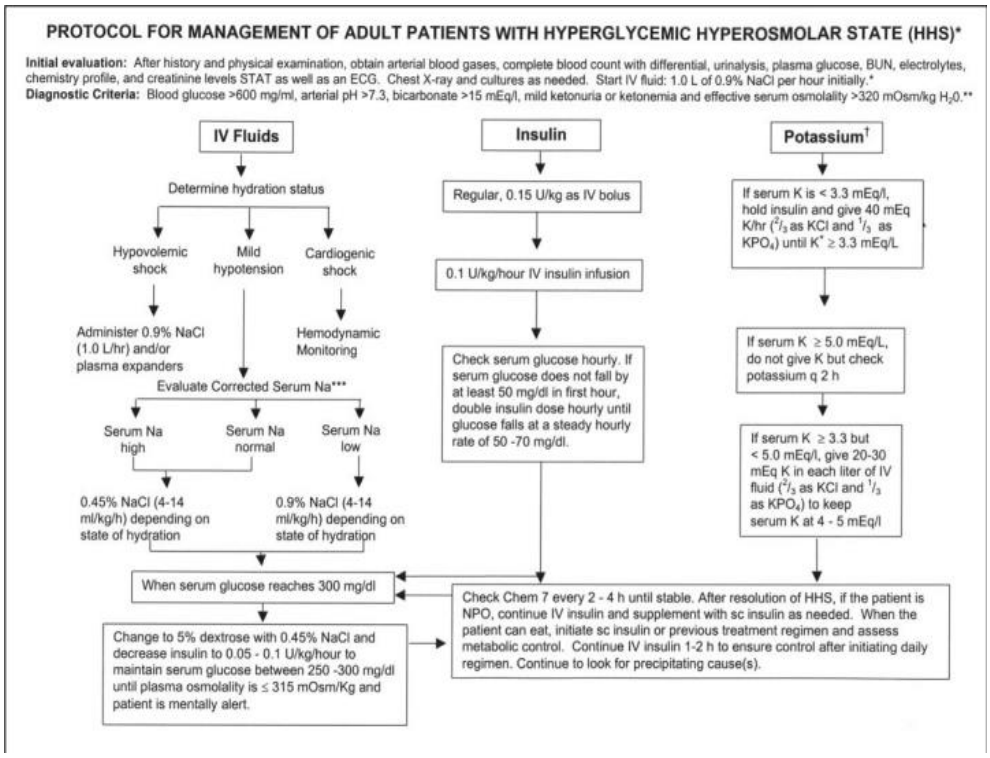
Diabetic Ketoacidosis Treatment

In patients presenting with hyperglycemic crisis, it should be aimed to improve the volume status and tissue perfusion, to gradually decrease the serum glucose and osmolality, and to correct the electrolyte imbalance. Meanwhile, comorbidities precipitating the event should be identified and treated promptly[5]. For the success of treatment, clinical and laboratory parameters should be closely monitored to see if these goals are achieved.

Fluid Therapy

While there is a deficit of approximately 6 liters in total body fluid in DKA, there is a deficit of approximately 9 liters in HHS[50,51]. Initial fluid therapy should expand the intravascular volume and provide adequate urine output. The first option, isotonic saline, is given as 15-20 ml/kg or 1.5-2 L per hour. The fluid is selected according to the patient's hydration status, electrolyte levels, and urine volume. DKA and HHS treatment recommendations are summarized in the tables below[7].


PROTOCOL FOR MANAGEMENT OF ADULT PATIENTS WITH DKA
Initial evaluation: After history and physical examination, obtain arterial blood gases, complete blood count with differential, urinalysis, plasma glucose, BUN, electrolytes, chemistry profile, and creatinine levels STAT as well as an ECG. Chest X-ray and cultures as needed. Start IV fluid, 1.0 L of 0.9% NaCl per hour initially (15-20 ml/kg/hour).
Diagnostic criteria: DKA: blood glucose >250 mg/dl, arterial pH <7.3, bicarbonate <15 mEq/l, moderate ketonuria or ketonemia.
IV Fluids
Determine hydration status
Hypovolemic shock
Mild hypotension
Cardiogenic shock
Administer 0.9% NaCl (1.0 L/hr) and/or plasma expander
Hemo-dynamic monitoring
Evaluate corrected serum Na*
Serum Na high
Serum Na normal
Serum Na low
0.45% NaCl (4-14 ml/kg/h) depending on hydration state
0.9% NaCl (4-14 ml/kg/h) depending on hydration state
Insulin
Intravenous Route
SC/IM Route
Insulin: Regular 0.15 U/kg B. Wt. as IV bolus
Insulin: Regular 0.4 U/kg B. Wt., ½ IV bolus, ½ IM or SC
0.1 U/kg/hr IV Insulin Infusion
0.1 U/kg/ hr Regular Insulin SC or IM
If serum glucose does not fall by 50-70 mg/dl in first hour
Double insulin infusion hourly until glucose falls by 50-70 mg/dl in first hour
Give hourly IV insulin bolus (10U) until glucose falls by 50-70 mg/dl
Potassium**
If serum K+ is <3.3 mEq/L, hold insulin and give 40 mEq K/hr (2/3 KCL and 1/3 KPO4) until K ≥3.3 mEq/L
If serum K ≥ 5.0 mEq/L, do not give K but check K every 2 hr.
If serum K ≥ 3.3 but < 5.0 mEq/L, give 20-30 mEq K in each liter of IV fluid (2/3 as KCL and 1/3 as KPO4) to keep serum K at 4 - 5 mEq/L
Assess need for Bicarbonate
pH < 6.9
pH > 7.0
No HCO3
pH 6.9-7.0
NaHCO3 (100 mmol) Dilute in 400 ml H2O. Infuse at 200 ml/h.
NaHCO3 (50 mmol) Dilute in 200 ml H2O. Infuse at 200 ml/h.
Repeat HCO3 administration q 2 h until pH >7.0. Monitor serum K.
When serum glucose reaches 250 mg/dl
Change to 5% dextrose with 0.45% NaCl at 150-250 ml/hr with adequate insulin (0.05 - 0.1 U/kg/hour IV infusion or 5-10 U SC every 2 hours) to keep the serum glucose between 150 and 200 mg/dl until metabolic control is achieved.
Check electrolytes, BUN, creatinine and glucose every 2 - 4 h until stable. After resolution of DKA, if the patient is NPO, continue IV insulin and supplement with SC regular insulin as needed. When the patient can eat, initiate a multidose insulin regimen and adjust as needed. Continue IV insulin infusion for 1 - 2 hr after SC insulin is begun to ensure adequate plasma insulin levels. Continue to look for precipitating cause(s).


PROTOCOL FOR MANAGEMENT OF ADULT PATIENTS WITH HYPERGLYCEMIC HYPEROSMOLAR STATE (HHS)*
Initial evaluation: After history and physical examination, obtain arterial blood gases, complete blood count with differential, urinalysis, plasma glucose, BUN, electrolytes, chemistry profile, and creatinine levels STAT as well as an ECG. Chest X-ray and cultures as needed. Start IV fluid: 1.0 L of 0.9% NaCl per hour initially.*
Diagnostic Criteria: Blood glucose >600 mg/ml, arterial pH >7.3, bicarbonate >15 mEq/l, mild ketonuria or ketonemia and effective serum osmolality >320 mOsm/kg H20.**
IV Fluids
Determine hydration status
Hypovolemic shock
Mild hypotension
Cardiogenic shock
Administer 0.9% NaCl (1.0 L/hr) and/or plasma expanders
Hemodynamic Monitoring
Evaluate Corrected Serum Na***
Serum Na high
Serum Na normal
Serum Na low
0.45% NaCl (4-14 ml/kg/h) depending on state of hydration
0.9% NaCl (4-14 ml/kg/h) depending on state of hydration
Insulin
Regular, 0.15 U/kg as IV bolus
0.1 U/kg/hour IV insulin infusion
Check serum glucose hourly. If serum glucose does not fall by at least 50 mg/dl in first hour, double insulin dose hourly until glucose falls at a steady hourly rate of 50 -70 mg/dl.
Potassium†
If serum K is < 3.3 mEq/l, hold insulin and give 40 mEq K/hr (2/3 as KCl and 1/3 as KPO4) until K+ ≥ 3.3 mEq/L
If serum K ≥ 5.0 mEq/L, do not give K but check potassium q 2 h
If serum K ≥ 3.3 but < 5.0 mEq/l, give 20-30 mEq K in each liter of IV fluid (2/3 as KCl and 1/3 as KPO4) to keep serum K at 4 - 5 mEq/l
When serum glucose reaches 300 mg/dl
Change to 5% dextrose with 0.45% NaCl and decrease insulin to 0.05 - 0.1 U/kg/hour to maintain serum glucose between 250 -300 mg/dl until plasma osmolality is ≤ 315 mOsm/Kg and patient is mentally alert.
Check Chem 7 every 2 - 4 h until stable. After resolution of HHS, if the patient is NPO, continue IV insulin and supplement with sc insulin as needed. When the patient can eat, initiate sc insulin or previous treatment regimen and assess metabolic control. Continue IV insulin 1-2 h to ensure control after initiating daily regimen. Continue to look for precipitating cause(s).

0.45% NaCl is given in hypernatremic or eunatremic patients and 0.9% NaCl is given as 4-14 ml/kg/hour in hyponatremic patients. Half of the water and sodium deficit should be given within 12-24 hours[52]. In hypotensive patients, aggressive fluid therapy may be required until blood pressure is stabilized. Hypotension may deepen in patients administered insulin without fluid replacement[33]. Hydration of the patient in the first hour of the treatment before starting to use insulin prevents this possible hypotension as well as ensures that the serum potassium reaches a certain level and decreases the osmolality[9]. Hydration also reduces the levels of counter-regulatory hormones and hyperglycemia[53]. Increasing the intravascular volume lowers serum glucose, BUN, and potassium levels without any change in pH and bicarbonate[54,55]. Excessive use of hypotonic fluids is associated with the development of cerebral edema[56], 5% dextrose+1/2 saline solution should be used when blood glucose drops to 300 mg/dl in HHS and 250 mg/dl in DKA. In order to prevent the osmotic passage of water into the intracellular compartment in hyperglycemic crises, experts recommend that the osmolality be reduced by no more than 3 mOsm/kg and the sodium value by 0.5 mmol/L per hour[57]. Water and electrolytes lost in the urine should also be considered.

Insulin Therapy

The basis of DKA and HHS treatment is the use of physiological doses of insulin. Insulin should be started after the potassium value reaches >3.3 mmol/L[5]. The recommended intravenous regular insulin dose in DKA is 0.1 U/kg bolus administration followed by continuous administration of 0.1 U/kg/hour. Since there is more severe dehydration in HHS, the insulin infusion rate should be kept lower. The optimal reduction rate of glucose should be 50-70 mg/dl. If the desired reduction is not achieved in the first hour, an additional bolus of 0.1U/kg can be administered. When blood glucose drops to 250 mg/dl in DKA and 300 mg/dl in HHS, the insulin infusion rate should be reduced to by half. Followed by a decrease in osmolality and sodium value within the desired limits, the hydration fluid should be replaced with 5% dextrose+1/2 saline. In DKA, the insulin dose should be adjusted to keep blood glucose between 150-200 mg/dl until ketoacidosis is resolved. In HHS, insulin should be administered at a blood glucose level of 300 mg/dl until the mental status and hyper osmolarity are corrected[1].

Potassium Therapy

Despite the decrease in total body potassium[58,59], patients with DKA have mild to moderate hyperkalemia due to acidosis and insulinopenia. Insulin

therapy, volume expansion, and correction of acidosis lower the serum potassium concentration. Initiation of potassium replacement after serum potassium level falls below 5.3 mmol/L and adequate urine output is achieved (50 ml/hour) prevents hypokalemia. During fluid replacement, 20-30 mmol potassium should be added to each liter of fluid to keep serum potassium levels within normal limits. DKA patients with severe vomiting or on diuretics may also have hypokalemia. In these patients, fluid replacement is initiated together with potassium replacement. Insulin therapy is not initiated until the potassium level reaches 3.3 mmol/L to prevent respiratory muscle weakness and arrhythmias[60].

Bicarbonate Therapy

The use of bicarbonate in DKA is still controversial. Bicarbonate use is not required in the patients with pH >7.0, insülin therapy inhibits lipolysis and improves ketoacidosis. . Bicarbonate therapy may have some side effects such as hypokalemia, decreased tissue oxygen uptake, and cerebral edema. In addition, recovery from ketosis may be delayed[61-64]. Patients with severe DKA with a bicarbonate level <10 mEq/L or a PCo2 <12 mmHg should be treated with bicarbonate. Otherwise acidosis may deepen. In patients with pH 6.9 and 7.0, infusion of 10 mmol KCL and 50 mmol sodium bicarbonate in 200 ml of sterile water within 2 hours can keep the pH above 7.0[65,66]. Since myocardial contractility will be impaired in severe acidosis, 20 mmol KCL and 100 mmol sodium bicarbonate are put into 400 ml sterile water or SF in patients with pH < 6.9. It is given as 200 ml/hour until the venous pH is >7.0. Venous pH should be evaluated every 2 hours until it reaches 7.0. If necessary, this treatment is repeated every two hours[1].

Phosphate Therapy

Phosphate therapy can be applied in patients with possible complications of hypophosphatemia, such as cardiac and skeletal muscle weakness[67]. It should be kept in mind that it may cause hypocalcemia when applied in high doses[68-71].

TREATMENT OF HHS

HHS treatment is similar to DKA treatment. However, bicarbonate treatment is not required and when blood glucose drops to 300 mg/dl, fluids with glucose are used. In HHS, some insulin can be detected in the plasma. In these patients with severe hyperosmolality and dehydration due to insulin resistance, the basic treatment is to correct the volume loss and decrease the

osmolality[72]. In patients with HHS, treatment with normal saline is started to determine the time of onset of hypotonic fluids and corrected sodium values are monitored. Since insulin resistance is expected to improve with rehydration, insulin therapy should be conservative. Rapid reduction of serum osmolality may cause cerebral edema formation. In elderly patients whose hyperglycemic level is unknown before hospital admission, this is very important[1].

Transition to Subcutaneous Insulin

Moderate to severe DKA patients should be treated with continuous intravenous insulin infusion until ketoacidosis resolves. The improvement criteria for DKA are blood glucose <200 mg/dl, serum bicarbonate level >18 mEq/L, venous pH>7.3, and calculated anion gap ≤12 mEq/L, and for HHS are blood glucose <300 mg/dl, serum osmolality <320 mOsm/kg, and improved mental status. When these levels are reached, subcutaneous insulin therapy is started. In patients who can eat, the insulin dose is adjusted by dividing it into short and regular-acting insulin. It is more practical to make the transition before breakfast and at dinner. Previous doses in DKA can be used in patients known to be diabetic. In newly diagnosed patients, an initial insulin dose of 0.6 U/kg/day can provide adequate metabolic control. The daily dose of insulin is divided into 2/3 in the morning and 1/3 in the evening.

In patients who cannot eat, intravenous insulin infusion should be continued while infusing 5% dextrose solution in ½ saline with 100-200 ml/hour fluid infusion[7]. During the transition to subcutaneous regular insulin, intravenous and subcutaneous insulin should be administered together for one to two hours to maintain adequate plasma insulin levels to prevent ketoacidosis and hyperglycemia recurrence.

Complications

The most common complication during insulin infusion is hypoglycemia. Despite the use of low-dose insulin protocols, hypoglycemia may still occur in 10-25% of patients with DKA[73]. The most important risk factor for hypoglycemia is failure to reduce the insulin infusion dose in a timely manner and/or not to start dextrose-containing fluids when blood glucose drops to 250 mg/dl. Blood glucose should be evaluated every 1-2 hours to understand the occurrence of hypoglycemia and other serious complications. In most of the patients presenting with hyperglycemic crisis, adrenergic symptoms such as sweating, irritability, fatigue, hunger sensation, and tachycardia do not occur despite low blood levels during the formation of hypoglycemia. Clinicians should be aware of this situation[7].

The risk of developing hypoglycemia in patients with HHS is lower than in patients with DKA, and hypoglycemia develops in <5% of patients with HHS who are treated with intravenous insulin[73].

In patients with DKA and HHS, serum potassium levels are usually high and decrease during treatment. Both insulin therapy and correction of acidosis decrease potassium levels by increasing potassium uptake in peripheral tissues. In order to prevent the formation of hypokalemia, potassium replacement should be started as soon as serum potassium levels fall to 5.3 mEq/L. Insulin therapy will deepen hypokalemia in patients presenting with normal and low potassium levels[74]. Therefore, potassium replacement should be started immediately in patients with a baseline potassium level of <3.3 mEq/L and insulin therapy should be suspended until the potassium level is >3.3 mEq/L.

The mortality of cerebral edema, which is a serious and rare complication of DKA, is around 40-90% and is seen in approximately 1% of DKA cases in children[75-77]. Rapid reduction of the increase in extracellular osmolality with treatment causes swelling of the brain. Seizures, sphincter incontinence, pupillary changes, papilledema, bradycardia, and cardiac arrest may occur, followed by impaired consciousness and headache.

The addition of hypoglycemia to ischemic injury increases blood-brain barrier dysfunction, edema formation, and the degree (severity) of neurologic damage. Hyponatremia that does not improve during treatment increases the likelihood of cerebral edema[78,79]. More cerebral edema formation in pediatric patients can be explained by the fact that the brain needs more oxygen in children and they are more sensitive to ischemia than adults.

In order to reduce the risk of cerebral edema formation in high-risk patients, sodium and water replacement should be done gradually, osmolality should be reduced to a maximum of 3 mOsm/kg per hour, and as soon as blood glucose drops to 250 mg/dl in DKA and 300 mg/dl in HHS Dextrose should be added to hydration fluids[5]. Patients who develop cerebral edema should be monitored in intensive care units and should be intervened immediately in the presence of herniation findings. Moderate lowering of CO2 levels with immediate intravenous administration of mannitol, fluid restriction, and mechanical ventilation may help reduce cerebral edema. Intravenous administration of mannitol is superior to corticosteroid and diuretic therapy. Only 7-14% of patients with herniation recover without sequelae[77].

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Part 8:

THE ROLE OF THORACIC SURGERY IN THE TREATMENT OF ENDOCRINE DISEASES

İsmail DAL

In a normal healthy individual, there is no endocrine gland in the thorax. However, in some clinical situations, adjacent endocrine glands may enlarge locally and protrude into the thorax and mediastinum, some endocrine glands may be found ectopically in the thorax and mediastinum. The emergence of a primary tumor with endocrine activity in this region is another possibility. Preoperative preparation and a multidisciplinary approach are essential in such clinical situations [1]. It is also recommended that such special surgeries be performed in reference centers [2].

1. MEDIASTINAL GOITER

Terminology and Epidemiology

In the literature, the terms “retrosternal goiter, substernal goiter and mediastinal goiter” are used to express similar clinical conditions. In this article, the term "Mediastinal Goiter" is preferred. Because this term also includes posterior mediastinal lesions. The term mediastinal goiter has been defined in different ways in the literature. In its simplest terms, it refers to the state of the thyroid gland extending below the sternal fork while the patient is in the supine position [3]. Some authors have preferred to call it “mediastinal goiter” when more than 50% of the thyroid gland extends into the mediastinum [4]. Some authors have defined mediastinal goiter as the condition where the thyroid is 3 cm or more below the thoracic inlet on computed tomography [2].

A modern classification for mediastinal goiter cases was proposed in a study published in 2017 [5]. According to this classification, type A refers to the thyroid gland extending to the mediastinum in the form of an inverted pyramid. Type B is a pyramidal thyroid gland extending into the mediastinum. Type C refers to the lesion extending to the mediastinum and attached to the pedicle and cervical thyroid. Type D refers to cases of mediastinal goiter independent of the cervical region.

85-90% of mediastinal goiter cases are located in the anterior mediastinum, the remaining 10-15% are located in the posterior mediastinum[6]. Among all goitre cases, the incidence of mediastinal goiter is reported to be 2.17%, and the mean patient age is 55.3 [4].

Symptoms and Radiological Imaging

The most common symptom in mediastinal goiter cases is dyspnea [1]. Dyspnea improves in 98-99% after surgery. The second most common symptom is dysphagia with 43% [7]. Dysphonia is a rarer finding, but when detected, vocal cords should be evaluated with preoperative laryngoscopy [8]. Superior vena cava syndrome develops in 5-9% of cases [7, 9]. Anteriorly located retrosternal goiter produces compression findings more quickly. The brachiocephalic artery is the most commonly compressed anatomical structure. Posteriorly located lesions, on the other hand, can become very large without any signs of compression [1]. In 3% of cases, the thyroid gland extends between the trachea and the esophagus. In this case, the operation becomes extremely complex.

Ultrasound (USG) is requested as the first radiological examination. Contrast-enhanced computed tomography (CT) is the gold standard for demonstrating the cervicothoracic extension [1]. The relationship of the mass with the brachiocephalic vein and azygos vein should be carefully examined before the operation. In cases with extensive adhesion and difficult exploration, these vessels may cause massive bleeding [10,11].

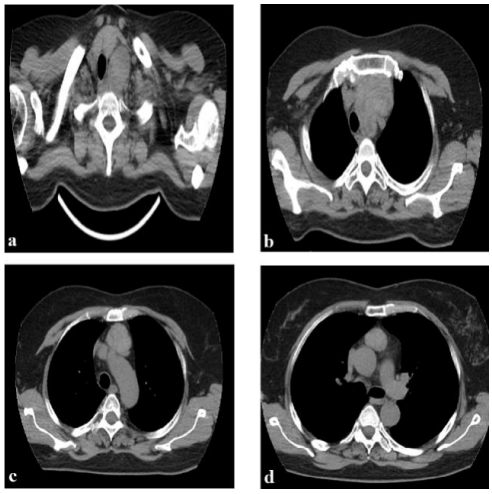

Figure A: CT Images of Cervical (a), Jugular (b), Arcus Aorta (c) and Carinal (d) Levels in Giant Mediastinal Goiter

Surgical Approach and Morbidity

In the preoperative period, airway compression can become life-threatening. The thyroid gland may bleed intraparenchymaly, either spontaneously or traumatically. In addition, as a result of tracheal infections, situations requiring emergency intervention may occur. In such cases, intubation or even semi-urgent thyroidectomy may be required [12]. Intubation of the patient should be performed by an experienced anesthesiologist. Be prepared for difficult intubation. The flexible bronchoscope should be readily available [13]. Probe should be available for recurrent nerve monitoring.

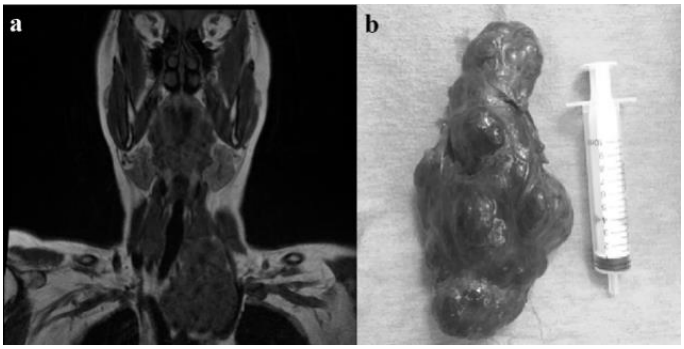

Figure B: Giant Mediastinal Goitre MRI Image (a) and Pathology Specimen (b)

The primary choice in mediastinal goiter should be the cervical approach. If necessary, sternotomy may be preferred [4]. Because complication rates are high in sternotomy cases, and in fact, sternotomy is not needed in most cases [2]. The rate of sternotomy has been reported between 1% and 14.8% in the literature [2, 4, 14, 15]. In cases extending below the aortic arch, sternotomy may be required [16]. Radiologically, high thyroid tissue density, retrovascular goiter extension, and subcarinal extension significantly increase the risk of sternotomy [17].

In cases where cervical incision is not sufficient, minimally invasive methods such as mediastinoscopy, video-assisted thoracoscopic surgery (VATS), and robot-assisted thoracoscopic surgery (RATS) are increasingly preferred to avoid complications of sternotomy and thoracotomy [18-20]. Manubriotomy can also be performed to avoid sternotomy [14].

In giant mediastinal goiter, the possibility of injury to the recurrent nerve is high with traditional surgical technique. Therefore, the retrograde dissection

technique is recommended in these cases [21-23]. In retrograde dissection, the inferior laryngeal nerve is detected with a nerve monitor where it enters the larynx. Then, the nerve is followed downward and dissection is performed [1].

While postoperative mortality is rare after mediastinal goiter operations, morbidity is seen at a rate of 5.5% [4]. In one study, unilateral vocal cord paralysis was found in 1.3% and bilateral paralysis in 0.6% [2]. In the same study, 14% transient hypoparathyroidism and 4.1% permanent hypoparathyroidism were reported. In patients with respiratory distress and stridor in the postoperative period, recurrent nerve injury should be considered and emergency bronchoscopy should be performed [13]. In conclusion, recurrent nerve injury and persistent hyperparathyroidism in mediastinal goiter are seen more frequently than in classical surgery [14, 24, 25].

Forgotten goiter is the recognition that there is goiter tissue behind after surgery and is more common in mediastinal goiter [2]. Forgotten goiter is seen in 2-16% of mediastinal goiter cases [26]. Forgotten goiter is often caused by a mediastinal goiter that is independent of the cervical goiter (Type D) [27-29].

2. MEDIASTINAL ECTOPIC PARATHYROID

Terminology and Epidemiology

Primary hyperparathyroidism is a bone and mineral metabolism disorder that develops as a result of inappropriate secretion of parathormone without suppression [30]. The prevalence of primary hyperparathyroidism is reported as 0.1 – 0.4%. It is more common in women and the incidence increases with age [31]. Ectopic parathyroid adenoma is seen in 6-20% of primary hyperparathyroidism [32-36]. Ectopic parathyroid adenoma is a major cause of persistent and recurrent hyperparathyroidism [37, 38]. Even in the operations of experienced surgeons, persistent hyperparathyroidism is seen in 4.7% [39].

Inferior parathyroid glands can be found anywhere along the thyrotymic tract [40]. The most common anatomical region is the thymic tongue (40%) [41, 42]. Ectopic localization of the superior parathyroid glands is rare. The fifth parathyroid gland is seen in 13% [40]. Ectopic parathyroid adenomas may also rarely present paraesophageal, aortopulmonary window, carotid sheath, and intra-thyroidal location [41].

Radiological Imaging

Ectopic adenomas are difficult to detect preoperatively and intraoperatively [39]. USG, CT, Scintigraphy and MRI help in diagnosis. With the

introduction of nuclear medicine, imaging of the parathyroid gland can be performed with a 90% success rate [43-45]. Ultrasound fails to show ectopic adenomas [46, 47]. The success rate of ultrasound fluctuates in a wide range of 44%-87%, so USG is not considered a reliable examination [48]. 4D computed tomography (4DCT) is an alternative imaging modality [42].

Surgical Approach and Morbidity

The key to success in persistent hyperparathyroidism is accurate localization of the lesion with preoperative imaging [42]. An accurate localization study performed preoperatively avoids unnecessary morbidity [49].

Primary hyperparathyroidism arising from parathyroid adenomas can be treated with a cervical approach with a success rate of 88–98% [50, 51]. Traditionally, sternotomy is preferred if the cervical approach is unsuccessful [52]. The use of sternotomy and thoracotomy for mediastinal parathyroid adenoma excision may cause various complications. These include innominate vein injury, sternum infection, mediastinitis, and death [52-54].

A sternal retractor can be used to facilitate exploration in the serivacal approach. This reduces the need for sternotomy and thoracotomy [44]. While it was argued that the transcervical method would be successful in cases above the aortic arch, VATS was recommended below this level [55]. In another study, the transcervical method was reported to be successful if the lesion was up to 6 cm below the superior edge of the clavicle [56]. If the lesion is more than 6 cm below the superior edge of the clavicle, the rate of successful transcervical surgery drops to 25%.

First VATS for ectopic mediastinal parathyroid adenoma performed in 1994, first RATS performed in 2004 [57]. VATS and RATS are effective and safe minimally invasive methods for the treatment of ectopic parathyroid adenomas [42, 49]. The length of hospital stay and complications are reduced in the VATS approach [58-60]. In addition, anterior mediastinotomy has been reported as a safe and effective option to avoid sternotomy [61]. In a recent study reported from Turkey, persistent hyperparathyroidism was successfully treated with a non-surgical method, selective arterial embolization [39]. Just like in other branches of medicine, treatment options in ectopic parathyroid adenomas are gradually shifting towards minimally invasive methods.

3. NEUROENDOCRINE TUMORS OF THE LUNG

Primary neuroendocrine tumors of the lung are typical carcinoid, atypical carcinoid, small cell carcinoma, and large cell neuroendocrine carcinoma. Neuroendocrine tumors account for 20% of primary lung tumors [62]. When the neuroendocrine tumor nature is determined pathologically, the tumor is classified according to the number of mitosis, necrosis and cytological features. However, diagnosis and classification of neuroendocrine tumors is difficult. Because it can be difficult to detect the neuroendocrine tumor nature from small biopsy samples. In addition, a focal sign of necrosis can easily be overlooked. Finally, it is difficult to distinguish whether the tumor is of primary lung origin or metastatic.

Typical Carcinoid

The typical carcinoid tumor, accounting for 1-2% of lung tumors, is unrelated to smoking and is detected in middle-aged people [63-65]. Men and women are equally affected [66]. It occurs at a younger age than other neuroendocrine lung tumors [67]. It is known that the frequency of typical carcinoids increases in MEN-1 syndrome [68].

The typical carcinoid tumor is detected clinically as a single lesion with a probability of 95% [64]. While some patients present with signs of bronchial obstruction, some of them are completely asymptomatic. Cushing's syndrome and other paraneoplastic syndromes occur in 5% [68]. N1 metastasis in the typical carcinoid tumor is not thought to affect prognosis [66]. Treatment options for unresectable typical carcinoid tumor are somatostatin analogues, mTOR inhibitors, and peptide receptor radionuclide therapy [69]. There is no consensus on the role of chemotherapy [70]. The 5-year survival rate after surgery for typical carcinoid tumor is 90% [63, 64, 71].

Atypical Carcinoid

Atypical carcinoid accounts for 0.2% of all lung tumors [63-65]. Metastatic lung tumors originating from the gastrointestinal tract and pancreas can mimic an atypical carcinoid tumor [62].

These tumors frequently involve the central airways and are associated with bronchial obstruction, carcinoid syndrome, or other paraneoplastic syndromes [68]. In the case of N1 metastases in atypical carcinoid tumors, adjuvant therapy or complementary lobectomy decisions are made [72, 73]. Treatment options for unresectable typical carcinoid tumor are somatostatin

analogues, mTOR inhibitors, peptide receptor radionuclide therapy and chemotherapy [70]. The 5-year survival rate for atypical carcinoid tumor has been reported to range from 50 to 80% [67, 74].

Small Cell Lung Cancer

Small cell lung cancer (SCLC) accounts for 10-15% of primary lung tumors and is frequently seen in heavy smokers [75]. SCLC may be difficult to distinguish pathologically from the following diseases; small blue round cell tumors, other neuroendocrine lung tumors, poorly differentiated adenocarcinoma, basaloid squamous cell carcinoma.

SCLC is an extremely aggressive cancer. Metastases to the liver, bone, and brain are frequently detected in patients [76]. Among neuroendocrine lung tumors, paraneoplastic syndromes are most frequently seen in SCLC. A proportion of patients have inappropriate ADH syndrome and other paraneoplastic syndromes [63, 68]. Treatment includes chemotherapy, radiotherapy and prophylactic carnial irradiation. There are publications reporting that surgery as part of multimodality therapy improves survival in patients with stage I and II SCLC [77]. Immunotherapy and treatments targeting poly(ADP-ribose) polymerase are under study. Survival in small cell carcinoma is very poor. In generalized disease, the 5-year overall survival is 5% [71]. In localized SCLC, the 5-year overall survival is 35% [63].

Large Cell Neuroendocrine Carcinoma

Large cell neuroendocrine carcinoma (LCNEC) is a highly aggressive neuroendocrine tumor [78]. It is more common in elderly, smokers and men [79, 80]. LCNEC is the most difficult pathological diagnosis among neuroendocrine tumors. It is difficult to distinguish LCNEC from SCLC, poorly differentiated adenocarcinoma, poorly differentiated squamous cell carcinoma, carcinoid tumor and metastatic disease.

Large cell neuroendocrine carcinoma most frequently metastasizes to the liver, bone, and brain [63, 71, 80]. In contrast to small cell carcinoma, LCNEC is often peripherally located, 50% is detected at an early stage and paraneoplastic syndrome is rare [81-84]. Surgery is performed in resectable LCNEC, chemotherapy and/or radiotherapy is applied in unresectable tumors. 5-year survival is in the range of 15-40%.

4. OTHER RARE TUMORS

Pheochromocytoma and paraganglioma are rare neuroendocrine tumors. Pheochromocytoma arises from chromaffin cells in the adrenal medulla. Paraganglioma arises from chromaffin cells in the ganglia of the autonomic nervous system [85, 86]. In the literature, pheochromocytoma and paraganglioma are defined as PPGL (PCC/PGL) tumors [85-87]. PPGL tumors secrete catecholamines uncontrollably. Pheochromocytoma often secretes epinephrine and neuroepinephrine. Paraganliomas secrete only neuroepinephrine. 10% of PPGL tumors are mediastinal and thoracic. The clinical significance of these tumors is that they have a high local recurrence rate and a 10% rate of distant metastasis [88].

Neuroendocrine tumors of the thymus are rare lesions of the anterior mediastinum. These tumors fall into the group of foregut carcinoid tumors. They show rapid local spread and metastasize rapidly [89]. These tumors can cause Cushing's syndrome by secreting ACTH [90]. Screening for MEN-1 should be performed as they are often associated with the MEN-1 syndrome. Treatment is surgical excision. The median survival time after surgery is 53 months.

Apart from these, ectopic ACTH-secreting intrathoracic tumors may cause Cushing's syndrome [91]. It has also been reported that pleural fibromas cause hypoglycemia by secreting insulin like gowth factor-1 [92].

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PART 9:

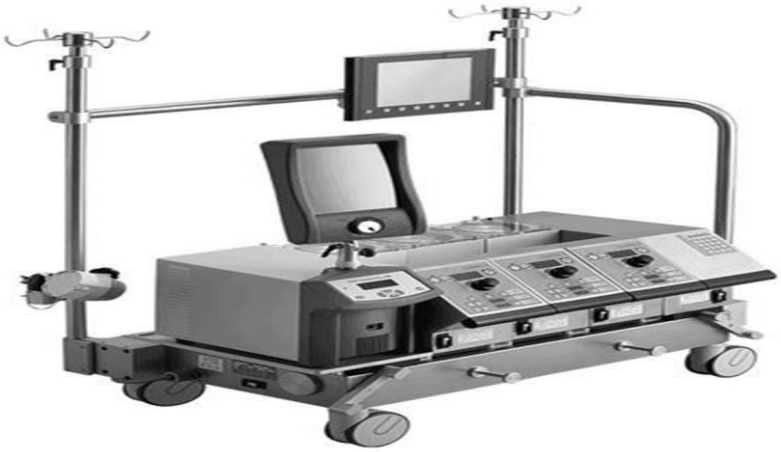
THE EFFECTS OF CARDIOPULMONARY BYPASS ON ENDOCRINE SYSTEM

Burak TAMTEKİN
Güler Gülsen ERSOY

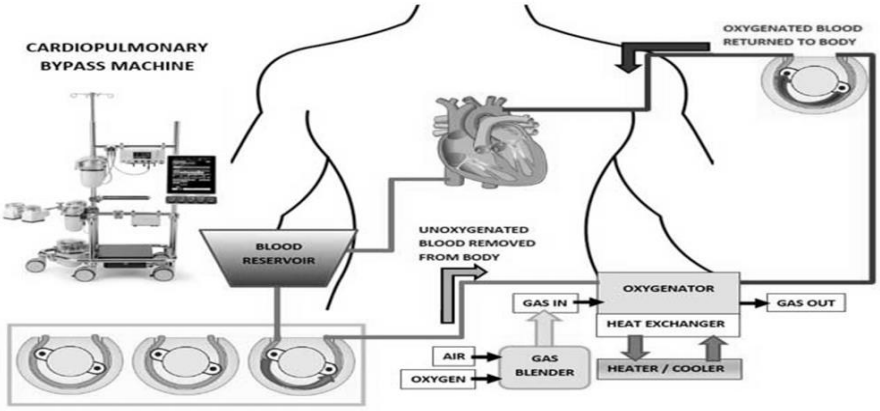
Open heart surgery consists of first coronary artery bypass and than aortic, mitral, tricuspid and pulmonary valves surgeries, congenital cardiac diseases, cardiac tumours, aortic surgeries and some arytmial surgeries. Conventional cardiac surgeries are referred as cardiopulmonary bypass used open heart surgeries with using new techniques in cardiac surgeries.

In 1896; first Dr. Ludwig Rehn has put primary stitch to myocardial injured patient [1]. This procedure; that first stitch was put to heart, is accepted as the turning point of cardiac surgery in the historical process of the open heart surgery [2]. About the historical development; Prof. Shermanin has said 'Even though the distance to heart is a few centimetres, however the surgeons have arrived this distance in 2400 years'[3].The development and exploration of extracorporeal circulation, also is known as heart lung machine, is accepted as the beginning of modern cardiac surgery[4].

The heart lung machines or cardiopulmonary bypass devices are doing cardiac pumping and lung ventilation functions during the surgery to protect to myocard and whole body, so these are providing immobile and bloodless area for surgery after stopped heart. Due to common using of these devices in the world, dysfunctions can be seen in some organs or tissues because of effects of extracorporeal circulation. However these systems are most common using techniques even though this harmful effect. The aim is to revive the heart and whole body after successfully cardiac surgery by supplying bloodless and immobile surgical area [5].



In cardiopulmonary bypass procedure; one venous canula that is placed to right atrium, inferior or superior vena cava is supplied to return of venous blood to the membrane oxygenator, after membrane oxygenator, oxygenated-cooled and heated blood come back to patient' s aorta via arterial canula[6].



Systemic inflammatory response starts due to circulation of blood in the unendothelialized cardiopulmonary bypass canulas during cardiopulmonary bypass [7]. Both neutrophiles and vascular endothelial activating factor become active and these increases CD11b and CD41 like adhesion molecules. Platelets are actived and degranulation starts after that activated platelets adhere to vascular endothelium. Free oxygen radicals, proteases, and cytokines and chemokines exist. IL-6, IL-8 and TNF- alpha like inflammatory mediators start

to increase. Complement system is actived both in the classical and in the alternative ways.

This formed humoral response increase to secrete proinflammatory cytokines by increasing cellular response. At the end; severe organ ischemia increases the inflammatory response by inducing to secrete more cytokines and free oxygen radicals from endothelial cells, circulating monocytes and macrophage in the organs. The worst of these systemic inflammatory responses provoke the organ damage also that is called as the bad end [8, 9].

Cardiopulmonary Bypass application primarily affects the central and peripheral nervous system, as well as the renal, hematological, gastrointestinal systems and organs.

Undesirable effects of cardiopulmonary bypass:

1. Lung; pulmonary edema, acute respiratory distress syndrome (ARDS), atelectasis, interstitial pulmonary edema

2. Heart: Decreased cardiac output, dysrhythmias

3. Metabolic and Endocrine System: Changes in carbohydrate metabolism, stimulation of glycogenolysis with increased secretion of adrenaline, and suppression of insulin secretion and hyperglycemia. Increase in renin, angiotensin, sodium and aldosterone, retention of antidiuretic hormone. Increased catecholamine secretion and hypertension

4. Serum dilution; intracellular-extracellular electrolyte disturbances, changes in acid-base balance,

hypernatremia, hyperchloremia

5. Coagulopathies; heparin-induced bleeding, heparin resistance, coagulation factors, and thrombocytopenia.

6. Fluid balance disorders decreased, decreased or increased urine output, increased or decreased intravascular volume.

7. Reduction of intravascular colloid osmotic pressure and interstitial edema and hemodilution with consequent pulmonary edema

8.Release of vasoactive amines: With the increase of capillary substances in the plasma, more fluid passage in the interstitial compartment

9. Vasoconstriction and capillary permeability increase with complement and neutrophil activation, 10.Changes in the central nervous system; due to events related to embolism or ischemia.

11. Hypothermia; increased systemic vascular resistance due to vasoconstriction; decrease in myocardial contractility and heart rate with consequent reduction in cardiac output and perfusion pressure (reduction in

renal perfusion and consequent decrease in urine output); Inhibition of insulin release from pancreatic islet cells and hence hyperglycemia and altered glucose transport across the cell membrane.

12. Changes in gastrointestinal function; It appears as splanchnic vasoconstriction and bleeding, which can cause intestinal ischemia [7,10]

Metabolic and Endocrine System:

Cardiopulmonary bypass causes the release of some hormones and vasoactive substances in the body. These released substances ultimately lead to the stress response. Hypothermia, hemodilution, nonpulsatile blood flow, and contact of blood with these foreign surfaces with cardiopulmonary bypass cause an increase in catecholamines during and after surgery. Cardiopulmonary bypass causes the release of some hormones and vasoactive substances in the body. These released substances ultimately lead to the stress response. Hypothermia, hemodilution, nonpulsatile blood flow, and contact of blood with these foreign surfaces with cardiopulmonary bypass cause an increase in catecholamines during and after surgery. With the onset of cardiopulmonary bypass, the blood adrenaline level rises and decreases after cardiopulmonary bypass. Noradrenaline level rises due to sympathetic nervous system discharge. Increased blood noradrenaline levels are also due to a decrease in pulmonary blood flow during cardiopulmonary bypass; because noradrenaline is inactivated in the lung as it is known. The inactivation of these substances, especially the deactivation of the lungs and heart, and the slowing of their metabolism due to hypothermia help their effects to come to the fore. Vasopressin also rises about 20 times in cardiopulmonary bypass. Blood cortisol levels peak especially on the first postoperative day.

Angiotensin II and vasopressin are known to be responsible for the increase in systemic vascular resistance in cardiopulmonary bypass. Hyperglycemia in cardiopulmonary bypass is also caused by glycogenolysis, induced by elevated adrenaline levels; Decreased tissue response to insulin, which is thought to be caused by hypothermia, binding of insulin to extracorporeal lines, and decreased glucose use[7,10,11]

The reason for the decrease in thyroid hormones with cardiopulmonary bypass is related to the hypothalamus, pituitary, thyroid and peripheral metabolisms. It has been shown in many studies that T3, T4 and TSH in the extracorporeal circulation decrease and return to their normal levels after days. Thyroid hormones are low until 24 hours after exiting cardiopulmonary bypass.

It has been determined that thyroid hormone levels are decreased especially in patients who underwent open heart surgery due to congenital heart disease, which may be associated with deterioration in myocardial functions, and is effective on morbidity and mortality[12] .

One of the most important effects of the stress response in cardiopulmonary bypass is hyperglycemia. In open heart surgery, which is a serious trauma, hyperglycemia is common during and after surgery [13] . This resulting hyperglycemia naturally increases postoperative wound infections and morbidity. For this reason, blood sugar regulation is very important, especially in surgeries with a high stress response, such as open heart surgery. In the meantime, while trying to reduce the bad consequences of hyperglycemia, the risk of hypoglycemia should not be forgotten. In particular, acute hyperglycemia attacks should be avoided. These attacks suppress the immune system as a whole. Therefore, tight blood sugar control is important in risky patients, even if the patient is not diabetic [14] .

Open heart surgery is surgery that has many complications as a result of affecting many systems in the body. These complications can range from loss of patient to myocardial infarction, severe arrhythmias, aortic dissection, stroke, bleeding, mediastinitis, liver failure, gastrointestinal bleeding, pancreatitis, lung problems, neurocognitive and psychiatric problems, acute kidney failure and endocrine disorders.

These complications impair the hemodynamics of the patient, It prolongs the extubation time, the length of stay in the intensive care unit and the hospital, and may even result in death.

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PART 10:

DIABETIC RETINOPATHY DIAGNOSIS AND TREATMENT

Emine SAVRAN ELİBOL

1. INTRODUCTION

Diabetic retinopathy (DR); it is an important complication of diabetes mellitus (DM), which continues to be the leading cause of vision loss in the working age group. The diagnosis of retinal vascular DR is by clinical signs of abnormalities. Clinically, DR; it occurs in two stages: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). The NPDR system represents the early stage of the DR, where vascular permeability and capillary occlusion are two mains in the retinal vasculature. Although patients are asymptomatic at this stage, retinal pathologies such as microaneurysms, hemorrhage, and hard extrudate can be detected by fundus examination. PDR, a more advanced stage of DR, is characterized by neovascularization. At this stage, patients may experience severe visual impairment when new abnormal vessels bleeding into the vitreous (vitreous haemorrhage) or when there is tractional retinal detachment. Diabetic macular edema (DME) is the most common cause of vision loss in patients with DR. DME is characterized by swelling or thickening of the macula due to subretinal and intraretinal fluid accumulation in the macula occured by the breakdown of the blood-retinal barrier (CRB) [1]. Current treatment strategies for DR aim to manage microvascular complications, including intravitreal pharmacological agents, laser photocoagulation, and vitreous surgery. Intravitreal administration of anti-VEGF agents is still the main treatment for both early and advanced stages of DR. While conventional laser therapy only stabilizes visual acuity, anti-VEGF therapy can improve vision with fewer ocular side effects.

2. ETIOLOGY

Diabetic retinopathy affects people with diabetes mellitus, even if undiagnosed diabetes mellitus. Poor glycemic control, uncontrolled hypertension, dyslipidemia, nephropathy, male gender and obesity are associated with worsening of diabetic retinopathy [2,3].

3. EPIDEMIOLOGY

One of the major vascular complications of diabetes is diabetic retinopathy and is the leading cause of low vision in productive adults. According to the latest epidemiological data shared by the American Academy of Ophthalmology, the global burden of diabetes is 387 million and it is estimated to increas to 592 million by 2035. Ninety-three million people worldwide are affected by diabetic retinopathy. The prevalence of diabetic retinopathy is 77.3% in patients with type 1 diabetes and 25.1% in patients with type 2 diabetes, of which approximately 25-30% are expected to develop vision-threatening diabetic macular edema [4]. 5% to 8% of patients with diabetic retinopathy i needs laser treatment [5]. Up to 0.5% of patients will require vitrectomy surgery[6].

4. PATHOPHYSIOLOGY

4.1. Hyperglycemia and Retinal Microvasculopathy

DR has long been known to be a microvascular disease. Hyperglycemia is thought to be an important factor in the pathogenesis of retinal microvascular damage. Many metabolic pathways are involved in hyperglycemia-induced vascular damage, including the polyol pathway, advanced glycation end products (AGEs) accumulation, protein kinase C (PKC) pathway, and the hexosamine pathway[7]. When hyperglycemia occurs, dilation of blood vessels and changes in blood flow are primarily observed in the retina. These changes protect the retina by creating a metabolic autoregulation [8]. Pericyte loss is another feature of the early events of DR. Evidence of apoptosis of pericytes induced by high glucose has been demonstrated in both in vitro and in vivo studies [9,10]. Since pericytes are responsible for providing structural support for capillaries, their loss causes regional protrusion of capillary walls. This process is associated with microaneurysm formation, the earliest clinical manifestation of DR [10]. In addition to pericyte loss, apoptosis of endothelial cells and basement membrane thickening are also detected during the pathogenesis of DR, which collectively contribute to

CRB degradation [11]. Also, prominent pericyte and endothelial cell loss, resulting in capillary occlusion and ischemia. Retinal ischemia/hypoxia leads to regulation of VEGF through activation of hypoxia-inducible factor 1 (HIF-1). VEGF increases vascular permeability by inducing phosphorylation of tight junction proteins such as occludin and zonula occludens-1 (ZO-1) and plays a role in the progression of PDR and DME [12]. Also, VEGF as an angiogenic factor, mitogen-activated promotes proliferation of endothelial cells through activation of the protein (MAP) [13]. Other angiogenic factors such as angiopoietins (Ang-1, Ang-2) also interact with endothelial receptor tyrosine kinase (Tie2) and play a role in the regulation of vascular permeability [13]

4.2. Inflamation

An important factor in the pathogenesis of DR is inflammation. Sustained low-grade inflammation has been widely demonstrated in different stages of DR in diabetic animal models and patients [14]. Leukocyte-endothelium adhesion caused by adhesion molecules has been associated with leukostasis in diabetes. Endothelial cell adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule (VCAM)-1 and selectins (E-selectin) were also found to be elevated in patients with diabetic retinopathy [15]. VCAM-1 and E-selectin in the plasma of patients, its expression is associated with the severity of DR [14]. Chemokines, which determine the adhesion and activation of leukocytes have also been reported to play a role in the pathogenesis of DR. It has been shown that chemokines such as monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-1 alpha (MIP-1α) and MIP-1β are increased in diabetic [16]. In addition, inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), IL-8 and IL-1β were significantly increased and regulated in diabetic patients and their expression levels were found to be correlated with DR severity [17]. Retinal glial cell dysfunction is also thought to play a role in the initiation and amplification of retinal inflammation in DR [18]. Glial cells in the retina, including astrocytes, Müller cells, and microglia, are responsible for providing structural support in the retina and maintaining homeostasis [19]. Under hyperglycemic stress, microglia are activated, followed by TNF Secretion of -α, IL-6, MCP-1 and VEGF is increased [18]. The involvement of Müller cells and astrocytes is also associated with the regulation of inflammatory responses by producing proinflammatory cytokines [19].

4.3. Retinal Neurodegeneration

Retinal neurodegeneration is seen in the early stages of DR. Upregulation of the proapoptotic molecule caspase-3, Bax and Fas has been detected in diabetic animals and patients [20]. Mitochondrial dysfunction contributes to retinal degeneration in DR. In donor eyes of diabetic patients, retinal expression of proapoptotic mitochondrial proteins such as cytochrome c and apoptosis-inducing factor (AIF) was found to be significantly [20]. In vitro studies have shown that high glucose exposure is associated with increased mitochondrial fragmentation and cell apoptosis [21]. In addition to mitochondrial damage, the role of oxidative stress in retinal degeneration caused by diabetes has also been widely investigated. Reactive oxygen species (ROS) production was significantly increased in the diabetic rats [22]. Suppression of ROS formation, visual disorders mediated retinal neuronal apoptosis and caspase-3 was inhibited in an effective way [22]. There is increasing evidence that the pathophysiology of retinal neurodegeneration DR may be an individual. In a rat model of diabetes, microvascular and retinal thickness was observed reduction in the loss of ganglion cells before the presence of the changes. In diabetic patients, DR minimal(microaneurysms) or without DR and the inner retinal thinning is detected [23]. Therefore, further investigation of the molecular mechanisms underlying the retina neurodegeneration may provide potential therapeutic targets for DR early intervention.

5. HİSTORY AND PHYSİCAL

Patient history should be taken with caution. The duration of diabetes, type of diabetes mellitus, past glycemic control (HbA1C), drug therapy, obesity, kidney disease, hypertension, pregnancy, associated systemic disorders such as dyslipidemia and nephropathy should be questioned. Patients may be asymptomatic in the early period and may be discovered incidentally on fundus examination. As the disease progresses, symptoms such as blurred vision, distorted vision, floaters, glare, partial or complete loss of vision, poor night vision, and impaired color vision may occur.

Symptoms seen in diabetic retinopathy on fundus examination are as follows:[24]

5.1. Microaneurysms

It is focal saccular dilatation of the capillary wall. It is located in the inner nuclear layer. They are the earliest lesions that can be detected clinically. It is clinically defined by ophthalmoscopy as small, round, red dots with sharp

regular margins. It can be 15-60 μm in diameter (less than 125 μm). Microaneurysms smaller than 30 μm in diameter may not be detected clinically. It appears initially in the temporal fovea. It may disappear over time. Microaneurysms are distinguished from spot hemorrhages by FFA (fundus fluorescein angiogram), where microaneurysms show small hyperfluorescent spots while spot hemorrhages show blocked fluorescence. Point hemorrhages are clinically larger and may have an irregular margin.

5.2. Hemorrhage

It is weakened capillary wall ruptures that lead to intraretinal point hemorrhages. Superficial or flaming hemorrhages originate from precapillary arterioles located in the retinal nerve fiber layer. Deep hemorrhages or spot and spot hemorrhages are found in the inner nuclear and outer plexiform layers of the retina.

5.3. Hard Exudates

They consist of lipoprotein and lipid-filled macrophages located in the outer plexiform layer. They develop at the junction of the edematous and non-edematous retina.

5.4. Cotton Wool Spots

They are located in the retinal nerve fiber layer (axoplasmic debris) and represent focal infarctions of precapillary arterioles.

5.5. IRMA (Intraretinal Microvascular Abnormalities)

IRMAs are communication between retinal arterioles and venules that bypass capillaries and appear near capillary closure sites. IRMAs are intraretinally located, do not cross major vessels, and do not leak on fluorescent angiography.

5.6. Vascular Changes

Venous changes; dilatation, folding, venous pilling, and sausage-like segmentation, while peripheral narrowing and disappearance of the arteries are observed.

5.7. Neovascularization

5.7.1. Neovascularization of the disc (new vessels) (NVD): neovascularization within or near a disc diameter of the optic disc

5.7.2. Neovascularization elsewhere (NVE): new vessels within one disc diameter of the optic disc.

5.7.3. Neovascularization of the iris: It is an indicator of poor prognosis and is associated with a tendency to develop neovascular glaucoma.

6. CLASSIFICATION

Early treatment diabetic retinopathy study (ETDRS) classification of diabetic retinopathy: [25,26]

6.1. Non-Proliferative Diabetic Retinopathy

6.1.2. No retinopathy: No retinal lesion

6.1.3. Very mild NPDR: Microaneurysms only

6.1.4. Mild NPDR: Few microaneurysms, retinal hemorrhage and hard exudate

6.1.5. Moderate NPDR: cotton wool spots in 1-3 quadrants, retinal hemorrhages (approximately 20 moderate-large in each quarter) (between mild and severe NPDR grades)

6.1.6. Severe NPDR: Fulfilling a rule of 4-2-1 rule

4-2-1 rule: Severe bleeding in 4 quadrants, venous pilling in 2 or more quadrants, and moderate IRMA in 1 or more quadrants.

6.1.7. Very Severe NPDR: Fulfilling two or more rules of the 4-2-1 rule.

6.2. Proliferative Diabetic Retinopathy

6.2.1. Mild to moderate PDR: NVD or NVE insufficient to meet high-risk specifications.

6.2.2. High-risk PCR:

NVD (about 1/3 disk space) larger than ETDRS standard photo 10A.

Any NVD with vitreous hemorrhage.

NVE greater than 1/2 disc area with vitreous hemorrhage.

6.3. Advanced Diabetic Eye Disease

It is an end-stage vision-threatening complication of diabetic retinopathy in patients for whom treatment is inadequate or unsuccessful. It may present as preretinal or vitreous hemorrhage, tractional retinal detachment, or rubeosis iridis.

With regard to diabetic macular edema, the presence or absence of macular edema should be noted. It can also be classified as mild, moderate and

severe according to the distance of thickening and hard exudates from the center of the fovea.

Mild DME; retinal thickening or hard exudates located far from the center of the fovea

Medium DME; retinal thickening or hard exudates that approach but do not contain the center of the macula

Severe DME; hard exudate and thickening involving the center of the fovea

7. PREVENTION AND TREATMENT OF DIABETIC RETINOPATHY

Currently, new modalities of treatment of DR are being explored to reduce the incidence and progression of the disease. New treatment modalities have emerged and these have been shown to be able to maintain vision in 95% of patients when treated without severe damage to the retina, giving hope even to patients with advanced DR. These new treatments are vitrectomy, corticosteroids or Anti-VEGF injection into the eye and laser surgery. All these treatment methods can save the patient's vision, although DR is not curative.

DR treatment depends on its stage or type. The recommendation for mild to moderate nonproliferative DR is a well-implemented screening program for blood glucose control and continuous ophthalmologic control. Controlling diabetes and keeping the HbA1c level in the 6-7% range are the goals in the optimal management of diabetes and DR. According to the 'Diabetes Control and Complications' study, the progression of DR will be significantly reduced if blood glucose levels are maintained [27]

7.1. Laser Photocoagulation

In the case of proliferative type or macular edema, the key treatment method is photocoagulation, in which retinal tissues are burned using thermal energy. The underlying principle is the injection of energy from a powerful light source, which is absorbed by the retinal pigment epithelium and converts it into thermal energy that triggers necrotic coagulation by denaturation of cellular proteins when the temperature rises above 65°C [28]. In fact, laser retinal photocoagulation is therapeutic in many retinal and eye conditions. is an option. The 'Early Treatment of Diabetic Retinopathy Study' found that laser surgery for macular edema reduced the incidence of moderate vision loss from 30% to 15% over a 3-year period [27]. In diabetic macular edema, ranibizumab alone with

rapid or delayed focal/grid laser Superior visual acuity and optical coherence tomography results were obtained compared to focal/grid laser treatment [29]

7.2. Corticosteroids

Corticosteroids have been shown to be useful in the treatment of DME. This complication of diabetes is actually treated using focal laser photocoagulation, vascular endothelial growth factor (VEGF) inhibitors, and intravitreal corticosteroid injections and implants. Anti-VEGF antibodies have revolutionized the treatment of DR, but a significant subset of patients do not respond to treatment, and accumulating evidence indicates that inflammatory cytokines and chemokines other than VEGF may contribute to the disease process [30]. Eyes with DME showed morphological and functional improvement 1 month after the use of intravitreal dexamethasone implant and 4 months after treatment [31]. In this case, switching to intravitreal corticosteroids may be especially beneficial in pseudophakic patients. Anti-VEGF combined with a sustained-release corticosteroid implant is a promising option for resistant DME [32]. Indeed, corticosteroids provide therapeutic benefit due to their anti-inflammatory, anti-angiogenic and blood-retinal barrier stabilizing properties.

Despite all these treatment options, laser photocoagulation remains the primary standard of care therapy in most communities, according to the Early Treatment of Diabetic Retinopathy Study (ETDRS) guidelines.

7.3. Anti-VEGF

Anti-VEGF drugs are injected into the vitreous gel to block the VEGF protein, which can stimulate the growth of abnormal blood vessels and leakage of fluid. VEGF is an endothelial cell-specific angiogenic factor that plays an important role in the pathological rather than physiological state and ocular neovascularization leading to PDR. VEGF is also a vascular permeability factor that increases vascular permeability by loosening endothelial cell connections, and this mechanism is known to contribute to the development of DME. Inhibition of VEGF blocks these effects to some extent in DR, as demonstrated in several recent clinical trials and case series involving anti-VEGF molecules. Currently, anti-VEGF molecules under DR management are: pegaptanib (Macugen), ranibizumab (Lucentis), bevacizumab (Avastin), and VEGF Trap-eye. Anti-VEGF therapy is currently indicated for DME associated with vision loss, whereas laser photocoagulation prevents severe vision loss in eyes with

proliferative DR. [33] Corticosteroids injected or implanted in the eye can be used alone or in combination with other medications or laser surgery to treat DME.

7.4. Vitrectomy

Vitrectomy is an important option for the treatment of long-standing vitreous hemorrhage, tractional retinal detachment, and combined tractional and tear retinal detachment. The 'Diabetic Retinopathy Vitrectomy Study' recommended the use of this procedure for the treatment of eyes with vitreous hemorrhage that did not resolve spontaneously within 6 months. Early vitrectomy (<6 months, mean 4 months) results in greater improvement in vision in patients with type 1 diabetes [34].

An in-depth understanding of the pathophysiology and underlying molecular mechanisms of DR is essential for the development of new screening modalities that will improve and enhance its timely detection and therefore its timely prevention or treatment. It is a proven fact that oxidative stress increases the progression of DR. Ensuring the integrity of retinal neurons is a key factor in DR management. If retinal neurons are preserved anatomically and functionally, retinal vascular damage can be preserved and progression of DR can be reduced. This highlights the importance of regular eye screening and aggressive control of glucose and blood pressure to prevent ocular damage, especially when we consider that more than half of young-onset diabetic patients show some degree of retinopathy within 10-12 years.

8. CONCLUSION

Obesity, poor glycemic control, and oxidative stress have been shown to contribute to the development of eye complications such as DR. Diabetes is a complex metabolic disorder with both short-term and long-term adverse events. Therefore, diabetics should be educated about eye complications that may arise from their condition. Regular eye scanning with a fundus camera should be part of the routine management of diabetic patients. To modulate postgrandial hyperglycemia and adipose tissue metabolism as well as carbohydrate and lipid metabolism, oxidative stress reduction and restoration of retinal antioxidant system should be provided by using exogenous antioxidants, anti-inflammatory drugs or foods that can improve dyslipidemia and insulin resistance. Treatment depends on the stage of DR. The use of anti-VEGF has been suggested in DME associated with vision loss, and laser photocoagulation may prevent severe vision loss in eyes with proliferative DR.

Oxidative stress plays an important role in the pathophysiology of DR. Understanding the mechanisms of oxidative stress is crucial in the development of new therapeutic strategies.

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PART 11:

CURRENT APPROACHES TO OSTEOPOROSIS AND OSTEOPOROTIC FRACTURES

Mustafa Caner OKKAOĞLU

1. Introduction

Osteoporosis has become one of the most important problems in terms of public health today with increasing life expectancy and related osteoporotic fractures. Only about 22% of patients with osteoporosis-related hip fractures die within the first year after hip fracture[1]. The rest continue their lives with the morbidities related to this fracture. This data about morbidity and mortality is only related to hip fractures due to osteoporosis. Considering other osteoporotic spine, proximal humerus, distal radius and other osteoporosis-related fractures and their mortality morbidity, it can be predicted how osteoporosis is an important problem in society.

1.1. Osteoporosis Definition

Quantitative identification of osteoporosis began with the advent of X-Ray absorptiometry. Different measurement techniques have been used over the years. Among them, methods such as peripheral quantitative Computed Tomography (pQCT), quantitative ultrasound (QUS), vertebral fracture analysis (VFA) were used. However, the most current quantitative definition at the moment is the Bone Mineral Densitometry measurement, which is measured by Dual X-ray absorptiometry (DXA), which is also accepted by the World Health Organization (WHO)[2]. With this measurement, a data called T score is obtained. According to WHO's definition: T-score is the difference between an individual's measured BMD and the mean reference BMD of a healthy young adult in the population divided by the standard deviation value. This score is interpreted with 3 diagnoses as follows:

T > −1: NORMAL: Bone Mineral Densitometry measurement result higher than −1 SD compared to the mean BMD value of a young adult

T ≤ −1 ve > −2,5: OSTEOPENIA: Bone Mineral Densitometry measurement result is between −1 and −2.5 SD according to the mean BMD value of a young adult

T ≤ −2,5: OSTEOPOROSIS : Bone Mineral Densitometry measurement result equal to or lower than −2.5 SD compared to the mean BMD value of a young adult.

The lumbar spine and proximal femur are usually used for DXA measurement. While BMD measurement can be made in all bone regions in theory, BMD measurement is mostly performed in these two regions because the reference data are not clear in every bone region and some devices do not have sufficient sensitivity in all bone regions.

The most important advantage of diagnosing osteoporosis is that it gives us an opportunity to prevent the associated morbidity and mortality. In the epidemiological study published by Melton et al., the lifetime risk aof hip fracture due to osteoporosis in women was 17.5%, the risk of a lifetime spinal fracture was 15.6%, and the risk of distal forearm fracture was 16%, while in men these rates were respectively. 6%, 5% is 2.5%[3]. In another study, it was stated that 1.3 million fractures occur each year in the United States due to osteoporosis, 70% of the fractures over the age of 45[4]. With such a high incidence of osteoporosis fractures, the World Health Organization developed a program called FRAX® using population-based cohorts from Europe, Asia, North America and Australia. The 10-year risk of major osteoporotic fractures can be estimated by entering the data of male and female patients aged 40 to 90 years into this model, which can be accessed via the website[5].

1.2. Pathophysiology of Osteoporosis

To make a short pathophysiological definition of osteoporosis, it can be defined as deterioration of bone quality, trabecular microstructure, bone turnover due to an underlying cause or aging. There are two main types of bones. These are called cortical bone, trabecular bone. While cortical bone is mostly found in the diaphyseal parts of long bones, trabecular bone is mostly found in the distal and proximal ends of long bones or in the direct internal structure of bones such as the spine and calcaneus.

Kemikte, başlıca 3 farklı tip hücre bulunur. Bunlar osteoblast, osteoklast ve osteositlerdir

There are three main types of cells in bone. These are osteoblasts, osteoclasts, and osteocytes.

Osteoblasts: They originate from pluripotent cells and are the cells that provide bone matrix formation and mineralization.

Osteoclasts: They are multinucleated and originate from monocyte-macrophage type hematopoietic cells. They are stimulated by RANKL produced by osteoblasts with the RANK receptors on them and responsible for bone resorption.

Osteocytes: They sense mechanical loads and tension changes originating from osteoblasts in the bone matrix and take part in remodeling.

1.3. Peak Bone Mass

Peak bone mass (PBM) is one of the most important signs of fracture risk in later life. It most commonly occurs during adolescence and childhood, with the highest trabecular BMD occurring between 12-16 years of age, with the highest cortical BMD occurring between 20-24 years of age. The most influential factors on Peak Bone Mass and BMD are genetic factors. In a previous study, it was shown that genetic factors affect 60-85% of BMD changes in the population[6]. Another one of the most important influencing factors is hormones. It is known that especially the sex hormones estrogen and testosterone have an important effect. Other major effecting hormones are growth hormone, insulin like growth factor and thyroxine. Finally, environmental factors are also effective in the formation of PBM. Among these, exercise, adequate vitamin D and calcium intake, and adequate nutrition are also important effective factors[7].

People who reach the highest BMD values with PBM at a young age begin to lose bone in their 40s. In women, bone loss increases with the decrease of estrogen, which plays an important role in bone mineral density with menopause. The deterioration of the balance between bone production and resorption between osteoblasts and osteoclasts in the direction of resorption is effective in the formation of this bone loss. This balance may deteriorate after physiological menopause or senility, as well as due to some secondary reasons. (Table 1)

Table 1. Secondary Osteoporosis Causes

Medications (epilepsy drugs, heparin, aromatase inhibitors, steroids)
Hormonal causes (hyperthyroidism, hyperprolactinemia, diabetes, hypogonadism, hyperparathyroidism … etc.)
Neoplasms (multiple myeloma, lytic bone tumors, metastasis
Celiac disease
Homosistinuria
Inflamatory bowel diseases
Rheumatoid diseases
Alcoholism
Immobilisation
Pregnancy

2. Management of Osteoporosis

2.1. Current Drugs

2.1.1. Anti Resorbtive Drugs

In the treatment of osteoporosis, the most commonly used agents, as classical information, are calcium and vitamin D supplements. In previous studies, calcium intake alone has been tried first, but it has been shown to be less effective, although it is beneficial[8]. In another study, in which calcium and 800 IU vitamin D were used together, these two were shown to reduce hip fractures by 43% and non-spine fractures by 32%[9]. In another study, no difference was found between the use of these two agents together or separately and the use of placebo[10]. In a study in which 36,282 postmenopausal women were given combined treatment, it was shown that there was a significant increase in hip BMD compared to placebo, but no difference in other region BMDs[11]. As a result, it can be said that the combined or individual use of these two agents in the treatment, without any additional agent, has a small effect, although it is not good enough.

In addition to calcium and vitamin D therapy, estrogen and progesterone treatments have also been recommended by some authors in early postmenopausal women. However, recommendations are limited due to the increased risk of breast cancer, increased risk of stroke and cardiovascular disease events[12-14].

Bisphosphonates have become the main treatment we use for osteoporosis today and over the last 20 years. It has been shown that bisphosphonates reduce osteoporotic vertebral fractures by 40-50% and non-vertebral fractures by 20-40% [15]. Bisphosphonates act by binding to the bone

mineral matrix and suppressing osteoclastogenesis. Alendronate, risedronate and zoledronic acid (intra venous use) are the most commonly used preparations in this group. It has been shown in different studies that these 3 preparations increase BMD and reduce vertebral or nonvertebral fractures[16-18]. Although ibandronate, another bisphosphonate preparation, has been shown to reduce vertebral fractures, its effect on nonvertebral osteoporotic fractures has not been proven[19]. Except for gastric irritation, which is common with oral tablets of bisphosphonates, two rare but important side effects of all bisphosphonate use have been described[20]. These are osteonecrosis of the jaw, and atypical femoral shaft or subthrocanteric femur fractures[20,21]. Especially osteonecrosis of the jaw is more common with zoledronic acid[22]. In order to prevent atypical femur fractures, it has been shown that drug holidays may be beneficial against the possibility of accumulation of bisphosphonates in the bone over the years[23].

Denosumab is another anti-resorptive treatment agent recommended by the American Association of Clinical Endocrinologists (AACE), its use is recommended in patients with high fracture risk and who cannot tolerate oral therapy[24]. Denosumab is a human monoclonal antibody and inhibits RANKL and prevents bone resorption. In a study involving 7868 postmenopausal women, it was shown that denosumab reduces vertebral fractures by approximately 61-68%, nonvertebral fractures by 20% and hip fractures by 40%[25]. Denosumab is a drug that is administered subcutaneously every 6 months. Therefore, it is a drug without gastric effects, but after injection, it may show symptoms such as muscle pain, hypersensitivity and flu-like symptoms. Very rare cases of atypical femoral subtrochanteric fractures and osteonecrosis of the jaw have been observed.

Calcitonin or salmon calcitonin, another agent used in the treatment of osteoporosis, is a synthetic polypeptide hormone. It is known that there are receptors for this molecule in osteoclasts and osteoblasts[26]. Calcitonin was investigated in a study involving 1255 postmenauposal women and was shown to reduce vertebral fractures by 33%[27]. However, it has been shown in another study that it has no effect on non-vertebral regions[28]. The general use of Calcitonin is mostly in the form of nasal spray. Therefore, its side effects are mostly nasal symptoms. A 2013 FDA study showed a small increase in cancer cases and recommended that clinicians consider other treatment options first when using this drug for osteoporosis[26].

2.1.2. Bone-Enhancing Drugs

So far, agents that reduce bone resorption have been described. Among the agents that increase bone formation, the first agent used in the treatment of osteoporosis is teriparatide, which is also a parathyroid hormone (PTH) analogue. When given in small doses at regular intervals, it increases bone formation by increasing osteoblastic activity[29]. AACE has also suggested that teraparetide can be used in the treatment of osteoporosis in patients at high risk of hip fracture, or when the use of bisphosphonates is discontinued[24]. The efficacy of Teriparatide has also been proven in clinical studies[30,31]. In a study, the effectiveness of teriparatide at different doses of 20 mcg and 40 mcg was studied, and it was shown that both 2 doses reduced vertebral and non-vertebral fractures and increased BMD in the whole body[30]. Again, in another study comparing alendronate, it was shown to be more effective than alendronate in reducing vertebral fractures[31]. The most frightening side effect of teriparatide is the suspicion of causing osteosarcoma. Since it has been shown to cause osteosarcoma after high-dose use in mice, its use has been limited to 2 years[32]. But Andrews et al. in a study with 7 years of follow-up, no relationship was established between the occurrence of osteosarcoma and the use of teriparatide[33]. However, due to these risks, it is not recommended for use in patients with Paget's disease who have previously received radiotherapy, who had primary or secondary bone malignancy before [32].

Abaloparatide, another PTH analog after teriparatide, was released to the market in 2017 with FDA approval[34]. The efficacy of this drug, administered as a daily subcutaneous dose of 80 mcg, was found to be very effective compared to other osteoporosis drugs in a phase 3 study, and it was shown to reduce vertebral fractures by 86% and nonvertebral fractures by 43%[35]. The advantage over Teriparatide is that it costs half as much. However, similar contraindications also apply to this preparation. Its use is limited to 2 years. Again, the use of this drug should be avoided in patients with previous primary or secondary bone tumors, metastatic diseases, or those with urolithiasis, orthostatic hypotension and hyperparathyroidism in which hypercalcemia is harmful.

2.1.3. Recent Drugs On Market

Another drug, romozumab, is a monoclonal antibody that inhibits sclerostin protein. Sclerostin is a protein secreted by osteoclasts, which reduces

bone formation, reduces proliferation and functions of osteoblasts. An international study of rhomozumab included 7,180 postmenopausal women and found that 73% fewer vertebral fractures were detected with this drug than placebo, but similar rates of non-vertebral fractures were detected, but both vertebral, femoral neck, and overall hip BMDs were all significantly increased[36]. However, this drug was not approved by the FDA in 2017 due to its cardiovascular risks, and then it was approved in 2019 on the condition that it should not be used in patients with previous cardiovascular disease[37].

Lasofoxifen, as a selective estrogen receptor modulator, has recently been approved in Europe for the treatment of osteoporosis. At 5-year follow-up, it reduced vertebral fractures by 42% and nonvertebral fractures by 24% compared with placebo[38]. This preparation has also been shown to reduce breast cancer and cardiovascular disorders.

2.1.4. Other Preventive Modalities

The current drug and osteoporosis treatments are listed above. However, one of the most important preventive treatment methods is exercise and physical activity. But of course, this physical activity must be within certain limits. Competitive heavy physical activity sports will increase fractures. Light aerobic exercises are both suitable for people in this age population and will also have positive effects on the general health of this age group, thanks to the additional benefits it provides. Although there is no strong evidence that light exercises directly increase BMD in studies, it has been stated that at least it prevents decreases in BMD[39,40].

Preventing falls is another important protective procedure. However, it is one of the most difficult tasks to prevent the people with systemic, neurological diseases and weakened musculoskeletal system in this age group. Muscle strengthening, aerobic and walking balance exercises can prevent these falls to some extent. Besides, vitamin D supplements, reducing psychotropic drugs, and providing training on home accidents will also reduce these risks. One of the subjects studied recently is "hip protecter" orthoses. In the first published studies, these orthoses were shown to work, reducing the number of fractures. However, its use has become controversial as higher-level studies have emerged. Currently, it has been shown that the use of these orthoses at homes is meaningless, and it has been concluded that their use in some areas where the risk of fracture is high, such as nursing homes, is controversial[41,42].

3. Major Osteoporotic Fractures and Their Treatments

The treatment of an osteoporotic fracture has certain principles, these are: fracture reduction, surgical or non-surgical immobilization of the fracture, rehabilitation after fracture healing, medical treatment of osteoporosis to prevent advanced fractures. One of the most important stages in the treatment of osteoporotic fractures is the treatment process. Mobilization of the patient should be ensured as soon as possible after fracture fixation. Patients who are not adequately mobilized will be more prone to osteoporosis, which will be a harbinger of future fractures. When deciding on fracture treatment, many entities such as the patient's age, activity level, cognitive status, location and type of fracture should be taken into consideration. Accordingly, it should be decided whether surgical or non-surgical treatment will be performed, and if it is surgery, which surgery will be performed. In surgery, fixation should be provided by paying attention to the osteoporotic fracture characteristics. To give examples of these:[43]

a) While fixation can be achieved with cortical screw-plates in a normal adult fracture, locking screw-plate systems should be preferred more in osteoporotic fractures.

b) Implants and instrumentation forms that cause stress shielding should be avoided.

c) Expandable screws, cement reinforced screws can be used.

d) Screw types with wider and deeper thread pitches can be used.

e) Due to the weakness of the mechanical bone structure, materials such as autograft, allograft, bone cements or calcium sulfate can be used for bone cavities.

f) If the healing process of fracture fixation is unreliable, considering the patient's age and osteoporotic bone structure, arthroplasty should also be considered for joint fractures or fractures close to the joint.

Since bone strength will be different from other fractures during fracture healing processes, it should be kept in mind that implant failures may develop at the same time while trying to mobilize as soon as possible. No matter how early mobilization is recommended for patients in this age group, unfortunately this cannot always be achieved due to the patients' cognitive status and comorbidities. Often due to immobilization; Disorders such as deep vein thrombosis, urinary tract infections, pressure sores, aspiration pneumonia are frequently seen in these patients and lead to future morbidity and mortality.

3.1. Vertebra Fractures

It is one of the most common types of osteoporotic fractures, 85% of which are symptomatic and 15% are asymptomatic, and 90% of these fractures are compression or burst fractures in the thoracolumbar region[43]. Most fractures occur after minor trauma such as a simple fall. X-ray is sufficient for diagnosis. However, to understand the morphology of the fracture, computed tomography may sometimes be required to evaluate the surgical indication and MRI. MRI can be used to evaluate spinal cord compression especially in burst type fractures. Conservative treatment can be applied in patients whose compression type posterior cortex is intact and the amount of collapse is less than 1/3. Follow-up can be provided with lumbosacral and thoracolombosacral braces and pain treatments, depending on the location. Kyphoplasty and vertebroplasty, which are also minimally invasive methods, can be performed in people with increased collapse and pain problems, but risk factors such as cement leakage for the canal should be considered[43]. These procedures should be performed under X-Ray or CT. In addition, open surgeries with posterior instrumentation can also be applied, especially in burst fractures, or severe compression fractures with impaired sagittal balance. An important aspect of osteoporotic spine fractures is that they are precursors of other future fractures, so their early detection will create an opportunity for us to prevent.

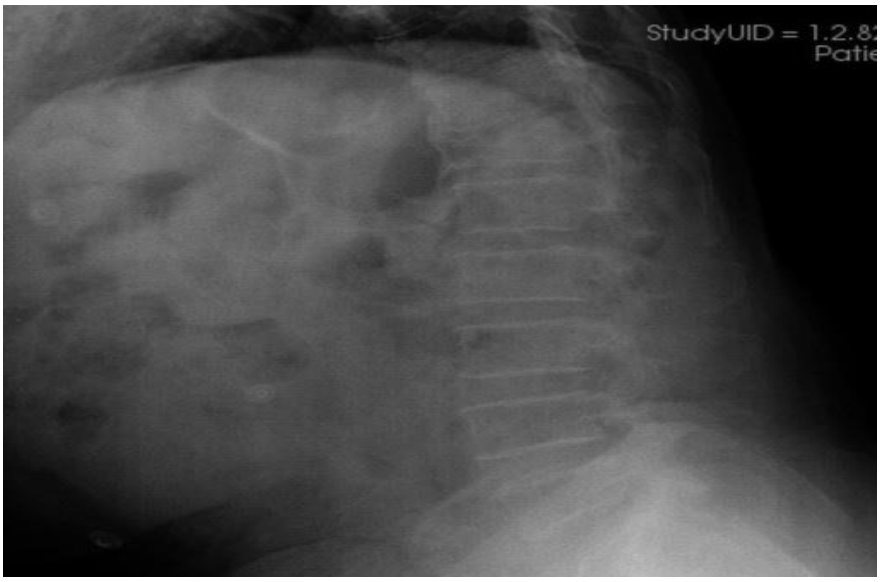

Figure 1. Osteoporotic Vertebra fracture

3.2. Hip Fractures

Hip fractures are among the fractures that require the most surgery for osteoporotic fractures, leading to advanced morbidity and mortality. These fractures usually occur in the femoral neck and intertrochanteric region. Causes, like other osteoporotic fractures, are minor trauma or simple falls. Diagnosis can be made with a simple X-ray, as well as CT may be required for better understanding of fracture morphology and treatment. The most common treatment method for femoral neck fractures in the treatment of osteoporotic fractures in this age group is arthroplasty. The type of arthroplasty may vary depending on the patient's age, activity level and the condition of the acetabulum. While total hip arthroplasty is more preferred in patients with acetabular arthrosis or high activity level, life expectancy longer than 5 years, and high expectation, partial hip arthroplasty is preferred more in patients with lower life expectancy and not high activity level. is done. The reason for this is the formation of erosion in the acetabulum after a certain period of time after the partial arthropalsty and the pain in the patients. The reason why arthroplasty is preferred rather than fixation in such fractures is both the high rates of avascular necrosis and nonunion after fractures in this region, and the need for immediate mobilization after surgery in these patients, as mentioned before. The most important advantage of arthroplasty is that it enables patients to bear weight on the injured limb earlier and to mobilize them.

The situation is slightly different in intertrochanteric fractures compared to femoral neck fractures. With the development of current treatment methods, partial hip replacement procedure, which was previously applied to these fractures, has become less common. With the development of closed methods, less invasive cephalomedullary nailing has become one of the most preferred methods. People with this fracture, who have surgery with smaller incisions, can therefore experience less blood loss and morbidity. Again, since these fractures have a higher union potential, extramedullary fixation methods, which are not preferred in elderly femoral neck fractures, may be preferred in intertrochaneric fractures. Among these, there are implants such as dynamic hip nail, proximal femoral plates, fixed angle femoral plates. Arthroplasty is also an option for multi-part fractures where adequate reduction is not achieved.

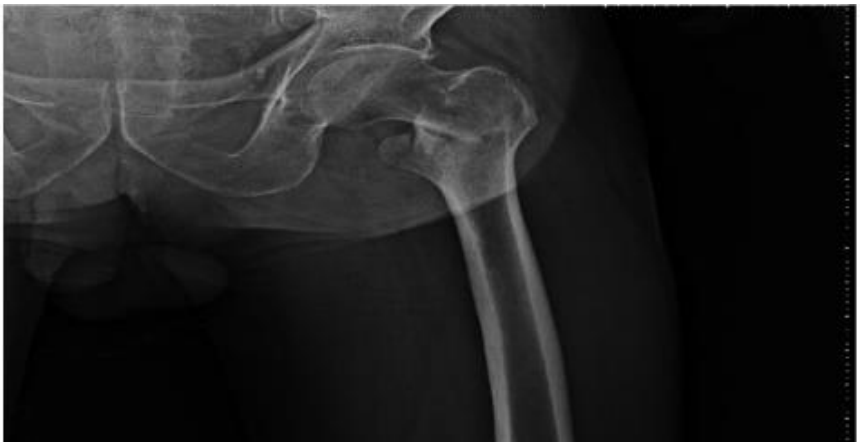

Figure 2. Osteoporotik Hip Fracture

3.3. Proximal Humerus Fractures

Proximal humerus fractures are among the most common fractures among osteoporotic fractures. Diagnosis is made by X-ray, but computed tomography is also required, especially in multi-part displaced fractures with surgical possibility. Its treatment is in the direction of conservative treatment as much as possible compared to hip fractures. However, surgical treatment is recommended for multi-part fractures with a gap of more than 5 mm between the fracture fragments. Closed pinning, open reduction plating or hemiarthroplasty, or even reverse shoulder arthroplasty can be preferred for treatment. The decision may vary depending on the type of fracture, the patient's expectation and the surgeon's decision. Arthroplasty can be considered in cases where fixation on a multi-piece, osteoporotic bone base is considered to be unsuccessful or unsustainable, and reverse shoulder arthroplasty is an option in cases with rotator cuff arthropathy.

3.4. Distal Radius Fractures

Distal Radius fractures in the elderly are usually multi-component fractures compared to young people, with a high amount of collapse due to less bone support due to osteoporosis. Due to the risk of surgeries in this age group, closed reduction and follow-up in a cast are recommended at the first stage. However, surgical treatment is indicated in intra-articular fractures, in cases where adequate reduction is not achieved, or in cases of unacceptable reduction losses. Compared to the distal radius fractures in young patients, reduction

losses in the cast are easier. Because of the lack of adequate bone support, they are more likely to switch to surgical treatment while being followed conservatively. In surgical treatment, plates and screws, closed pinning and external fixators can be used.

4. Conclusion

Osteoporosis and osteoporotic fractures have become a public health problem with the aging population all over the world and will preoccupy physicians much more in the future. Although osteoporosis is a disease that has more effects on some bones, it is actually a disease that affects all bones in the body, but the most frequently affected areas are: the metaphyseal parts of bones such as hip, vertebra, radius distal end, proximal humerus. In recent years, many medicopharmaceutical preparations that prevent these fractures, at least reduce the incidence, have been put on the market. With the developing technology, the emergence of many different drugs has enabled the reduction of fractures and the last technology medical devices used in the treatment have enabled us to cope with these fractures. However, osteoporosis, related fractures with the morbidities and mortalities they cause, which we cannot bring to a sufficient level, show us that there is still a long way to go.

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PART 12:

SURGICAL TREATMENT OF ADOLESCENT GYNECOMASTIA

Mehmet Özgür KUZDAN
Süleyman Arif BOSTANCI

Introduction

The term gynecomastia is derived from the Greek words gyne (woman) and mastos (breast). Bening hypertrophy of male breast tissue. It is seen between 4 and 40% in adolescents. Adolescent gynecomastia usually starts between the ages of 10-12 and reaches the highest frequency between the ages of 13-14; It can undergo involution between the ages of 16–17[1,2]. Gynecomastia classification is based on clinical examination measuring the volume of glandular tissue and the degree of ptosis[3].

Etiology

Etiology of gynecomastia is not known exactly, hormonal changes are blamed. It is observed physiologically in 3 periods of life. These are after birth (role of maternal estrogen), adolescence (imbalances in serum estrogen and androgen metabolism), and late life. Adolescent gynecomastiaconstitutes the majority of cases. It is often bilateral. There is usually tenderness in the enlarged breast. The main cause of gynecomastia in puberty is estrogen hormone stimulating breast growth, while inhibition of testosterone is the main responsible mechanism in the development of gynecomastia. Although most of them are idiopathic in adolescents, secondary causes should be investigated[4]. Diseases such as hyperthyroidism, chronic liver disease, primary or secondary gonadal insufficiency, and drug use can be counted among the causes of gynecomastia[5] . Primary gynecomastia is usually transient and spontaneous remission occurs in 75% of cases.

Diagnosis

Pubertal gynecomastia is usually detected incidentally by the patient or his family. The swelling in the breast is often asymptomatic, and in some cases there may be pain and tenderness with or without touching. Evaluation begins with a detailed history. The patient's age, the onset of breast enlargement, the presence of pain or tenderness, the history of drug use, and the psychological and sociological effects of the current situation are questioned. By examining the breast with palpation and "pinch" tests, the breast tissue is felt and information about its consistency and content is obtained. The growth in breast tissue is distinguished from adipose tissue. The glandular tissue is more rubbery, mobile, and spreads under the areola. The skin sagging of the breast tissue is evaluated. In this sense, pseudogynecomastia consisting of fat should be kept in mind in obese patients. Afterwards, testicular examination is also important in patients. An increase in testicular tumors has been reported in patients with bilateral gynecomastia[6].

Treatment

In the presence of a detectable condition, treatment is to eliminate the cause. There are three approaches in the treatment of pubertal gynecomastia: observation, drug therapy and surgical treatment. In cases with pubertal gynecomastia for which no etiological cause has been identified, observation is the basis of treatment. Follow-up of patients should continue with 6-month follow-ups, and control examinations should be performed by ensuring that obese patients lose weight[7,8]. For those with physiological gynecomastia, no symptoms, and no features suggestive of underlying disease or malignancy, bi-annual follow-up is appropriate.

Medical Treatment

The aim of medical treatment is to regulate the estrogen/androgen disorder that causes gynecomastia and the increase in estrogen sensitivity. Medical treatment is recommended for patients who have pain and tenderness in the breast area within 1 year after the onset of pubertal gynecomastia and the condition causes psychological trauma. Different medical treatment approaches such as testosterone, dihydrotestosterone, testolactone, danozol, tamoxifen, clomiphene citrate, anastrozole, raloxifene have been tried and different results have been obtained[9]. However, there is still no drug approved for the of pubertal gynecomastia.

Surgical treatment

There is no definite indication for surgical treatment. Breast pain should be treated in conditions such as avoidance of social activities, low self-esteem, and impaired sexual development[10]. Affected children, as well as their parents, should receive comprehensive education about the advanced clinical course.

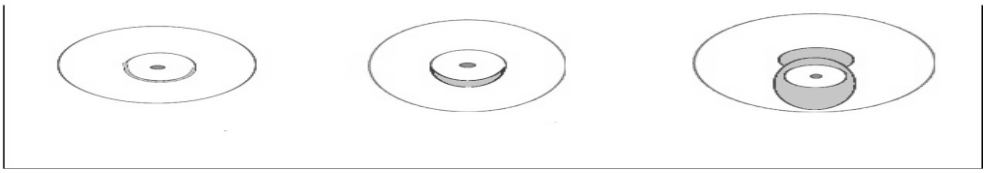
Surgical treatment of gynecomastia has made progress from past to present. Initially, transareolar or periareolar subcutaneous mastectomy was the gold standard for the treatment of gynecomastia[11].

Laituri et al.[6] the reverse T technique used in severe gynecomastia in adolescents and reduction mammoplasty in the lower pedicle are another surgical technique, while milder degrees of gynecomastia can be treated with subcutaneous mastectomy. Teimourian et al.[12] the risk of scar dehiscence and scar formation was minimized with minimally invasive liposuction without skin excision [13]. However, it has been observed that liposuction is not sufficient in severe gynecomastia and excessive skin excess (Table-1) (Fig-1-5).

Table-1: Simon gynecomastia classification
Stage I: Slight volume increase, no excess skin
Stage IIA: Moderate volume increase, no excess skin
Stage IIB: Moderate volume increase, excess skin
Stage III: There is a high degree of volume increase, excess skin

Which technique should be used in which phase? (Fig-1)
Stage I and IIA: Infra-areolar semicircular subcutaneous mastectomy
Stage IIB: Mastectomy with infra-areolar crescent skin island excision
Stage III: Vertical reduction mammoplasty

Fig-1: Surgical techniques selected according to Simon classification

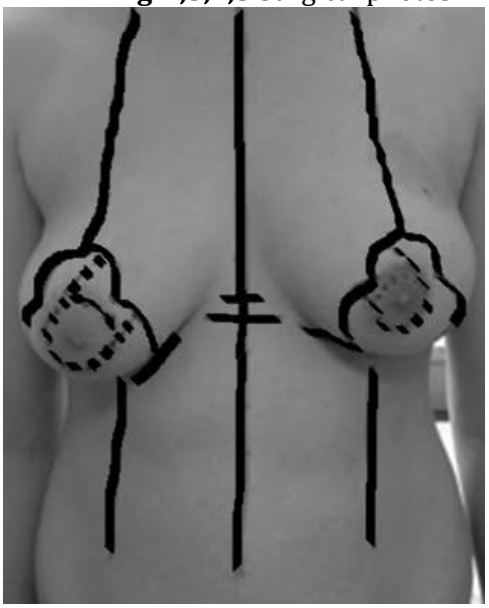


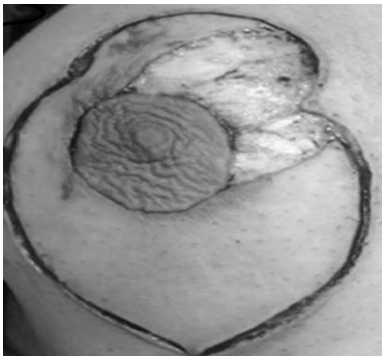
Simon-IIA İnfraareolar Semicircular Subcutaneous Mastectomy

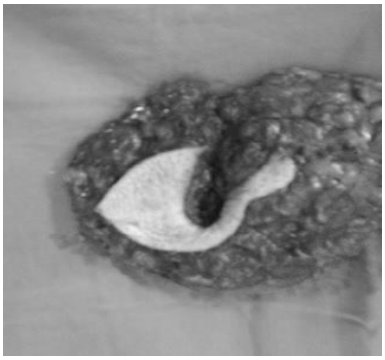
Simon-IIB İnfraareolar Crescent Skin Excision With Mastectomy

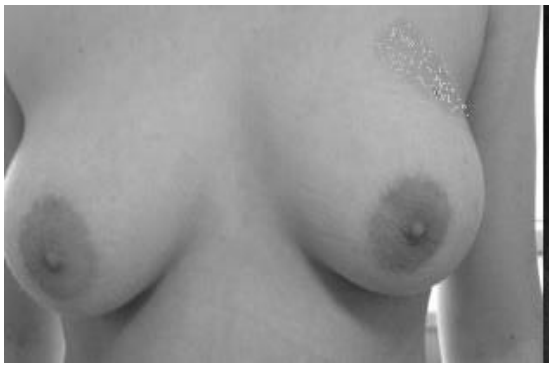
Simon III Vertical Reduction Mastectomy

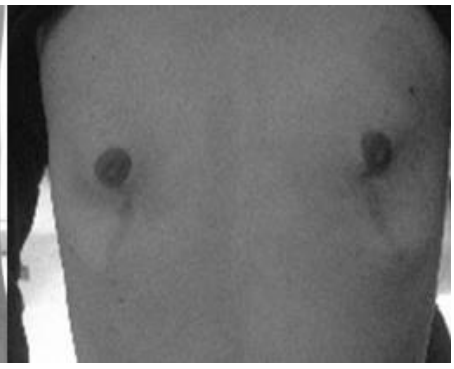
Fig-2,3,4,5 Surgical photos











Conclusion

Gynecomastia is a common and usually benign condition, but it may rarely be associated with serious underlying diseases. A careful history and physical examination with limited laboratory tests will suffice for most patients. Treatment of underlying disorders, discontinuation of drugs that may cause gynecomastia, medical therapy and surgery can be used in selected patients with symptomatic or recent gynecomastia.

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PART 13:

ENDOCRINE HEALTH IN PEDIATRIC CANCER

Begümhan Demir GÜNDOĞAN

1. INTRODUCTION

The delayed endocrine effects was reported in 50% of pediatric cancer survivors >5 years after treatment.[1,2] Most endocrine disorders are manageable; awareness of symptoms is therefore very important. Timely treatment of endocrine disorders improves quality of life and may prevent complications, such as short stature, skeletal and cardiovascular disorders, and depression. However, since most of these symptoms are nonspecific, their recognition may be delayed. Therefore, risk should be regularly and systematically monitored in survivors. A summary of the most common delayed endocrine effects in survivors is presented in this article, with the exception of delayed effects on the reproductive system, which are described in a separate article.

2. HYPOTHALAMIC-PITUITARY DYSFUNCTION

Cancer therapy may cause a deficiency of several hormones synthesized and/or released by the hypothalamus or the pituitary. This is common following treatment of central nervous system (CNS) tumors and cranial radiotherapy (CR). [3,4]All anterior pituitary hormones may be affected, causing GH deficiency (GHD), LH/FSH deficiency (LH/FSHD), TSH deficiency (TSHD), or ATCH deficiency (ACTHD). In rare cases, posterior pituitary damage due to tumor or subsequent surgery leads to central diabetes insipidus/antidiuretic hormone deficiency. Additionally, hyperprolactinemia and precocious puberty in children may be observed as a result of pituitary hyperactivity due to cancer treatment.

2.1. Growth Hormone Deficiency

GH is the most common HP deficiency associated with cranial radiation (CRT). Severe or partial GHD is the most common HP axis insufficiencies following CR, as the somatotropic axis is the most vulnerable to radiation damage. [5,6]Cranial irradiation in pediatric cancer survivors leads to severe GHD

in 50% to 100% of patients. [7-9]The time to the manifestation of GHD depends on the dose and fractionation of the radiation and the underlying tumor. The risk of GH deficiency and a short-term onset is directly related to radiation dose, whereas inversely related to the number of fractions used during radiotherapy. GH deficiency has been reported after a single fraction of 10 Gy, after fractioned doses of 12 Gy given as total body irradiation (TBI), and is common after conformal radiotherapy for CNS tumors .[10] New agents, such as immune checkpoint inhibitors and tyrosine kinase inhibitors (TKI) may impair normal growth, have caused autoimmune hypophysitis .[11] Several causes of poor growth in survivors are not associated with GH deficiency. Poor nutrition, suboptimal body mass index (BMI), and long-term glucocorticoid treatment may cause transient decreases in growth velocity. [12]Spinal radiation may cause disproportionate growth with deficits in the upper segment especially at young age, resulting in arm span being greater than standing height. [13]GH deficiency is screened by height, sitting height, weight, BMI percentiles, and height velocity every 6 months and should be interpreted by past height percentiles, mid–parental height, and Tanner stage.

2.2. Adrenocorticotrophic hormone deficiency

The symptom of ACTH deficiency is adrenal insufficiency, including fatigue and vulnerability to medical stressors, adrenal crisis, shock, hypoglycemia, seizures, and death. Low cortisol level after stimulation with low-dose or high-dose ACTH is required for the diagnosis. Treatment is hydrocortisone replacement at maintenance doses and stress dosing during illness.[14]

2.3. Central precocious puberty

Increased intracranial pressure or neoplasms in the HP region are risk factors for CPP. Children with CPP present with pubertal development and growth acceleration before 8 years old in girls (breast development) and 9 years old in boys (testicular enlargement). Untreated CPP may lead to short stature and psychosocial adjustment problems. [15]

2.4. Hyperprolactinemia

Hyperprolactinemia reduces hypothalamic release of the inhibitory neurotransmitter dopamine and is more common in adult cancer survivors, may trigger gonadal dysfunction. Prolactin levels are often only mildly elevated and

may normalize with time, reflecting a direct radiation-induced damage to pituitary lactotrope cells in decades after cancer treatment .[16]

2.5. Central diabetes insipidus

CDI is not considered a delayed effect of survivors but is most common from the outset or immediately after neurosurgery in patients with neoplasms near the HP region (craniopharyngioma, germinoma, Langerhans cell histiocytosis). Patients with CDI present with polyuria and polydipsia due to antidiuretic hormone deficiency. A small subset with extensive hypothalamic injury experiences loss of thirst sensation. Management is the desmopressin treatment and monitoring fluid intake and output .[17]

3. THYROID DISORDERS

3.1. Thyroid Dysfunction

The main risk factors are radiation to a field consisting the thyroid gland and 131I-meta-iodobenzylguanidine (MIBG) treatment. Hypothyroidism is higher among the survivors of neuroblastoma and Hodgkin lymphoma (50% and 32%, respectively). The hypothyroidism risk increases with radiation dose, with 50% of survivors exposed to doses 45 Gy would develop hypothyroidism in 20 years of follow-up. Other risk factors include younger age during radiotherapy and female gender. Some evidence suggests that chemotherapy may affect thyroid function .[18]Immunotherapy, such as treatment with cytokines and check-point inhibitors, may cause thyroiditis resulting in an increased or decreased thyroid function. [19]Also TKI treatment may cause thyroid dysfunction probably due to thyroiditis, although other mechanisms have been proposed.

3.2. Thyroid Neoplasia

Patients exposed to incidental or therapeutic ionizing radiation had effects on thyroid nodules or carcinomas years to decades after exposure. The time to the development of thyroid neoplasia with a minimum latency period of 5 to 10 years .[20]The risk depends on the radiation dose and the age of the patient. Younger subjects, especially patients exposed to external radiation before 4 years old, appear to have higher risk than older children and the risk decreases further in adulthood.[21] Studies in irradiated children, however, show that the rate of thyroid cancers is not decreased in time after radiation exposure.[20]Thyroid cancer risk increases linearly with radiation dose up to 20 Gy but decreases at higher doses of radiation, along with thyroid destruction.

4. METABOLİC SYNDROME

HP deficiencies and obesity associated with (neurosurgical) damage in HP region increase the risk for metabolic syndrome. In addition, insulin resistance may result from excess insulin secretion from the pancreatic b cells due to overactive vagal neural transmission. Corticosteroids have been repeatedly identified in the metabolic risk for survivors. Acute corticosteroid administration may impair glucose levels while causing weight gain and height loss. It is known that the corticosteroids increase circulating free fatty acids, resulting in dyslipidemia and inhibition of myocellular glucose transport, increased gluconeogenesis and fatty acid synthesis, with decreased adiponectin levels. Multiple chemotherapy agents, most notably heavy metals and alkylating agents, have been associated with metabolic syndrome components.[22]Survivors with a history of TBI, radiation to the chest or abdomen, and CRT have increased risk for the metabolic syndrome.

SUMMARY

Although significant research on delayed endocrine effects after cancer therapy were performed during the last decades, large, longitudinal studies evaluating the individual risk for long-term cancer survivors are still limited. Endocrine, metabolic, and skeletal disorders are common in survivors. Since the symptoms of HP deficiency may be unnoticed, the (pediatric) endocrinologist should be a part of the team to evaluate the delayed-effects for early recognition and treatment.

In conclusion, the main goal in cancer treatment is shifting from getting rid of cancer to living beyond cancer, and therefore early detection and treatment of sequelae is essential to improve quality of life and reduce late morbidity and mortality.

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PART 14:

THE ROLE OF SURGERY IN GENDER DEVELOPMENT DISORDER IN CHILDREN

Mehmet Özgür KUZDAN

1. Introduction

Sex development disorder (DSD), is a disease characterized by multiple genital differentiation anomalies. It is defined as the situations in which the chromosome structure, gonads or anatomical structure are incompatible with each other, which develops as a result of disruptions in the sex development stages, especially in the first trimester of pregnancy. Different transcription factors, signaling molecules and activation of different hormones play a role in its development [1].

Gender is a multifaceted concept. It is insufficient to examine gender, which is determined by genetic structure, internal and external sexual organ structure and psychosocial development process, under a single heading. It is also important for the individual to feel himself or herself as a man or a woman. Sexual identity, male or female-specific clothing, play, and occupation determines the sexual role of the person, and the choice of partner as male or female determines the sexual preference of the person. Each of these three characteristics that make up gender are developmental processes in which highly complex factors play a role and interact with each other [2].

The main factors that play a role in determining gender in general are:

1-Genetic

2-Endocrine factors

3-Internal and external genital anatomy

4-Environmental factors

In the embryological period, until the 7th week, external and internal genital structures have not yet developed in the direction of male and female. Development in the male direction SRY gene and Hy antigen on the Y chromosome provide differentiation in the testis direction. If there is a Y

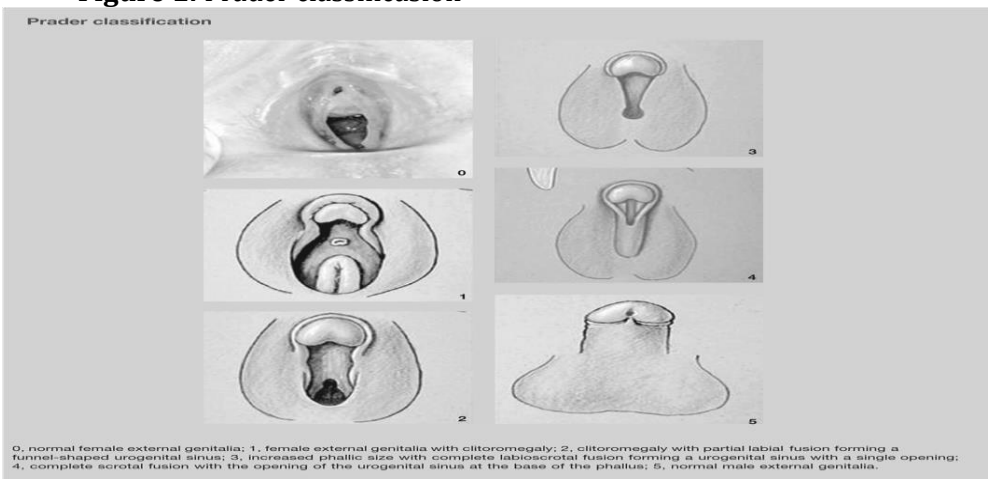
chromosome, no matter how many X chromosomes there are, sex development is in the male direction. If there is no Y chromosome, the genital tubercle differentiates in the female direction. The ovaries have no role in this differentiation. Hormonally, at the 7th week, Sertoli cells Müllerien inhibitory substance (MIS), which are Müllerien structures; It provides regression of uterus, tuba uterina, proximal vagina. Leydig cells secrete testosterone in the 8th week, allowing the development of wolf channel structures. These are epididymis ductus deferens vesicula seminalis. With the effect of dihydrotestosterone on the external genitalia in men; With the enlargement of the phallus, the penis is formed, the inner genital folds merge into the urethra, and the outer genital folds merge into the scrotum [2,3].

2. Clinical Features

2.1. Suspicion of DSD in physical examination

Diagnosis of DSD as soon as possible. Therefore, a careful examination in the first examination of the physician during the newborn and infant period may be diagnostic. Initial clinical examination should include the Prader classification (Figure 1) [3].

Figure 1: Prader classificasion [(3)]



Early diagnosis is vital, especially since classic salt-wasting adrenal hyperplasia requires urgent intervention. in female; Clitoris hypertrophy, labia

fusion, palpable gonad are observed. In men; non-palpable testicles, Severe hypospadias, Undescended testis with hypospadias

The appearance of the ambiguous genitalia should make the physician suspect in terms of gender development disorder. In adolescents, virilization findings, especially amenorrhea, should raise suspicion of DSD. Also, amasty, cyclic hematuria are suspicious findings. In suspected patients, determination of genetic sex, endocrine studies, revealing anatomy, and interventions for gonad histology should be planned, respectively.

3. Classification

Simple examination of the external genitalia at birth is usually all that is necessary to confirm the sex of a neonate. In a small number of newborns, assignment of sex is not possible simply based on appearance. In the past, these neonates were described using a variety of terms including ambiguous genitalia, intersex, hermaphroditism and pseudo-hermaphroditism. These terms were confusing and potentially stigmatizing for parents and children. Following a consensus statement in 2006, the term 'disorders of sex development (DSD)' was introduced to replace all the above terms and defined as a 'congenital condition in which development of chromosomal, gonadal or anatomical sex is atypical' (Table 1) [4].

Table 1. Classificassion of DSD[4]

46,XY DSD (under-virilized genetic male)
Disorders of testicular development
Complete gonadal dysgenesis (Swyer syndrome; 46,XY sex reversal)
Partial gonadal dysgenesis
Gonadal regression Ovotesticular DSD
Disorders of androgen synthesis/action
Synthesis: 17-hydroxysteroid dehydrogenase or 5a-reductase deficiency
Action: complete or partial androgen insensitivity syndromes
Receptor defects: Leydig cell hypoplasia
Disorders of AMH and receptor: persistent mullerian duct syndrome
Others
Severe hypospadias
Cloacal exstrophy
46,XX DSD (over-virilized genetic female)
Disorders of ovarian development Ovotesticular DSD
Testicular DSD (e.g. duplication SOX9) Gonadal dysgenesis
Androgen excess
Fetal: congenital adrenal hyperplasia (21- or 11- hydroxylase deficiency)

Fetoplacental: aromatase deficiency
Maternal: luteoma, exogenous Sex chromosome DSD (variable)
45,X (Turner's syndrome)
47,XYY (Klinefelter syndrome and variants)
45,X/46,XY (mixed gonadal dysgenesis, ovotesticular DSD)
46,XX/46,XY (chimeric, ovotesticular DSD)
AMH: anti-Mullerian hormone.

4. The Role of Surgery in DSD Disease

Surgical interventions are the main factors in both diagnosis and shaping of gender. Diagnostic cystoscopy, laparoscopy and Gonad biopsy are very important in shaping the treatment. The aims of surgical treatment in sexual development problems can be summarized under three main headings:

1- Providing a gender-specific anatomical and aesthetic appearance,

2-Creation of genital and urinary system without incontinence, infection and obstruction,

3- Providing sexual satisfaction and reproductive functions in adulthood.

Gender-specific surgical reconstructions include orchiopexy, urethroplasty, and testicular prosthesis placement in boys. Rarely, Müllerian duct remnants may need to be removed due to obstruction and urinary infection. in girls On the other hand, there are clitoroplasty, vaginoplasty, labiaplasty and gonadectomy operations [3,4].

4.1. Feminizing genitoplasties:

According to the literature, it has been reported that 90% of adrenal hyperplazia cases underwent female genitoplasty [1,3]. It is easier to create a surgically good cosmetic and functionally acceptable external genitalia. Especially in patients with congenital adrenal hyperplasia, regardless of the external genitalia, genitoplasty should be performed strictly in the direction of the female gender, since the chromosome structure is completely normal in terms of internal genital organs and is potentially fertile.

4.1.1. Gonadectomy

It is performed especially in streak gonads because of the risk of developing gonadoblastoma. The risk of malignancy has been reported as 55% in partial XY gonadal dysgenesis and 30-66% in complete XY gonadal dysgenesis [3].

4.1.2. Clitoral reduction

It is a method defined by Spance and Allen [1,3]. has gained more acceptance in recent years. Cliterectomy, in which the clitoris is completely resected, which

was popular until the early 1970s, is no longer performed. In clitoral recession, which is another alternative technique, it has been suggested to hide the clitoris behind the pubis without resection [1,3]. This method is applied in cases with mild clitoral hypertrophy. It may cause dyspareunia in cases with excessive hypertrophy [4].

4.1.3. Vaginoplasty

In cases where the vagina enters the urethra proximal to the external sphincter, pull-through vaginoplasty should be performed from the age of two, and in cases where the vagina is completely absent, it should be waited until adolescence to form a neovagina [(4)] . Perineal vaginoplasty can be applied from the newborn period. The best way to determine the location of the vagina relative to the external sphincter is retrograde genitogram and endoscopy [1]

4.2. Virilizing genitoplasty

It has been reported that the number of operations performed for virilizing genitoplasty is approximately twice that performed for feminizing genitoplasty. Excision of Müllerian structures utriculus excision is gradual penile surgery and phalloplasty, often prepared from soft tissue in the forearm or pubic region [6].

5. Timing of Genital Surgery

5.1. Arguments

Reduction in stigma associated with growing up with atypical genitalia Parent's wishes and desire to align the genitals with the gender of rearing The unknowns of later surgery: C limited surgical expertise in performing genital surgery on adolescents C lack of outcome data Psychological impact of surgery which may be reduced in an infant compared to an adolescent Positive feedback from previous patients who have undergone early surgery Infants cannot give informed consent The irreversibility of genital surgery, thus taking away an open future and right for a patient to choose for themselves Rejection of binary gender and the need to conform to societies description of 'normality' Previously reported poor surgical outcomes; reduced clitoral sensitivity and the need revision surgery Early surgery is medically unnecessary as the vagina is functionally unused in a child Negative feedback from previous patients who have undergone early surgery [5].

6. Long Term Results of Genitoplasty

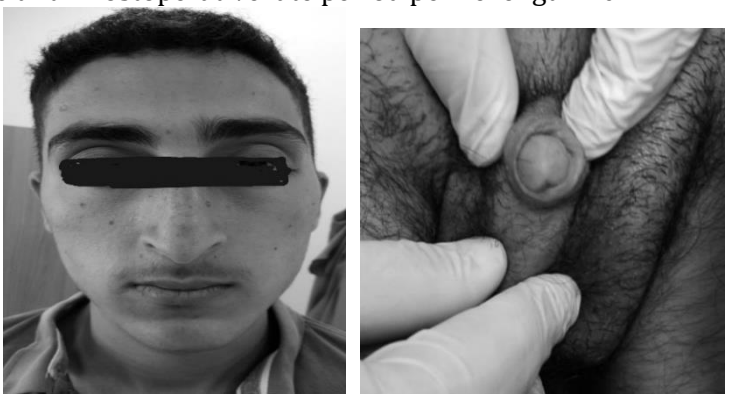
In a study conducted on 1040 patients who had undergone surgery for DSD in Europe 6, the group with the lowest XY karyotype was found to have undergone masculine genitoplasty surgery. Although these patients were not satisfied with the appearance of the penis, it was reported that they were satisfied with its function [6,7], but these patients stated that their genital organs were better than before the surgery. It has been shown that females with PAIS have fear of sexual intercourse, dyspareunia and fear of injury [8]

It has been reported in the literature that men with Klinefelter syndrome have a better sex life after surgery. Still, 1/3 of them experience erectile dysfunction. There is a similar picture in premature ejaculation. In previous studies, disorders such as hypoactive sexual desire, premature or delayed ejaculation have been reported in up to 67.5% of this patient group [9].

Among females, women with Turner syndrome are the most satisfied with their sexual life in the late postoperative period. Sexual intercourse is rare. But they start to find sexual partners in their later years.

Testicular feminization patients are also cases that confuse clinicians. Among them are tall strong famous female stars. Success is almost complete in incomplete types (Figure 2).

Figüre 2: Partial Testicular Feminisation .19 years old, 16 years old lived as a female until. Postoperative late period penile length 4 cm.



On the other hand, Kraukels et al.[10] showed decreased sexual satisfaction in those who underwent genital surgery. however, as a deficiency in this study, they reported that comparing those who are suitable for genital surgery and who do not have surgery, and those who are suitable and have surgery will give

more accurate results. It has been reported that the results of surgery on the quality of sexual life in individuals with DSD need further research.

DSD is a disease that can be better diagnosed and treated now. However, dissatisfaction is noted in individuals who are predominantly male. The majority of individuals become female with feminizing genitoplasty. The problem in these patients is the masculine effect of exposure to androgens.

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PART 15:

POSSIBLE EFFECTS OF DIABETES MELLITUS ON ROOT CANAL TREATMENT OUTCOME AND PERIAPICAL TISSUE HEALING

Cihan KÜDEN

1. Introduction

Diabetes mellitus (DM), which causes hyperglycemia, is one of the most common chronic metabolic disorders across the world.[1] DM (Diabetes: Greek: urinating, Latin: mellis = sweet or honey) usually is caused by a combination of hereditary and environmental factors.[2] DM is characterized by changes in carbohydrate, fat and protein metabolism, which occurs due to the lack, absence or ineffectiveness of the hormone insulin secreted from the pancreas, or the presence of these factors and progresses with hyperglycemia.[3] The number of patients diagnosed with diabetes has reached approximately 451 million people as of 2017. By 2045, this number is estimated as 693 million.[4] In a study conducted in Turkey, it was found that 8.28% of individuals with systemic diseases constitute endocrinological pathologies and diabetes has a rate of 57.83% among endocrinological pathologies.[5]

Acute or chronic inflammation of the bone tissue surrounding the tooth, mostly due to microbial infection of the root canal system, is called apical periodontitis (AP).[6] The lesions occur following the periapical inflammatory response to root canal-derived polymicrobial irritants and continue chronically.[7] In the presence of AP, it is aimed to restore the health of the periradicular tissues, usually only by endodontic treatment and in some cases by surgical endodontic treatment.[8]

DM is the most common metabolic disorder amongst dental patients. There is evidence that the need for root canal treatment, the extensive periapical lesion, bone loss, and failure after root canal treatment are higher in patients with uncontrolled diabetes.[6,9] Hyperglycemia may cause increased risk

of the pulp necrosis as a result of impaired blood circulation and ischemia in the pulp tissue, resulting in increased toothache and sensitivity.

There are several types of diabetes, including Type 1, Type 2, gestational and diabetes insipidus.[10,11] Existing data on DM reflected in the endodontic literature are limited to types 1 and 2. Although it has been explained at the molecular level that hyperglycemia increases bone resorption and decreases osteoblastic activity, the relationship between diabetes and AP cases has not been fully elucidated.[9] Having knowledge about DM and its relationship with oral health is significant for treatment planning and follow-up of root canal treatment.

2. Diabetes mellitus and disease mechanism

There are many studies in the literature examining the relationship between AP and DM. However, no definite conclusion has been reached regarding the relationship between DM and the prognosis of endodontic infections.[6] About 5 to 10 percent of all DM patients have Type 1 diabetes. In type 1 diabetes, insulin production decreases as a result of the loss of ß cells of the islets of Langerhans in the pancreas due to auto-immune, toxic or viral causes. Type 2 diabetes constitutes 85-90% of all DM patients. Type 2 diabetes; It occurs with the development of resistance to insulin, the decrease in the sensitivity of insulin receptors, and the decrease or complete disappearance of insulin synthesis and secretion.[9] Diabetes and its treatment methods can lead to many complications. If the disease is not under control, acute complications such as hyperglycemia, ketoacidosis or nonketotic hyperosmolar and coma may develop.[6]

Although our clear information about the molecular mechanism of diabetes is limited, the development of insulin resistance is mainly caused by disruptions in post-receptor signaling pathways rather than receptor dysfunction. Post-receptor insulin resistance is caused by signal transduction disorders, mutations in the GLUT-4 isoform in skeletal muscle, cardiac muscle, and adipose tissue. Thus, although the insulin hormone binds to its receptor, it cannot exert its effect due to the disruption in post-receptor mechanisms. Stopping the insulin signaling system as well as starting it is an important step. Inhibition can be achieved by phosphatases as well as by activation of serine/threonine phosphorylation. Disruptions in inhibition can also lead to insulin resistance.[12]

One of the most important underlying mechanisms of insulin resistance is the excess of free fatty acids and therefore suppression of IRS-1 signal transduction. In recent studies, it has been shown that fatty acids impair the tyrosine phosphorylation of IRS-1. It has been shown that the number of insulin receptors decreases and the target tissues become less sensitive to insulin in conditions such as obesity and acromegaly where the plasma insulin level increases.

Insulin receptor gene mutations and receptor isoform activity differences may play a role in the pathogenesis of insulin resistance. Numerous mutations have been identified in the insulin receptor. Extreme insulin resistance is seen in these mutations, which are very rare and usually only seen in a single patient or in a single family.[12,13] Our knowledge about the formation mechanisms and physiopathology of peripheral insulin resistance is still insufficient and studies on this subject are continuing. Finding new candidate molecules is important not only for understanding the physiology but also for identifying new therapeutic targets in the future. Recently, the number of studies showing a relationship between insulin resistance and peptide mediators such as "tumor necrosis factor α" (TNF-α), angiotensinogen, plasminogen activation inhibitor-1, leptin and complement has been increasing.[13]

3. Endodontic treatment

The dental pulp is a sterile connective tissue protected by enamel, dentin, and cementum.[14] Endodontic treatment eliminates damaged or necrotic pulp tissue that normally provides nutrition and sensory function within the root canal of the tooth and then fills it with gutta-percha, an inert natural latex material. As a result of this treatment, the bone lesion is expected to heal by preventing further leakage of bacteria and toxins from the root canal to the tissues surrounding the tooth.

3.1. Diagnosis of endodontic infections

Usually diagnosed by routine radiographic examination or by acute toothache.[14] Periradicular lesions (>90%) dental granuloma, radicular cyst, or abscess (Fig 1.).[15] The radiographic examination of apical lesions cannot distinguish whether they are cysts or granulomas. Moreover, the size of the lesion is not of sufficient importance in the diagnosis of cyst, granuloma or apical scar.[16] Among these lesions, the definitive diagnosis can only be made by histological examination. However, the clinical diagnosis of a periapical cyst

may be based on (i) one or more non-vital teeth containing the periapical lesion, (ii) the size of the lesion greater than 200mm^2, (iii) the lesion limited by a thin radiopaque line, Radiographic image as a well-defined radiolucent area (iv) Straw colored fluid is observed during aspiration or from the root canal system.[15]

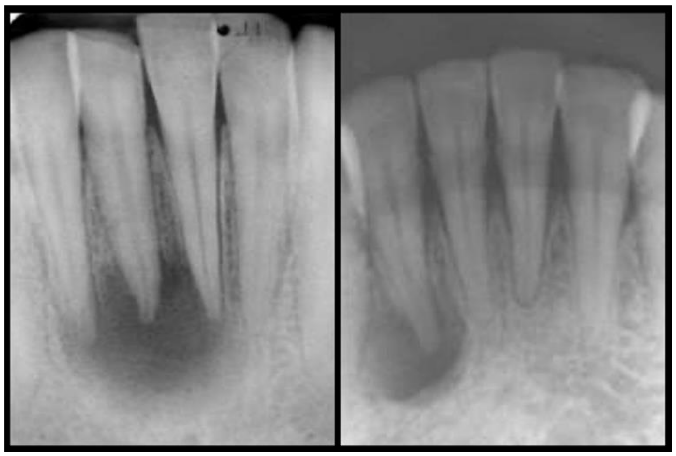

Figure 1. Mandibular teeth associated with a large periapical lesion[15]

3.2. The healing process of periradicular lesions

Nair et al.[17] showed that as a result of conventional root canal treatment, 85% to 90% of periapical lesions disappeared radiographically or a significant reduction in the size of the lesion was achieved. Çalışkan;[18] reported that healing was completed within 2 years in approximately 70% of cases with periapical lesions. However, it has also been reported that in many cases with periapical lesions, recovery may take 1-12 months after treatment.[19]

3.3. Failure of endodontic treatment

The most important factor of failure of root canal treatment is microorganisms in the root canal system.[20] In addition to local factors such as the curvature angle and diameter of the root canals and the presence of lateral or accessory canals, it has been reported that conditions such as residual necrotic pulp tissue, broken instruments, overflowing root canal filling, mechanical perforations, root fractures, presence of periradicular lesions and periodontal disease may also be the cause of failure.[21-23] Although application errors such as broken instruments, perforations, overflow fillings, and step

formation have been thought to be the direct cause of endodontic failure, application errors do not jeopardize the outcome of endodontic treatment in most cases unless a persistent infection and systemic diseases is present.[24-26] In particular, it has been reported that systemic diseases that impair bone formation or reduce the immune system's defense can be directly related to the formation of periapical lesion and/or the healing of periapical tissues after root canal treatment.[25-27] DM, one of these systemic diseases, has been noticed to be considerably correlated with decreased and stopped healing outcome of the endodontic treatment in infected teeth.[28,29]

4. Periodontal disease

Periodontal disease, which is a devastating chronic disease that affects the surrounding dental tissues, is one of the common chronic infections. Periodontal infections are associated with a complex microflora of about 350 bacterial species. Microflora predominantly consists of anaerobic gram-negative rods. [30] Plaque-related periodontal diseases are divided into gingivitis and periodontitis. Gingivitis is an inflammatory condition of the gingiva without periodontal attachment or alveolar bone loss (Fig 2.). Periodontitis leads to the advanced destruction of collagen fibrils and alveolar bone. [31] Periodontal disease is initiated by oral microorganisms, but the severity of periodontal destruction is related to the inflammatory response of the host (Fig 2.).[32] It should be considered that the inflammatory response is not limited to the periodontal focus, but bacteremia originating from the periodontal focus or the distribution of bacterial endotoxins may also stimulate the inflammatory response systemically. [33,34]

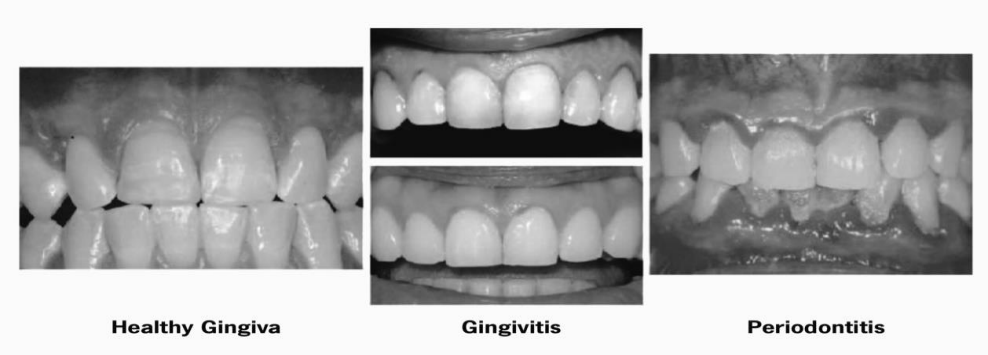

Figure 2. Periodontal Health, gingivitis, and periodontitis[35]

4.1. Relationship between Periodontitis and Diabetes Mellitus

The prevalence, severity, and progression of periodontal disease have been shown to increase in patients with DM.[36] Mealey et al.[37] reported that diabetic adults had a three times higher risk of developing periodontal diseases when compared to non-diabetic adults. However, it has been reported that there is a bidirectional relationship between DM and periodontal disease, and periodontal disease has a significant effect on the metabolic status of DM patients.[38]

The presence of periodontal disease increases the risk of worsening glycemic control over time.[39] It has been suggested that periodontal disease may initiate or increase insulin resistance, similar to obesity, by increasing the activation of the overall systemic immune response initiated by cytokines.[40]

Chronic gram-negative periodontal infections can induce or maintain an increased chronic systemic inflammatory state. This leads to increased insulin resistance and poor glycemic control.[39] There are similarities between periodontal diseases and AP in terms of some factors. Therefore, it is thought that the presence of chronic periapical infection may contribute to the pathogenesis of Diabetes Mellitus and may be a risk factor for worsening glycemic control in DM patients.[41] Bender et al.[26] reported that the presence of periapical infection and the associated local inflammation in DM patients also caused an increase in blood sugar and brought the patient into an uncontrollable diabetic state. This requires an increase in insulin dosage or therapeutic dose. When the effect of DM disease on pulp tissue and cells is examined, it is seen that there is a direct relationship and poor glycemic control has a negative effect on the pulp (Fig 3.). Hyperglycemia causes an increased likelihood of pulp necrosis, toothache, and sensitivity as a result of impaired blood circulation and ischemia in the pulp tissue[42,43]

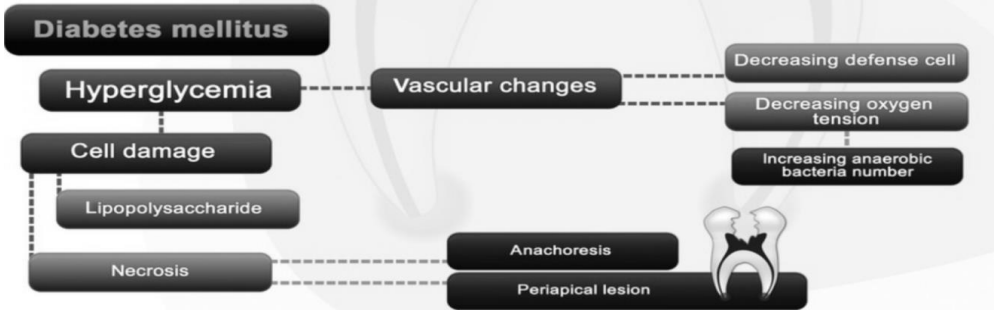

Figure 3. The negative effect of hyperglycemia on the pulp of tooth[28]

4.2. Relationship between Diabetes Mellitus and Pulp tissue

For healthy adults, as a result of progressing caries in the enamel and dentin tissue to the pulp tissue, a number of mediators are secreted. However, the defense capacity of the pulp tissue confined to a restricted area is also limited. The pulp tissue exposed by caries becomes necrosis and the microorganisms migrate towards the periapical tissues. Polymorphonuclear neutrophils or epithelial plugs surround the periapical lesion as a defensive response to the development of the infectious process. Periapical inflammatory exudates contain many defense components such as leukocytes, macrophages, lymphocytes CD4+, CD8+ and CD30+, plasma, natural killer, mast cells to eliminate microorganisms.[44,45] This exudate contains many cytokines that are effective in bone remodeling and the development of the periapical inflammatory response.[45] IL-4, IL-5, IL-6, IL-10, and IL-13 produced by type 2 T helper (Th2) cells are inhibitors of bone resorption while cytokines such as tumor necrosis factor (TNF)-a, interferon (IFN)-c, interleukin (IL)-2 and IL-12 produced by Type 1 T helper cells (Th1) are bone resorption activators.[44,46] High glucose levels in DM patients cause a decrease in IL-4 in response to inflammation and an increase in IL1b, IL-6, IL-8, IL10, TNF-a. Bone healing and deterioration in bone turnover associated with hyperglycemia have been shown in many studies, and histological studies have shown a decrease in the number of osteoblasts and an increase in the number of osteoclasts.[47]

Hyperglycemia inhibits osteoblastic differentiation and alters the response of parathyroid hormone which regulates phosphorus and calcium metabolism. Diabetic osteopenia, one of the complications associated with diabetes, is characterized by decreased bone mineral density, osteoporosis, increased risk of bone fractures, deterioration in bone healing and bone regeneration potential.[48]

4.3. Follow-up studies after endodontic treatment for healthy and diabetic adults

In the comparison of root canal treatment healing outcomes in type 2 DM patients and healthy individuals using the periapical index (PAI), 81% of DM patients detected the presence of AP in one or more teeth, while this rate was found to be 58% in healthy individuals.[49] Also, it was shown that the percentage of teeth with AP was higher in DM patients (7%) than in healthy individuals (4%).

Marotta et al.[50] showed that the presence of teeth with AP is more common in DM patients (15%) than in healthy individuals (12%), although it is not statistically significant. Lopez-Lopez et al.[51] evaluated panoramic x-rays of patients with type 2 DM under control (50 individuals; 20 males, 30 females) and healthy individuals without a history of DM (50 individuals; 22 males, 28 females). According to the results, the incidence of AP in one or more teeth in Type 2 DM patients (74%) was found to be significantly higher than in healthy individuals (42%). However, unlike all these studies, Britto et al.[52] showed that there was no difference between healthy individuals and DM patients in terms of the presence of AP in teeth that did not undergo root canal treatment.

Root canal therapy is the primary treatment option in the presence of periapical lesions. Lopez-Lopez et al.[51] examined the root canal treatment needs of DM patients and evaluated 50 individuals with type 2 DM; While the rate of root canal treatment in one or more teeth in DM patients was 70%, it was 50% lower in healthy individuals. Unlike the results of this study, Marotta et al.[50] showed that there was no significant difference in the number of teeth which applied root canal treatment between type 2 DM patients and healthy individuals.

Fouad & Burleson[29] reported that DM patients have a higher risk of acute flare-ups than healthy adults due to the weak defense response during root canal treatment, and it was emphasized that intracanal disinfection and decontamination are particularly important in these patients. In order to reduce the risk of acute exacerbation, the use of coronal to apical shaping techniques has been recommended.[53] It has also been reported that the use of antibiotics may be recommended in patients with completely or partially uncontrolled DM to reduce the risk of post-procedure infection and to support delayed wound healing. As long as there is no other systemic problem, there is no harm in applying similar protocols with healthy individuals in the approach of treatment.[54]

Fouad & Burleson[29] evaluated the healing of periapical lesions after root canal treatment by including 5494 individuals (284 individuals with DM) who completed root canal treatment and 540 individuals (73 individuals with DM) who were followed up for two years or more after root canal treatment. It was observed that the success rate of root canal treatment was high in 540 patients followed for a long time, but DM reduced the success rate in the presence of periapical lesion.

Dominguez et al.[55] evaluated 83 individuals with DM in two groups as controlled (HbA1c<6.5%) and uncontrolled (HbA1c>6.5%). According to the results of this study, there is a significant relationship between the periapical condition of the root canal treated teeth and HbA1c levels.

In their review, Segura-Egea et al.[56] reported that a definitive conclusion could not be reached that DM has a negative effect on the healing of the periapical lesion after root canal treatment, that there is a possibility of improvement in follow-up periods of more than 2 years, and that epidemiological studies may produce more accurate results instead of comparative studies. When the literature is examined, there are also epidemiological studies that observe the relationship between DM and healing after root canal treatment and evaluate the relationship between the rates of extracted teeth.[57,58] According to the results of these studies, it was emphasized that DM was directly related to the decrease in the retention rate of the teeth which applied root canal treatment and the increase in the extraction rate.

5. Conclusion

Uncontrolled diabetes predisposes to intraoral infections, including pulp infections. However, considering the limited number of epidemiological studies, if adequate control is not provided in DM patients, the presence of AP and the possibility of failure in endodontic treatment may increase. It is thought that dentists should determine the diagnosis and treatment protocols by considering the possible relationship between endodontic infections and DM.

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PART 16:

ANESTHESIA MANAGEMENT DIABETIC DISEASES

Öztürk TAŞKIN

Endocrine system diseases require special preparation because anesthesia responds to surgery and carries significant risks in terms of anesthesia. Endocrine and metabolic disorders may affect many physiological parameters in the intraoperative period. Therefore, preoperative evaluation, intraoperative and postoperative observation of patients is very important.

Diabetes mellitus (DM) is the most common endocrine disease in patients undergoing surgical intervention [(1)]. DM, a chronic metabolic disease characterized by hyperglycemia, is among the major causes of morbidity and mortality with an increasing prevalence all over the world. Between 2010 and 2030, a 20% increase in the number of diabetic patients in developed countries and a 69% increase in developing countries is predicted [(2)]. According to the Diabetes Atlas published by the International Diabetes Federation in 2015, there are 6.3 million (12.8% of the population) adult diabetic patients in our country [(1)].

25% of the patients who will be operated on are patients with a diagnosis of DM [(3)]. Due to surgical stress; proinflammatory cytokines are over-released and there is an increase in catecholamine, cortisol, glucagon and growth hormone levels due to increased sympathetic activation. Accordingly, endogenous glucose production and insulin resistance in the liver are facilitated and glucose utilization in skeletal muscle decreases. As a result, hyperglycemia develops. Even in the absence of surgical stress, anesthesia modulates the glycemic response by affecting the neuroendocrine response or directly altering the pancreatic insulin release [(4)].

Due to the mechanical stimulation of the supraglottic region by laryngoscopy and intubation, tachycardia and hypertension develop in patients without autonomic nervous system pathology. It is extremely difficult for patients with diabetes-related autonomic neuropathy to tolerate the developing hemodynamic instability. However, there is an increased sensitivity to stress

hormones, and uncontrollable or even fatal hemodynamic changes may develop during the operation [5].

Surgical mortality in diabetic patients is 5 times higher than in non-diabetic patients [6]. In order to reduce mortality and morbidity, a good preoperative evaluation and careful intraoperative and postoperative observation are required.

1. Preoperative Period

Comorbidities such as cardiovascular diseases, renal diseases, cerebrovascular diseases and obesity may be present in DM patients. In the preoperative period, determining the type and duration of diabetes, existing end-organ damage, complications and treatment strategies is important in terms of reducing the rate of mortality and morbidity [7]. For this reason, in the preoperative period, glycemic status, ECG, kidney function tests, electrolytes or, if necessary, additional tests and airway examination together with the recommendations of the relevant department should be carefully evaluated [3].

The type and duration of diabetes, the pharmacological agents and doses used by the patient, the frequency of hyperglycemic and hypoglycemic attacks are recorded and evaluated. Determining the HbA1c level, which reflects the glycemic status of the last 3-4 months, and blood glucose level are important indicators to evaluate the glycemic status before the operation [8]. Perioperative glucose regulation may reduce the risk of postoperative complications in patients with high HbA1c levels [9].

It is recommended to study HbA1c in all diabetic and hyperglycemic patients if it has not been done in the last 3 months. In patients with high HbA1c, perioperative blood glucose control may reduce the risk of intraoperative complications [10].

It has been reported in studies that keeping blood glucose level between 140-180 mg/dL during the preoperative 48-hour period minimizes the possibility of postoperative complications [11]. Oral antidiabetics (biguanides, sulfonylureas, glinides) carry the risk of causing hypoglycemia due to their highly variable pharmacokinetics and half-lives. Therefore, it should be discontinued 48-72 hours before the operation. Insulin use should be continued until the morning of the operation [12].

Acute and chronic complications due to DM should not be ignored during the preoperative evaluation. Patients should be investigated in detail for acute complications such as diabetic ketoacidosis, hyperosmolar nonketotic coma,

and chronic complications such as angiopathy, autonomic neuropathy and nephropathy. For this purpose, kidney function tests, serum electrolyte values, electrocardiography and cardiac performance tests should be evaluated [11]. In addition, the glycosylation caused by chronic hyperglycemia in tissue proteins may cause limitation in joint movements and thus intubation difficulties. In order to predetermine the risk, the temporomandibular joint and cervical joint movements should be evaluated with radiographs together with physical examination [13].

Cardiac autonomic neuropathy, which is a microvascular complication of diabetes, is held responsible for hemodynamic instability that may occur in conditions such as induction, laryngoscopy and intubation. In the preoperative period, the presence of resting tachycardia, exercise intolerance, orthostatic hypotension and silent ischemia should suggest cardiac autonomic neuropathy. In this case, diagnosis and treatment should be provided with hemodynamic monitoring [14].

Delayed gastric emptying without mechanical obstruction is gastroparesis. During anesthesia induction, symptoms such as nausea-vomiting, abdominal pain, bloating and early satiety should be questioned due to the risk of full stomach and aspiration. Metoclopramide and erythromycin can be used to increase motility [15].

The surgical preparation protocol recommended by the Turkish Society of Endocrinology and Metabolism for patients with type 1 and type 2 diabetes is shown in table 1[16].

Table 1. Preoperative Preparation Protocol in Patients with Type 1 and Type 2 Diabetes

In the preoperative period, glycemic control should be ensured.
For minor surgery, switch to short-acting agents if using a long-acting sulfonylurea.
For major surgery, he is hospitalized 2-3 days before the operation and switched to short-acting insulin in Type 2 DM.
The operation should be planned in the morning, if possible.
If minor surgery is to be performed in Type 2 DM who does not use insulin, the blood glucose level is determined every two hours on the day of the operation. Oral antidiabetic treatment is started from the meal after the intervention.
The patient should not have breakfast on the morning of the operation, and should not take oral sulfonylurea or insulin.

Glucose-insulin-potassium (GIC) infusion should be applied in all type 1 DM and in Type 2 DM where major surgical intervention will be performed.
GIK solution (*): It is prepared with 500ml 5% dextrose + 10 U short-acting insulin + 10 mMol potassium (1 ampoule of 7.5% KCL).
Infusion is started between 08:00 and 09:00 on the morning of the operation.
The infusion rate is set at 100ml/hour.
The solution is renewed every 6 hours
The infusion rate is adjusted so that the plasma glucose level detected every 1-2 hours is 100-125mg/dl (**).
GIC infusion is continued until the patient switches to oral feeding. If the infusion will continue for more than 24 hours, sodium and potassium control should be performed.
(*) GIK (glucose insulin potassium) solution can be prepared with 10% dextrose + 15 U insulin + 10mMol potassium (**) If the risk of hypoglycemia is high, the target plasma glucose level should be 120-180mg/dl.

2. Intraoperative Period

In patients with diabetes, the operation should be planned early in the morning, even as the first case if possible, in terms of the risk of hypoglycemia [17]. DM complications should be considered while determining the anesthetic agent and method [18]. Nephrotoxic agents should be avoided in patients with nephropathy, attention should be paid to fluid replacement, and diuresis should be followed closely. It should not be forgotten that the stomach may be full in patients with gastroparesis and prophylaxis should be questioned in terms of aspiration risk [19]. Intravenous anesthetic agents may be preferred in these patients, since it is known that inhalation agents theoretically have the potential to suppress the insulin response to glucose [20].

Although there is no definitive evidence that regional anesthesia reduces morbidity and mortality rates compared to general anesthesia, it is known to provide various advantages. Since the patients are awake, hypoglycemia can be detected earlier and there is no risk of difficult intubation due to limitation of joint movement. In addition, regional anesthesia reduces the catabolic response to surgery and the need for insulin. Oral feeding starts earlier. However, opioid use also reduces the risk of postoperative nausea and vomiting [20]. In terms of autonomic neuropathy, there is a risk of severe hypotension due to the sympathetic blockade of eppidural and spinal anesthesia. It has also been

reported that epidural and spinal anesthesia increase infective complications in these patients with susceptibility to infection [20]. Sterility should be given importance during the procedure in patients who are scheduled for regional anesthesia. Peripheral nerve blocks are not safe because of peripheral neuropathy. In addition, the local anesthetic agents used have a risk of causing toxicity [19].

It should be noted that regional anesthesia, especially spinal anesthesia, may increase morbidity in unregulated diabetic patients with autonomic or peripheral neuropathy [18,20].

The advantages and disadvantages of all anesthesia methods should be evaluated together and a decision should be made by considering the blood glucose levels, diabetes medications used, and diabetes complications for each patient.

There is a positive correlation between intraoperative mortality and intraoperative hyperglycemia [21]. The 2020 American Diabetes Association (ADA) Guidelines specify the acceptable perioperative blood glucose range as 80-180 mg dL, and recommend starting treatment when >180 mg/dL [22]. Acute lowering of blood glucose values in patients with uncontrolled DM may lead to hypoglycemic symptoms [23]. Hypoglycemic symptoms such as sweating, palpitations, unconsciousness, and brain damage are masked by anesthesia and may increase morbidity [24]. When hypoglycemia is detected, 50% dextrose 25-50 ml intravenously should be administered and frequent glucose monitoring should be performed. In cases where there is no vascular access, 1 mg of glucagon can be administered subcutaneously [23-25].

Subcutaneous (fast-acting) application in operations with unpredictable hemodynamic instability and major fluid shifts expected to last less than four hours; Intravenous insulin administration is preferred in operations that are expected to last longer than four hours and have hemodynamic fluctuations [26].

In the presence of hyperglycemia, GIC (glucose-insulin-potassium) infusion or a separate route infusion treatment method may be preferred. For GIC infusion, 500 ml of 10% dextrose fluid containing 15 U of regular insulin and 10 mmol potassium is used. It is started at a rate of 100 ml/h and the rate is adjusted according to the blood glucose value [3]. The application of recommended insulin dose regimens that minimize the risk of hypoglycemia is as in Table 2 [17].

Table 2. Glucose - Insulin - Potassium (GIC) Infusion Protocol

Blood glucose level (mg/dl) Infusion rate (ml/hour)	
>280 140	>280 140
279-220 120	279-220 120
219-180 100	219-180 100
179-120 80	179-120 80
119-80 60	119-80 60
<80 Infusion is interrupted for 2 hours	<80 Infusion is interrupted for 2 hours

In the separate route method, 500 ml of 5% dextrose is administered at a rate of 100 ml/h, 50 ml of 0.9% isotonic, containing 50 U of regular insulin, at a rate of 2-4 U/h, through two different intravenous routes [3]. In both methods, blood glucose level and electrolyte values should be closely monitored.

Nausea-vomiting should be avoided with caution in diabetic patients for whom nutrition is even more important. Dexamethasone, one of the antiemetics, increases the risk of hyperglycemia in a dose-dependent manner. The use of 4 mg dexamethasone or together with droperidol or 5-HT3 antagonists is recommended for prophylaxis of nausea and vomiting [15,23].

3. Postoperative Period

Close monitoring of blood glucose levels is very important in the postoperative period as well as in the preoperative and intraoperative period. Hyperglycemia increases the risk of infection as it may cause deterioration in collagen synthesis, decrease in wound tensile strength and neovascularization [23,27]. It is also known that intraoperative insulin resistance causes toxic effects on the myocardium, protein catabolism and delay in wound healing due to an increase in free fatty acids [28,29].

It is recommended to keep the postoperative blood glucose level between 140-180 mg/dl. The treatment protocol should be planned according to the prescribed times for oral feeding. Oral nutrition should be provided as soon as possible, and insulin-glucose infusion is continued until oral nutrition is provided in patients followed up with intravenous insulin therapy in the intraoperative period. Parenteral or enteral nutrition should be started in patients who cannot be started on oral nutrition [30].

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PART 17:

OBESITY AND ANESTHESIA

Tuğçehan SEZER AKMAN

Obesity is a global health problem that has increased in countries of all income levels, especially in recent years.[1,2] It is probable that the organization and costs of the health system will be affected substantially by the increase in the population of obese patients who will undergo emergency and/or elective surgery in the coming years.[1] Multifactorial diseases accompanying obesity increase the risk of perioperative complication development and mortality.[1] Special equipment, beds, chairs and operating room tables are required for obese patients [2]. Diagnostic, clinical and therapeutic evaluations of patients in this group should be optimized with a multidisciplinary approach in preoperative, intraoperative and postoperative periods.[1] The main problems that anesthesiologists may experience with obese patients are venous access difficulty, associated comorbid conditions, endotracheal intubation, and the risk of postoperative complications.[2]

1. OBESITY AND ANESTHESIA

1.1. Preoperative Evaluation

Health problems such as hyperlipidemia, type 2 diabetes, heart disease, hypertension, gastroesophageal reflux, respiratory problems, liver disease, obstructive sleep apnea (OSA) and stroke may accompany obesity.[3,4] Obesity-related comorbidities complicate intraoperative management and may complicate the postoperative period. Therefore, the history and clinical evaluation should help to understand the degree of functional impairment and determine which disorders (e.g., blood sugar, blood pressure regulation) can be improved by the physician.[3] The anesthesiologist should definitely consider these aspects in the preoperative evaluation.[3,4]

The drug use of patients and the drugs they use should be questioned well.[4] It is recommended to continue chronic medications until the day of surgery and then to start their postoperative use to prevent withdrawal. Oral hypoglycemic agents should be discontinued 1-2 days before the operation and restarted when patients continue to eat. Instead of long-acting insulin, a medium-acting form should be started 1-2 days before the surgery. Perioperative intravenous administration of glucose/insulin/potassium can be considered. Perioperative close blood glucose monitoring should be performed. The risk of infection, re-intervention and death increases in patients whose perioperative blood glucose levels exceed 180 mg/dl.[5]

The appearance of some physiological and inflammatory changes in obesity may complicate the perioperative period.[6] Morbidly obese patients do not have high mobility. Therefore, they may be asymptomatic even if they have significant cardiac or respiratory problems. Heart failure and OSA symptoms should be investigated carefully. Many patients cannot tolerate lying flat on their back and can sleep by sitting on the sofa. The patient's distress in the supine position may indicate respiratory distress, desaturation and airway obstruction that may occur during anesthesia.[7]

Neck circumference (collar size >17.5 inches), mallampati score, mouth opening which may help predict difficult airway, should be noted.[7] OSA affects 40-90% of obese patients. While most of the patients with severe obesity can maintain eucapnia, a few of them develop obesity hypoventilation syndrome (OHS).[6] OHS is characterized by alveolar hypoventilation (PaO_2<70 mmHg, $PaCO_2$>45 mmHg), obesity (BMI-Body Mass Index ≥30 kg/m2) and no associated respiratory system disease.[8] OSA may worsen the perioperative outcomes. OSA has been observed to be associated with a significant degree of venous thromboembolism, death, re-intervention and re-admission 30 days after discharge. However, preoperative intervention can fix this situation.[9] Snoring, apnea attacks, frequent stimulation during sleep, morning headaches, and daytime sleepiness of patients at risk of OSA should be questioned during the evaluation before bariatric surgery. Airway, nasopharyngeal characteristics, neck circumference and tongue size should bechecked in the physical examination. The STOP-BANG Questionnaire developed for surgical patients

with BMIs>30 can be used (Table 1). In scoring, a range of 0-3 indicates low risk, 4-5 medium risk and 6-8 high risk for OSA.[6,9]

Table 1. STOP-BANG Questionnaire

Snoring	**Do you snore loudly?**
Tired	Do you often feel sleepy and tired during the day?
Observed	Has anyone observed that your breathing stops or is interrupted during sleep?
Pressure	Do you have high blood pressure disease? Are you receiving treatment?
BMI	>35kg/m2
Age	>50
Neck Circumference	Shirt collar For men >17 inches/43 cm For women >16 inches/41 cm
Gender	Male

The American Society of Anesthesiologists (ASA) recommends initiating continuous positive airway pressure (CPAP) application perioperatively, especially if there is severe OSA.[9] If the patient has severe OSA or OHS, CPAP should ideally be initiated at least 4 weeks prior to surgery to alleviate the cardiometabolic effects of these diseases.[5] In patients who have previously received non-invasive positive pressure ventilation (NIPPV) or CPAP therapy, these treatments should be continued uninterruptedly in the postoperative period unless there is a contraindication.[9] NIPPV may be attempted if the patient does not respond adequately to CPAP.[5]

The approach to the patient should be 'personalized' and adapted to comorbidity and the type and urgency of the surgery. Electrolytes, liver and kiney function tests, complete blood count and glucose test are the basic tests in patients. Arterial blood gas analysis is useful when respiratory problems are suspected. Preoperative ECG should be used as a guide to perform a detailed cardiac examination of the patient and exclude diseases such as arrhythmias and cor pulmoale.[7]

Echocardiography can predict systolic and diastolic function and sizes of heart chambers. Evidence of heart failure can be evaluated with chest X-ray and

cardiothoracic ratio can be determined. Pulmonary function tests may reveal a patient's limiting defect, but they are not routinely applied to all patients. Young patients with good exercise tolerance and those close to the lower limit of the BMI range do not need testing unless there is a specific indication.[7]

The preoperative functional capacity (MET- metabolic equivalents) of the patient should definitely be questioned. If MET>4, the patient has a low cardiac risk. The complication rate (stroke, renal failure, venous thromboembolism, myocardial infarction, unstabil angina and death) was observed as 26.5% in patients with MET<4, who underwent bariatric surgery. This rate was 2.8% in those with MET>4. It can sometimes be difficult to evaluate functional capacity in patients with severe obesity since they also experience a limitation in moving.[6,10] Exercise ECG testing is not practical.[7]

Acid pH and residual stomach contents can often cause problems in obese patients. Proton pump inhibitors (PPIs), H2 receptor antagonists, prokinetic agents and antacids can be administered in the perioperative period. Ranitidine or a PPI can be given orally as routine prophylaxis in premedication. 0.3 M sodium citrate can be given to patients with severe reflux symptoms.[7]

Alcohol and tobacco use should be ceased at least 4 weeks before surgery. A study conducted on obese patients within a general surgery patient population showed that smoking cessation significantly reduced the overall risk of perioperative complications. Alcohol intake is an independent predictor for postoperative surgical site infection, sepsis/septic shock, pneumonia, delayed wound healing, and prolonged hospital stay.[5]

In obese patients, deterioration in fibrinolysis and chronic inflammation in the perioperative period, combined with stasis and immobilization, increase the incidence of postoperative thromboembolism.[6] Compression stockings of appropriate sizes and low-molecular-weight heparin should be used from entrance to the operating room to full postoperative mobilization. [6,7]

Especially in patients for whom bariatric surgery is planned, the psychosocial states of patients (depression, deterioration in social relations, etc.) should be evaluated. If the obese patient has a history of gastric bypass or other bariatric surgery that may lead to malabsorption, the patient may have a significant vitamin, iron, protein or calcium deficiency. Other tests may be needed to evaluate metabolic changes.[4]

1.2. Perioperative Management

Perioperative management of obese patients is complicated and requires the coordinated care of nurses, surgeons, anesthetists and other hospital personnel.[11]

The operating table must be resistant to weight. Most anesthesiologists prefer induction on the operating table. There should be an adequate number of well-equipped staff in the operating room to move the patient quickly and safely. A blood pressure cuff of the correct size for the patient should be used. A central venous route may be necessary since venous cannulation can sometimes be difficult. Invasive arterial monitorization can be employed in patient groups with rapid hemodynamic changes.[7]

Due to the decrease in functional residual capacity (FRC), long apnea periods cannot be tolerated, rapid desaturation develops, and preoxygenation may be less effective compared to other patients.[7,11] Especially the head position of the patient is extremely important before induction, and support under the shoulders (ramped technique) may be required. Tilting the head up may slow down the desaturation that may occur in the supine position.[7,11] After the induction of anesthesia in the supine position, the lung volume was revealed to decrease by 69%.[8] Tilting the head up between 25-40 degrees or the reverse Trendelenburg position is commonly used for intubation.[11] In morbidly obese patients, 20% better results were obtained with the administration of preoxygenation in the 25-degree head-up position compared to the supine position.[12] Furthermore, the head-up position prevents reflux and aspiration by preventing the abdominal content from rising to the diaphragm, increases FRC and prevents the occurrence of atelectasis.[11,12] Some publications suggest the use of 10 cm H2O CPAP before intubation to prevent the development of atelectasis.[11] Awake fiberoptic intubation is routine in many bariatric surgical procedures. This method should be taken into consideration in the patient who is hypoxemic at rest or has airway problems. In morbidly obese patients, awake intubation in a sitting or semi-recumbent position can be tolerated better than anesthesia induction in a supine position and endotracheal intubation under general anesthesia.[7]

Standard intubation can be administered in most obese patients, but obesity is an independent indicator for difficult mask ventilation and difficult laryngoscopy.[13] In fact, a high BMI does not directly predict laryngoscopy or intubation difficulty, but a large neck circumference (>40 cm) and a high

Mallampati score (>3) indicate the difficulty.[11] A polio handle and long blade may be needed depending on the head, neck and chest wall geometry.[7]

Effective temperature control reduces postoperative wound site infection. Attention should be paid to pressure areas to prevent wound formation and nerve injury. If pneumoperitoneum is going to be used, it should be remembered that static respiratory system compliance will decrease and there may be an increase in inspiratory resistance. Ventilation variables should be adjusted accordingly, and PEEP should be used to maintain oxygenation during controlled ventilation.[7]

In obese patients, monitoring the depth of anesthesia should be considered to abstain from accidental intraoperative awareness, particularly when total intravenous anesthesia is used or end-tidal anesthetic concentrations are not monitored during inhalation anesthesia.[5]

The use of short-acting anesthetic agents such as desflurane or sevoflurane, remifentanil enables rapid recovery from anesthesia and minimizes hypoventilation and hypoxemia. If neuromuscular blocking agents are going to be used, monitoring the neuromuscular block should be considered.[7]

The patient should be extubated while awake and obeying orders, after muscle strength and protective airway reflexes are restored. During extubation, the patient should be placed in the reverse Trendelenburg position.[11]

1.3. Postoperative Follow-up

Patients should be transferred to the appropriate postoperative unit after extubation and followed up continuously with pulse oximetry.[7,11] Where the patient will be taken care of after the surgery depends on the type, duration, and scope of the surgery and the individual evaluation of the patient. There is little evidence of an increased perioperative risk in patients who have no risk factors apart from obesity and have undergone minor surgeries. These patients can be taken care of in surgical wards. However, patients with obesity-related comorbidities are at higher risk of perioperative complications. Obese patients, who have undergone major surgeries or have a history of comorbidities, should be transferred to the appropriate 2nd- or 3rd-level postoperative care area.[7]

Some clinicians recommend administering oxygen support therapy for at least 24-48 hours after a major surgery.[19] Most morbidly obese patients have a CPAP device at home. In addition, patients with desaturation or significant sleep

apnea benefit from the use of CPAP after surgery. CPAP application following extubation may provide an advantage to the patient.[7]

The opioid drug group, which has a wide area of use, has an undesirable side-effect profile such as respiratory depression, nausea, and vomiting. Obesity is a specific disease type in which the use of opioids can complicate anesthesia management.[14,15] Especially in bariatric surgeries, opioid-free anesthesia protocols are used in intraoperative and postoperative periods, and patients are protected from the side effects of opioids.[16] NSAIDs are a part of the multimodal postoperative analgesic regimen. However, they should be used carefully since they may cause postoperative renal dysfunction.[7] A relationship has been observed between obesity and acute kidney injury in patients admitted to the intensive care unit in the postoperative period.[11] NSAIDs should not be preferred in obese patients with diabetic nephropathy or high intra-abdominal pressure (especially those undergoing laparoscopic surgery) because the risk of postoperative renal dysfunction is increased in these patients. Regional anesthesia, acetaminophen or patient-controlled opioid analgesia (PCA) are also useful. Since the volume of distribution of acetaminophen is largely limited to the central compartment in morbid obesity, it should be used in standard doses. However, clinicians should consider increasing the dosing frequency in cases when analgesia is problematic since its clearance increases.[7] IM injections should be avoided owing to unpredictable absorption.[7]

Postoperative fluid treatment can be complicated in obese surgical patients because the body fluid compartments are different. An average urine output of 1 ml/kg/h, based on lean body mass (LBM), is an indication of adequate fluid treatment.[11]

Surgical site infections are commonly observed in this patient group due to reasons such as inadequate antimicrobial dose, decreased tissue oxygenation/perfusion and obesity and diabetes-related immune dysfunction. The 2013 Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery recommended that the optimal time for initial antibiotic dose should be 60 minutes before incision and 120 minutes before for fluoroquinolones or vancomycin. Moreover, it is also recommended to use 3 g of cefazolin if the patient weighs over 120 kg and 2 g if the patient is taking cefoxitin or cefotaxime. [11]

If possible, patients should be mobilized early after surgery. Thus, the risk of venous thromboembolism and atelectasis can be reduced.[7] Even if perioperative prophylaxis is applied, the estimated deep vein thrombosis (DVT)

and pulmonary embolism (PE) incidences in obese patients range between 0.2% and 2.4%. A protocol consisting of intermittent pneumatic compression, compression stockings, lower extremity devices, and anticoagulant chemoprophylaxis is required to decrease the risk of DVT and PE.[8,11] There is no literature available on the routine use of vena cava filters in obese patients.[8] Oral anticoagulants (dabigatran, rivaroxaban) can be used without dose adjustment for patients with BMIs≤40 kg/m2. However, dose monitoring is recommended for patients with BMIs>40 kg/m2.[8] There are several protocols with respect to low-molecular-weight heparin (LMWH) dosing. The Association of Anaesthetists of Great Britain and Ireland recommended the use of 4000 IU/day enoxaparin or its equivalent if the patient weighed between 50-100 kg, 4000 IU twice a day if the patient weighed between 100-150 kg, and 6000 IU twice a day if the patient weighed over 150 kg for obesity and bariatric anesthesia. The European guidelines recommended a low dose of low-molecular-weight heparin (3000-4000 anti-Xa IU/12 hours subcutaneous) for obese patients at a low risk in terms of venous thromboembolism prophylaxis, and 4000-6000 anti-Xa IU/12 hours subcutaneous LMWH dose for patients at a higher risk. They underlined that higher doses of anticoagulants could be recommended for patients with BMIs over 40 kg/m2.[8]

In the postoperative period, glycemic control may be impaired due to the catabolic response and insulin may be needed to maintain normoglycemia. Thus, protection is provided against wound infections and infarction during periods of myocardial ischemia.[7]

1.4. Selection of Anesthesia and Regional Anesthesia in Obese Patients

If possible, loco-regional anesthesia should always be preferred to general anesthesia. If general anesthesia is required, easily reversible and fast-acting agents should be preferred for induction.[8]

In obese patients, a decrease in lung volumes is observed after surgery. After premedication, there is a linear inverse correlation between BMI and vital capacity, while there is a curvilinear inverse correlation with FRC. Most anesthesiologists consider perioperative epidural anesthesia a part of a multimodal approach to improve patient outcomes and analgesia and reduce systemic opioid use. The superiority of epidural anesthesia in obese patients has not been proven yet, but it can be planned in patients who have undergone major abdominal surgeries. In a study, when the groups receiving epidural

anesthesia and opioids were compared, it was observed that the group receiving epidural anesthesia had less decrease in their spirometric values and vital capacities in the postoperative period, and their lung volumes recovered earlier. However, the abdominal wall muscles, which will function in case of forced expiration, may be blocked in the presence of an epidural block.[7]

It can be difficult to identify cue points for spinal, epidural anesthesia or nerve blocks in morbidly obese patients [17]. Furthermore, practical difficulties may be experienced in epidural catheter placement in morbidly obese patients, and extra-long needles may be required [7]. The seventh cervical vertebra and gluteal cleft can be used to determine the midline in these patients. It becomes difficult to predict the fat infiltration of the epidural space and local anesthetic distribution caused by increased intra-abdominal pressure, and the use of lower doses (75-80% of a normal dose) may be required. Ultrasonography can be helpful in block applications.[17]

In obese patients, multimodal analgesia is required in general. Opioids, NSAIDs, acetaminophen and other local anesthetics (e.g., rectus sheath block or wound site infiltration) can be combined.[7]

1.5. Pharmacokinetics of Anesthetic Agents

There are uncertainties about whether the appropriate drug dose should be calculated according to ideal body weight (IBW), total body weight (TBW), or LBM in obese patients. The pharmacokinetics of most general anesthetics are influenced by adipose tissue mass and produce a less predictable but longer effect. The volume of the central compartment does not change substantially, but owing to changes in the volume of distribution (Vd), the doses of lipophilic and polar drugs need to be adjusted.[7] The volume of distribution of lipophilic drugs increases in obesity.[13] The increase in Vd prolongs the half-life of the elimination despite increased clearance. A significant increase is observed in the volume of distribution of drugs with high fat solubility (barbiturate, benzodiazepine, etc.). For such drugs, the dose calculation should be performed according to the IBW. For less fat-soluble drugs (e.g., some neuromuscular blockers), LBM (or IBW +20%) can be used in dose calculation.[7] The dose of succinylcholine should be calculated according to TBW.[7,18]

Sugammadex is mainly a hydrophilic molecule distributed in extracellular fluids. Final recommendations for sugammadex dose are to use IBW and then monitor the degree of neuromuscular blockade.[8]

The dosing of opioid group drugs such as remifentanil and fentanyl should be adjusted according to IBW or LBM.[13] When opiates are used for postoperative pain in PCA attention should be paid to using limited doses without baseline rate to limit the risk of respiratory depression. The recommendation for PCA is adjusting the opioid dose according to LBM.[11]

Propofol is highly fat-soluble but has an extremely high clearance. In a steady state, its volume of distribution and clearance are proportional to TBW.[7] However, it is recommended to be dosed according to LBM when used in the 'induction' phase and according to TBW when used for the maintenance of anesthesia with 'infusion'.[7,13]

In recent years, dexmedetomidine has drawn attention with its use in the intraoperative period in bariatric surgery, reducing the need for opioids and antiemetics and accelerating the recovery process. A study revealed an increased drug serum concentration when the dexmedetomidine dose was administered according to TBW. The reason for this is an increase in its Vd and a decrease in its clearance.[13]

Obesity is regarded as a condition that increases the significance of the fat-blood solubility coefficient. However, in a study conducted on morbidly obese patients undergoing elective surgery, no difference was detected between recovery profiles when desflurane and sevoflurane were titrated according to bispectral index.[19] Another study asserted that high BMI and prolonged use of sevoflurane delayed the return of airway reflexes. It was suggested that the contribution of high BMI to this delay was more evident after the use of sevoflurane instead of desflurane.[20]

In addition to pharmacokinetic changes in obese patients, there may be comorbidities able to change the final clinical effect of drug administration. If the patient has hepatosteatosis, changes may occur in hepatic metabolism and plasma protein binding that will affect clearance. Again, in patients with OSA, pharmacodynamic changes accompanying increased susceptibility to some sedatives may occur.[13]

Maximum local anesthetic doses recommended for infiltration should be calculated according to IBW. In block applications (epidural or subarachnoid), the doses of local anesthetic drugs should be reduced by 25%.[7]

1.6. Bariatric Surgery

Studies have suggested that an average of 10-15% weight loss is experienced via diet, lifestyle change, and pharmacotherapy. Bariatric surgery comes into prominence in patients for whom a higher rate of weight loss is

planned, but permanent outcomes cannot be ensured. Before deciding on surgery, patients should be followed up by the department of endocrinology for at least 6 months.[21] Appropriate patient selection, adequate preoperative and postoperative preparation, and a multidisciplinary approach are necessary.[21,22,23] If diseases accompanying obesity are detected in the preoperative period, cases for which bariatric surgery may be contraindicated will be determined, and morbidity and mortality rates can be reduced by preventing complications.[23]

Surgery is the last option for morbidly obese patients who could not achieve their goals despite trying other methods such as diet and exercise. Surgery is effective and safe, but there are risks as in any operation. Surgery is indicated by BMI≥40kg/m2 without the condition of obesity-related comorbidity presence, or BMI≥35 kg/m2, and at least one accompanying comorbidity such as obesity-related type 2 DM, hypertension dyslipidemia, sleep apnea syndrome.[21,24]

The obesity surgery mortality risk score was created to predict the risk of perioperative death in obese patients. This scoring system has 5 parameters: Male gender, BMI of 50 kg/m2 and above, hypertension, being 45 years and older, and increased susceptibility to pulmonary embolism (presence of thrombosis, etc.). According to this scale, the risk of death is predicted to be as high as 6-7 percent if it contains 4 or 5 parameters.[5]

There are many surgical procedures for obesity. Laparoscopic techniques are applied in surgery since they both shorten recovery time and are less invasive. Primary methods are sleeve gastrectomy, mini gastric bypass, gastric bypass, duodenal switch+biliopancreatic diversion and adjustable gastric band.[21]

After bariatric surgery, patients should be followed for at least 2 years by a team of dietitians, nurses and surgeons. Nutritional, hematological and biochemical parameters should be evaluated and psychologist support should be provided if necessary.[25]

In conclusion, obese patients are also frequently encountered in surgical procedures other than bariatric surgery. If the obese patient is evaluated in the preoperative period and risk classification is made, subsequent care can be optimized. In obese patients, preparation for possible difficult intubation should be made, careful hemodynamic monitoring should be performed and protective mechanical ventilation should be considered. The importance of starting physiotherapy and early mobilization in obese patients should not be forgotten in the postoperative period.

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PART 18:

ANESTHESIA MANAGEMENT IN PATIENTS WITH METABOLIC DISORDERS

İlter SOYTÜRK

Metabolic diseases often involve genetic factors. However, patients may be symptom-free for days, months, or even years. A stressor that affects metabolism can trigger the onset of symptoms. The onset of symptoms usually occurs when the body's metabolism is under stress. Congenital metabolic diseases are mostly genetically inherited diseases that develop as a result of disorders in the biochemical functions of the baby's body. There are many types of metabolic diseases and there are important considerations regarding perioperative anesthesia management.

1. DISORDERS OF CARBOHYDRATE METABOLISM

1.1. Galactosemia

Galactosemia is a congenital disorder of carbohydrate metabolism. Disorder of any of the galactose metabolizing enzymes is the cause. Galactokinase, galactose-1-phosphate uridilyltransferase (GALT) and UDP-galactose 4-epimerase are galactose metabolizing enzymes. Defects in these enzymes cause hypergalactosemia. GALT is the most common disorder in galactose metabolism and its deficiency causes the disease called classical galactosemia.

1.1.1. Hereditary Galactosemia

Accumulation of galactose-1-phosphate can damage the kidneys, liver, eyes and brain. It usually presents as a life-threatening disease in the first 2 weeks of life. In newborns, Escherichia coli (E. Coli) may present with sepsis, hypoglycemia, organomegaly, jaundice, vomiting, seizures, lethargy, irritability, feeding difficulty and insufficiency, cataract, vitreous hemorrhage, liver cirrhosis, ascites. Symptoms improve with a lactose-free diet. Galactosemia

caused by galactokinase or epimerase deficiency is more common and may even be asymptomatic.

Points to be considered in the preoperative evaluation; hepatic and renal dysfunction, impaired coagulation tests, hemolysis, E. Coli sepsis and albuminuria. Preoperative evaluation should include liver function tests, coagulation panel, complete blood count, and tests including basic metabolism.

During the operation; hemolysis and coagulation disorders make the patient at risk for anemia and bleeding. Albuminuria and osmotic diuresis make the patient's urine output unreliable in estimating intravascular volume. Hypotension and organ hypoperfusion should be avoided, and attention should be paid to agents toxic to the liver and kidney. Sterility rules should be observed in perioperative line placements and drug applications to prevent E.Coli sepsis[1,2].

Observation of the respiratory consequences of postoperative hypotonia is necessary. Hypotension may require aggressive treatment.

2. GLYCOGEN STORAGE DISEASES

Glycogen, a branched polysaccharide, is the main storage form of glucose. It is a complex polymer consisting of more than one chain of glucose molecules and is found in all cell types except erythrocytes. metabolism can synthesize glycogen from glucose or break down glycogen into glucose to optimize blood glucose level.

Glycogen storage diseases are a group of inherited diseases that affect glycogen metabolism regardless of gender. In each type of glycogen storage disease, there is a problem with one of the proteins involved in the synthesis or degradation of glycogen. Glycogen is most abundant in the liver and muscle, which are most affected by these disorders. Hepatomegaly and hypoglycemia are the most basic and first manifestations in the forms in which the liver is involved. In glycogen storage diseases with muscle involvement, muscle cramps, exercise intolerance, muscle weakness, easy fatigue and progressive weakness are the leading clinical findings. There are many subtypes of GSD. The most common type of GSD is type 1 (90%)[3].

2.1. Glycogen Storage Disease Type I (GSD I)

It is an autosomal disease caused by the deficiency of one of the proteins contained in the glucose-6-phosphatase complex, which is attached to the microsomal membrane. Glucose-6-phosphatase enzyme deficiency is

responsible for classical type Ia glycogen storage disease called von Gierke. The defective microsomal transport of glucose-6-phosphate is called Type Ib. Imperfect transport of phosphate is classified as Ic and defective transport of glucose as Id.

Among the clinical findings, abdominal distension, truncal obesity, round, stony face, hypotrophic muscles and growth retardation are the most common ones. Short stature is characteristic. Hypoglycemia and lactic acidosis may become evident during malnutrition, intercurrent infection, or skipping meals. Even if liver functions are impaired, the increase is mild and progression to cirrhosis is not expected. Adenoma may develop in the second or third decade of life. Splengaly is also not expected in type I, but it can happen in type Ib. Frequent and easy bleeding may occur due to platelet dysfunction. Xanthomas may be seen on the skin due to hypertriglyceridemia. In patients with hyperuricemia, gouty arthritis may develop. Neutropenia may develop before 1 year of age. Frequent and severe respiratory tract infections, abscesses and urinary tract infections can be seen. Inflammatory bowel disease, perianal infections and persistent diarrhea may accompany.

The aim of treatment is to prevent hypoglycemia as much as possible and thus to prevent metabolic problems that may develop secondary to hypoglycemia. Patients with GSD type I should avoid fructose, lactose, and sucrose in their diet because their metabolism cannot convert these sugars into glucose. In the treatment of GDH, raw corn starch is used to control blood sugar. Corn starch is not used in the treatment before the age of 1 because the amylase enzyme activity is not sufficient[4]. Liver transplantation is recommended in patients with multiple liver adenomas at risk of poor metabolic control or malignant transformation[5].

Anesthetic risks for von Gierke disease include lactic acidosis, hypoglycemia, and platelet dysfunction. Preoperative fasting should be minimized as much as possible. To maintain normoglycemia, intravenous glucose solution should be used. Preoperative hyperalimentation is beneficial in reducing liver glycogen stores. Preoperative tight glucose control; It also helps to keep bleeding times at normal values. Vasopressin (DDAVP) can be used to reduce perioperative platelet dysfunction and bleeding complications.

Intraoperative glucose level should be monitored. In order to keep the glucose level under control, the 10% dextrose infusion rate should be titrated and the glucose level should be kept within the normal range throughout the surgery. Intravenous dextrose infusion is necessary since the enteral feeding of

the patient cannot be started immediately in the postoperative follow-up of the patient. While using the Bispectral index (BIS) to monitor the depth of anesthesia, hypoglycemia should be kept in mind in the differential diagnosis in case of a decrease in BIS. In these patients, lactate cannot be completely converted to glucose. Therefore, the use of liquids containing lactate can cause lactic acidosis. Arterial cannulation facilitates blood pH and base deficit monitoring. Metabolic acidosis necessitates the administration of bicarbonate as an intravenous infusion. Respiratory alkalosis due to hyperventilation can cause lactate release from muscle tissue and metabolic acidosis[1,3,6].

2.2. Glycogen Storage Disease Type II

It is a glycogen storage disease caused by acid alpha-glucosidase enzyme deficiency. It is also known as Pompe disease. This deficiency leads to the accumulation of glycogen in the lysosome in all tissues. Stored glycogen is in normal structure. The clinical picture in Pompe disease varies widely as a result of the altered involvement of skeletal and cardiac muscle. Clinical findings in infantile-onset Pompe disease begin before 12 months. Hypertrophic cardiomyopathy is characterized by left ventricular outflow obstruction, hypotonia, macroglossia, and respiratory distress. Difficulty breathing, motor retardation, and feeding problems are common symptoms. It is fatal up to 1 year of age without enzyme replacement. Late-onset Pompe disease has milder symptoms and less cardiac involvement. Symptoms are associated with progressive skeletal muscle dysfunction. Enzyme replacement therapy is used in the treatment of Pompe disease.

Hypertrophic cardiomyopathy may be associated with left ventricular outflow tract obstruction (LVOT), and also glycogen accumulation in the conduction pathways may cause arrhythmias. Therefore, preoperative electrocardiography and echocardiography should be considered to evaluate both cardiac rhythm and function. If elective surgery is required, it should be considered after initiation of enzyme replacement therapy. In this way, the risk of LVOT and arrhythmia can be reduced. Increasing preload with perioperative hydration may reduce the risk of LVOT obstruction.

The presence of an arterial catheter provides an advantage for anesthetic drug titration in induction, blood pressure regulation and intraoperative blood pH and glucose monitoring. For the diagnosis of myocardial ischemia, ST segments should be followed with 5-lead ECG. Because patients may have diaphragmatic weakness, preoperative pulmonary function testing should be

requested. Regional anesthesia is safer in these patients. Difficult ventilation and intubation can be seen in the presence of macroglossia. Awake fiberoptic intubation may be considered in the presence of hypotonia. Myopathy makes patients more susceptible to nondepolarizing neuromuscular blockers and increases the risk of rhabdomyolysis and hyperkalemia. Therefore, succinylcholine should be avoided[1,7].

2.3. Glycogen Storage Disease Type III

It is also called Cori or Forbes disease. It is caused by amylo-1,6-glucosidase deficiency and is inherited in an autosomal recessive manner. Accumulation of an abnormal glycogen can cause both hepatic and myopathic symptoms. Hepatomegaly, short stature, hypoglycemia and hyperlipidemia, and high serum tansaminase levels are seen. With age, improvement in clinical findings and even disappearance around puberty can be expected in many patients with GDH type III.

Fasting hypoglycemia, ketosis, and hyperlipidemia are expected in infancy and older childhood. While serum transaminase levels are usually high in childhood, they return to normal values in adults. The blood lactate level is normal.

The aim of treatment is to prevent hypoglycemia and correct hyperlipidemia. Fasting causes hypoglycemia and ketosis. Since renal dysfunction is not expected, there is no need for fructose and galactose restriction in the diet. With increasing age, both clinical and biochemical abnormalities decrease and disappear. Adenoma may develop in the liver and transform into hepatocellular carcinoma. In these cases, a transplant is recommended.

Anesthesia management in type III GSD includes taking precautions against the risks of problems such as hypertrophic cardiomyopathy, arrhythmia, hepatomegaly, liver dysfunction, hypotonia, sensitivity to non-depolarizing muscle relaxants, and hypoglycemia. In these patients, macroglossia may develop as a result of glycogen accumulation in the tongue muscles. Tracheal aspiration, which may develop as a result of abdominal distention and gastroesophageal reflux due to hepatomegaly, poses a great risk for patients[3,8].

ECG and echocardiography should be used to evaluate preoperative cardiac functions. In these patients, macroglossia is an issue that should be

considered in airway management. The reverse trendelenburg position can be used to both facilitate the work of ventilation and reduce the risk of aspiration.

Liver function and coagulation tests can give an idea about the choice of anesthetic. Neuromuscular blockers should be chosen carefully because of hypotonia. Succinylcholine should not be used because of the risk of rhabdomyolysis and hyperkalemia. There is increased susceptibility to nondepolarizing neuromuscular blocking drugs and long-acting agents should be avoided.

Finally, hypoglycemia should be carefully managed and preoperative fasting should be limited. Preoperative initiation of intravenous dextrose infusion may be considered. Arterial blood pressure monitoring will both facilitate intraoperative blood glucose and pH level measurement and be a precaution against muscle cramps that may occur due to repetitive measurements of blood pressure cuffs[9,10].

2.4. Glycogen Storage Disease Type IV

Glycogen storage disease type IV, also known as Andersen's disease; It is inherited autosomal recessively and is seen in glycogen branching enzyme deficiency. Since glycogen branching is disrupted, it causes abnormal glycogen to be stored in the cell. Hepatosplenomegaly, growth retardation, and hypotonia can be seen in the infantile period. Fasting hypoglycemia is not typical unless liver cirrhosis is present. The adult form has a milder course and may present as a multisystemic disorder accompanied by myopathy or neurological involvement. Cardiac effects include dilated cardiomyopathy and congestive heart failure. There is no specific treatment method for GSD type IV and normoglycemia is aimed. Without cardiac and central nervous system involvement; however, for those with liver involvement, a liver transplant may be necessary[11].

Difficult airway risk is low in GSD type IV. It is necessary to evaluate the risk of bleeding due to preoperative hepatic dysfunction. Careful pre-operative evaluation and planning should be done to prepare for transfusion and administration of blood products. A hematology opinion can be made for support and advice. The status of neurological deficits should be reviewed with a careful preoperative evaluation. In order to prevent dehydration and hypoglycemia, the preoperative fasting period should be minimized and the required maintenance fluids should be started as soon as possible. Blood sugar regulation should be ensured. ECG, blood pressure, pulse oximetry, temperature

and end-tidal carbon dioxide monitoring should be performed even in all anesthesia procedures, including sedation. After the operation, it is necessary to continue with close monitoring[3,12].

2.5. Glycogen Storage Disease Type V

GDH type V, also called McArdle, is an autosomal recessive disease caused by a deficiency of the glycogen phosphorylase enzyme in the muscle. Muscle cramps, exercise intolerance, muscle weakness and rhabdomyolysis are seen. In continuous exercise, skeletal muscle cannot mobilize glycogen stores and exercise-induced cramps develop. Transient myoglobinuria and sometimes acute renal failure may occur due to rhabdomyolysis. There is no specific treatment for the disease, oral sucrose is used before exercise to prevent exercise intolerance[13].

In these patients who are sensitive to rhabdomyolysis and myoglobinuria; tremors or inappropriate positions can cause muscle ischemia and acute renal failure. Tourniquets should not be used and frequent automatic blood pressure measurements should be limited. It is important to maintain normothermia; In this way, the patient's tremor can be prevented. Forced diuresis can be applied to preserve kidney function. Perioperative dextrose infusion is necessary to prevent inadequate glucose and energy delivery and to supply the increased demand. Depolarizing muscle relaxants are not suitable for McArdle patients when general anesthesia is required. Drugs that can trigger rhabdomyolysis and malignant hyperthermia should be avoided. There is a weak link between McArdle's disease and malignant hyperthermia. Close blood glucose level monitoring and continuous dextrose infusion are recommended. Monitoring should include continuous measurement of body temperature as well as ECG, blood pressure, pulse oximetry, and capnography in ventilated patients. It is necessary to continue the follow-up in terms of postoperative malignant hyperthermia[1,3,14,15].

3. DISORDERS OF AMINO ACID METABOLISM

3.1. Homocysteinemia

Homocysteinemia is a methionine metabolism disorder that occurs due to the deficiency of cystathionine β-synthase, an enzyme involved in the formation of cysteine from methionine via homocysteine. Clinical findings such as mental retardation, ectopia lentis and thrombosis may be detected.

Antiplatelet and anticoagulant applications should be continued before and after the operation, and drugs that increase the patient's coagulation status (eg, oral contraceptives) should be discontinued. In this way, the risk of thromboembolism is tried to be reduced. The preoperative fasting period should be under control with fluids containing dextrose. Echocardiography and electrocardiography should be performed in these patients to rule out any cardiac abnormalities. Since high arched palate and Marfanoid habitus can be found, it is necessary to be careful in terms of difficult intubation. Conditions such as mental retardation or lack of cooperation make general anesthesia mandatory. In addition, regional anesthesia carries a risk of thromboembolic events as it may promote peripheral vascular stasis due to sympathetic blockade. In the intraoperative period, it should be aimed to avoid hypovolemia and protect cardiac output, reduce peripheral vascular resistance and improve peripheral perfusion. Venodins should be administered to prevent peripheral stagnation of blood. Blood sugar monitoring is required. Nitrous oxide increases homocysteine levels by preventing the conversion of homocysteine to methionine. Therefore, the use of nitrous oxide as an anesthetic is not recommended in patients with hyperhomocysteinemia. Early ambulation is encouraged after surgery. Patients with homocystinuria are prone to spontaneous thromboembolic phenomena. Serious complications of thromboembolism include optic atrophy, hemiparesis, hypertension due to renal infarction, focal seizures, and fatal pulmonary embolism. In addition, strict glucose monitoring and early initiation of antiplatelet and anticoagulants after consultation with the surgical team are issues to be considered after surgery[1,16,17].

3.2. Phenylketonuria

Phenylketonuria (PKU) is a rare, familial metabolic disease. Phenylalanine (Phe) in protein foods cannot be metabolized in the liver due to deficiency of the phenylalanine hydroxylase enzyme or the cofactor tetrahydrobiopterin. Phenylalanine, which accumulates excessively in the blood, competes with other amino acids to cross the blood-brain barrier, thus reducing some essential metabolites in the brain. It also impairs the absorption of other amino acids from the gastrointestinal tract (GIST) and kidneys, and as a result, other amino acids along with tyrosine are reduced in body fluids.

The main affected system in PKU is the central nervous system. Microcephaly, hyperreflexia, hypertonia, seizure, mousy odor, mental

retardation are clinical findings. Skin disorders such as eczema and seborrheic rash may occur. In some cases, severe vomiting resembling infantile pyloric stenosis is encountered.

PKU treatment basically involves restriction of Phe in dietary intake. Pharmacological treatments include tetrahydrobiopterin, long chain polyunsaturated fatty acids, pegylated phenylalanine ammonia lyase, and large neutral amino acids.

In the preoperative evaluation of these patients, the stability of the metabolic status of the patient should be learned by consulting the relevant pediatrician or neurology specialist, as well as the general examination. It is important that the blood Phe level is within the targeted range. Oral intake should not be stopped for a long time before surgery in patients with PKU. In catabolic conditions, the blood Phe level rises. Cardiovascular status and renal function of patients should be evaluated before surgery. Dietary proteinuria and decreased glomerular filtration may be present. Preoperative intravenous continuous administration of dextrose is appropriate. Nitrous oxide, which inactivates B12-dependent methionine synthase, is not a good choice. Although gelatin-based colloids are excreted in the urine without being metabolized, they are a potential source of Phe and should be used with caution. Due to the increased skin sensitivity and risk of eczema, it is necessary to be careful in skin and mucous membrane contacts. Chronic use of L-dopa may cause orthostatic hypotension and reduce sensitivity to indirect vasopressors such as ephedrine. Therefore, direct vasopressors may be a better option in case of hypotension. Dopamine antagonists such as metoclopramide should be avoided. Due to its monoaminergic mechanism of action, the use of tramadol in PKU patients should be avoided. Intraoperative blood glucose and sodium levels should be monitored. It should be noted that blood in GIST is a source of Phe. Postoperative patients should be administered iv electrolytic solution containing glucose unless they return to their normal diet[1,18,19].

Synthesis of catecholamines may be decreased in PKU patients due to the absence of tyrosine. A case of bronchospasm after endotracheal intubation with an induction using propofol, fentanyl and vecuronium was reported in a 10-year-old patient with phenylketonuria. They concluded that bronchospasm was associated with catecholamine deficiency induced by phenylketonuria[18].

As in the propofol infusion syndrome; Phenylalanine also inhibits mitochondrial complex I. So, the use of propofol in patients with PKU may increase the risk of hyperthermia and acidosis.[1,20]

3.3. Maple Syrup Urine Disease

MSUD is an autosomal recessive inherited metabolic disease caused by a deficiency in the mitochondrial branched chain α-ketoacid dehydrogenase complex. The body cannot properly convert the three amino acids (leucine, isoleucine, and valine) known as branched-chain amino acids (BCAA) into other substances. The accumulation of leucine and α-ketoisocaproic acid leads to conditions such as hypotonia, hypoglycemia, ketoacidosis, seizures, coma, sweet smell of uri.

Acute metabolic and neurological disorders should be managed in the treatment of MSUD and a strict semi-synthetic diet should be given to limit lifelong BCAA intake to reduce the accumulation of toxic metabolites. The aim of treatment is to remove branched-chain amino acids and their products and metabolites from tissues. Peritoneal dialysis is the most effective treatment in decompensated cases. The long-term approach is a lifelong low-protein diet with restriction of branched-chain amino acids. If nutritional therapy is started early, neurological damage is minimized. Decompensation can occur in any situation involving a catabolic process such as starvation, illness or exercise. If these patients are not treated, they may progress to severe ketoacidosis, hypoglycemia, and even cerebral edema.

Even minor surgical procedures of patients with MSUD should be performed in centers with expertise and experience in the treatment of these patients. It is prudent to schedule it as the first case of the day and to minimize the operative fasting time as much as possible. If there is acidosis and dehydration, it is important to correct it using intravenous fluids before surgery. The target is normovolaemia because the fluid regimen used can cause severe hydration, increased intracranial pressure, and cerebral edema. Catabolic states cause branched-chain amino acids to reach a toxic level and trigger an episode of hypoglycemia. The use of hypertonic glucose solutions may create an additional stress factor. Applications that increase intracranial pressure should be avoided. The accumulation of blood in the stomach leads to a protein load and may cause metabolic decompensation. For procedures that carry this risk, patients should have an intraoperative nasogastric tube placed. Intraoperative blood gas monitoring and pH and glucose monitoring are appropriate. Continuation of intravenous dextrose infusion is necessary to avoid catabolic process in postoperative patient follow-ups[21-23].

4. ORGANIC ACIDEMIAS

Organic acidemia is an autosomal recessive group of inherited metabolic diseases that can be life-threatening in newborns due to the accumulation of organic acids in body fluids due to various enzyme deficiencies. As a result of the deficiency of enzymes involved in amino acid catabolism, organic acids that appear as intermediate metabolites in physiological events accumulate and affect the acid-base balance and intracellular biochemical and metabolic pathways. The main ones of this disease group are; propionic acidemia (PA), methylmalonic acidemia (MMA), isovaleric acidemia and glutaric aciduria. PA and MMA are among the more common organic acidemias.

PA and MA result from defects in the metabolic pathways of some specific amino acids, single-chain fatty acids, and cholesterol side chains. Metabolic acidosis attacks in patients with PA or MMA are usually due to a stress factor or excessive protein intake. In newborns, tachypnea, lethargy, feeding problem, vomiting, muscle hypotonia, lethargy are observed after a few days or weeks of well-being after birth. Laboratory findings that may be observed in patients during acute metabolic crisis are hypoglycemia, hypocalcemia, increased anion gap metabolic acidosis, ketonuria, hyperammonemia and increased lactate levels. In the following periods, growth retardation, vomiting, seizure, developmental delay, hypotonia and encephalopathy can be seen in the patients. Cardiac involvement is more common in propionic acidemia. Renal failure is more common in patients with MA.

The diet of patients with PA and MMA should contain low protein. In individuals with organic acidemia, the intake of isoleucine, leucine, threonine and methionine is limited. L-carnitine and bicarbonate supplementation is applied. Prolonged starvation should be avoided. Vitamin B12 supplementation is also necessary in MMA patients. In addition, supportive treatments include fluids with dextrose, carnitine, bicarbonate, and cobalamin. Some patients may require hemodialysis[24].

Early admission to hospital before the operation; suitable for the implementation of treatment strategies. Preoperative blood pH and ammonia level should be examined. The patient's mental status, nutritional status, and muscle tone should be examined. Metabolic acidosis/hyperammonemia is a sign of decompensated disease and is indicative of the timing of elective surgery. Preoperative echocardiography and 12-lead electrocardiogram should be seen. Diffuse dilatation of the heart chambers, hypokinetic left ventricle, thickening of the ventricular walls and prolonged QTc can be detected. Pre-operative

medications may include L-carnitine, metronidazole, B12, MMA, and bicarbonate. In procedures requiring anesthesia, the duration of NPO should be minimized and intravenous fluids containing dextrose should be given during this period. Axial hypotonia; may cause weakening of the cough reflex and the development of perioperative atelectasis[25].

Patients with MMA may be pancytopenic as a result of bone marrow suppression. This may require a transfusion depending on the surgery performed. Organic acidemias are not associated with thrombosis or the need for anticoagulation[3].

Intraoperative strict blood glucose and temperature monitoring is required. The patient's oxygenation and fluid balance should be well adjusted. These patients have a higher risk of vomiting and tracheal aspiration due to GERD, and RSI and nasogastric tube application are prudent. The catabolic state is avoided by maintaining hemodynamic stability. Periodic serum glucose monitoring is recommended. Adequate depth of anesthesia and analgesia should be provided to avoid surgical stress. Caution should be exercised in the use of muscle relaxants (succinylcholine, cisatracurium, and mivacurium), which may cause hyperkalemia in myopathic conditions or are metabolized to single-chain organic acids by ester hydrolysis in patients with PA and MMA. Use of short-acting muscle relaxants; is more cautious about respiratory complications. Among the non-steroidal anti-inflammatory drugs, some are derived from propionic acid. Examples of these drugs are naproxen, ketoprofen, fenoprofen, ibuprofen, flurbiprofen and oxaprozin. Since nitrous oxide has a role in cobalamin synthesis-related enzyme inhibition, it is not suitable for use in MMA patients. There are no contraindications for the use of volatile agents in patients. However; opioids or volatile anesthetics should be used with caution in patients with hypotonia. The unsaturated lipids contained in propofol are metabolized to propionic acid. Therefore, it is recommended to use propofol with extreme caution in long-term surgery or severe traumatic cases. There is a theoretical concern with the use of lactate-containing fluids, but a recent study did not show an association between the use of Ringer's Lactate and metabolic decompensation[26,27].

In case of any delay in recovery from anesthesia, blood gases, glucose, electrolytes and ammonia levels should be controlled.

With regional anesthesia, the use of drugs that are identified as risky can be limited, however, local anesthetic systemic toxicity (LAST) may become more

serious in patients with MMA or PA. Furthermore, the efficacy of intralipid for salvage is uncertain if LAST develops in a patient with organic acidemia[28].

Postoperatively, patients should be observed for signs of clinical deterioration or respiratory failure. Intravenous fluids should be continued until the patient tolerates enteral feeding, or TPN should be continued if TPN-dependent. Monitoring of acid-base status and glucose is necessary to detect decompensation[1].

5. MITOCHONDRIAL DISORDERS

The primary cause of mitochondrial disorders (MD's) is dysfunction of the oxidative phosphorylation system. Tissues and organs that are highly dependent on aerobic metabolism are the systems most affected in mitochondrial disorders. The transfer of fatty acids to the mitochondrial matrix occurs by the enzyme acylcarnitine transferase. Irregularities in fatty acid metabolic pathways constitute the main category of mitochondrial disorders.

Patients with mitochondrial disorders may be diagnosed in infancy or early childhood. These patients may have myopathy, dystonia, cardiomyopathy, arrhythmia, metabolic disorders, encephalopathy, seizures, renal failure, and gastrointestinal dysfunction.

Pediatric patients with MD often require general anesthesia for surgical procedures. General anesthetic drugs also add an additional depressive load to the insufficiency such as respiratory failure, cardiac depression, conduction defects or dysphagia in these patients. Concomitant diseases; is the main determinant for the choice of anesthetic drug. While the use of benzodiazepines may be limited in patients with respiratory failure or liver dysfunction, some patients may already be taking benzodiazepines for various indications.

In the pre-anesthesia evaluation, a careful history and physical examination should be performed to evaluate for possible problems such as cardiac arrhythmias, cardiomyopathy, hypotonia and seizures. Blood tests such as glucose, hemogram, electrolytes, liver function tests, coagulation parameters, lactate, creatinine kinase should be examined in detail. A detailed electrocardiogram should be performed to diagnose possible conduction abnormalities in the heart. In order not to increase the risk of hypoglycemia, the preoperative fasting period should be kept short and the patient should be supported with intravenous continuous dextrose during this period.

Existing myotonia may complicate the work in patients with respiratory failure. Glucose-containing intravenous fluids are not suitable for patients with

epilepsy who are on a ketogenic diet. In these patients, lower doses of general/local anesthetics, sedatives, analgesics and muscle relaxants are usually sufficient to reach the targeted awareness.

Most general anesthetics suppress mitochondrial function. Fatty acid metabolism defects do not appear to alter susceptibility to volatile anesthetic drugs. However, acylcarnitine transferase defects may increase bupivacaine cardiotoxicity and the risk of ventricular arrhythmias[29].

Propofol inhibits mitochondrial respiratory chain and acylcarnitine transferase; since it may cause propofol infusion syndrome, it limits its long-term use. Opioid sparing techniques with remifentanil and dexmedetomidine involve less risk. Succinylcholine; it should not be used because of the risk of developing severe hyperkalemia. Patients with MD may not be able to metabolize lactate normally; therefore, intravenous fluids containing lactate should be avoided. Autonomic maintenance of body temperature is impaired in mitochondrial disease. Therefore, strict control of body temperature is necessary. In addition, post-operative tremor increases the energy requirement and puts the metabolic balance at risk. It is recommended that intravenous fluids be warmed to body temperature. Minimizing the use of tourniquets, providing adequate analgesia and preventing postoperative nausea and vomiting; These are effective methods that can reduce the risk of metabolic decompensation in these patients[1].

The use of remifentanil is wise as it is rapidly metabolized by serum cholinesterases. Non-opioid analgesics can be used safely, as can non-steroidal anti-inflammatory drugs.

Patients should be kept under close observation for postoperative respiratory complications. Postoperative infection is likely due to low hepatic mitochondrial activity. Prolonged immobilization should be avoided[1,29,30,31].

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PART 19:

ANESTHESIA MANAGEMENT IN PITUITARY DISORDERS

Elif Kaya ARGADAL

1. INTRODUCTION

The pituitary gland is located within sella turcica (also known as the pituitary fossa) which is located (which takes place) at the base of the skull. It is found adjacent to the cavernous sinus containing the carotid artery and some of its branches, as well as the cranial nerves III, IV, VI and the optic chiasm.

It consists of two distinct lobes that develop from different embryonic origins. The frontal lobe contains five different cell types that secrete different hormones as well as non-functional "null" cells. The posterior lobe stores and releases vasopressin and oxytocin produced by the hypothalamus. The table below enumarates the different types of cells of the pituitary cells, along with its secreted hormones, and their respective effects

Cells	Hormones	Clinical Outcome and Disease
Somatotrophic	Growth Hormone (GH)	Stimulates bone and cartilage growing, increases protein synthesis and lipolysis, Acromegaly
Laktotrophic	Prolactine	Secretes breastmilk, Prolactinoma
Corticotrophic	Adrenocorticotrophic Hormone (ACTH)	Increases serum cortisol levels, Cushing's disease
Thyrotrophic	Thyroid Stimulating Hormone (TSH)	Increases triiodothyronine and thyroxine synthesis, Hyperthyroidism
Gonadotrophic	Follicle Stimulating Hormone (FSH), Luteinising Hormone (LH)	Maturation of the ovarian follicles Ovulation and spermatogenesis, Policystic Ovary Syndrome(PCOS)

Table 1: The Cell Types of Anterior Lobe, The Hormenes Secreted by the Cells and Their Clinical Effects

The most common lesion of the pituitary gland is the adenome, a benign neoplasm, that originates primarily from the anterior pituitary gland. Pituitary tumors accounts for approximately 10% of intracranial tumors. It commonly occurs between 30-50 years of age. It incidence is increased by multiple endocrine adenomatosis and multiple endocrine neoplasms[1]. Adenomas smaller than 1cm, are named microadenome and those greater than 1cm, bare the name macroadenome. Clinical signs present as a result of hormonal abnormalities and mass effect of the tumor. Functional adenomes lead to hormonal abnormalities such as prolactinoma, Cushing's disease, acromegaly, hyperthyroidism, infertility. Macroadenomes and non-functional adenomes can apply pressure on the optic chiasm and oculomotor nerve resulting in visual field disorders. In addition, the tumor can block the cerebrospinal liquid (CSL) accumulating it resulting in increasing intracranial pressure (ICP) causing the follwing symptomes: headache, neusea and vomiting, rhinorrhea, impaired sense of smell;

2. PREOPERATIVE MANAGEMENT

Patients who have pituitary disorders can urdergo surgery for the pituitary gland, but also related to other organ dysfunctions. In both cases, the anesthesiologist should focus on the hormonal abnormalities, increased ICP and airway management related to structural disorders found in specific pituitary disease, in addition to the standart preanesthetic examination.

2.1. Specific Pituitary Disorders

2.1.1. Prolactinoma

Prolactine is a hormone syntesized and secreted by the lactotrophic cells which are located in the anterior lobe of pituitary gland, and whom are respocsible for milk production. Causes of increased prolactine levels can be the following:

- Pregnancy and lactation (as physiological)
- Hyphotalamopituitary diseases
- Systemic disorders that effects pituitary gland
- Pharmacological (anesthetic agents, anticonvulsant drugs, antidepressant drugs, cholinergic agonists, dopamine antagonist drugs, antipsycotics, opioid drugs...)

Dopamine inhibates the secretion of prolactine. The follwing medications (bromocriptine, cabergoline) are the priority approach to the prolactinomas.

Dopamine agonist drugs can cause neusea, vomit, dizziness, constipation, dry mouth, orthostatic hypotension. Moreover these drugs stimulate fibroblasts by using seretonine receptors and causing fribrosis in heart, lungs and retroperitoneal area. Therefore, patients undergoing dopamine agonist drugs for a long term or elderly patients should be further investigated regarding heart disease (valvulopathy. etc.) and undergo ecocardyography.[2]

2.1.2. Cushing's Disease

Cushing's disease can occur from an adenome originating corticotrophic cells, presenting increased serum cortisol levels. İt has a multi organs and multisystemic affection: Hypertension, left ventricule hypertrophy, congestive heart failure, electrocardyography findings as dysrhythmia, long QT period, central obesity, obstructive sleep apnea, diabetes mellitus, hypokalemia, hypernatremia, osteoporosis, delayed wound healing, thin skin, ecchymosis.[3] Antihypertensive drugs other than angiotensin converting enzyme(ACE) inhibitors and angiotensin II receptor blockers, should be continued until the day of surgery. Drugs inhibating glucocorticoid synthesis and secretion (ketoconazole, metyrapone, mitotane, aminoglutethimide), should be continued until the day of surgery and stopped postoperatively. The anesthesiologyst should be careful about difficult airway and decreased respiratory functions due to obesity and sleep apnea. Preoperative pulmonary function tests are a useful preditor in postoperative respiratory failure, especially in obese patients.

2.1.3. Acromegaly

Acromegaly is a chronic disease caused by increased secretion of growth hormone (GH). Clinical findings include acral enlargement, coarsening of face, headache, macroglossia, increased sweating, arthralgia, skin thickening and snoring.[2] Upper airway changes are an important point in patients with acromegaly. Malocclusion, prognatism, hypertrophy of airway soft tissues, narrowing of the glottic space can result in difficult airway management. Mallampati score, upper lip bite test, thyro-mental distance and the imaging techniques (lateral skull x-ray, CT) can be usefull prédictors in difficult airway management. [4,5] Nevertheless, the anesthesiologist should be prepared for videoscopic laryngoscopic intubation, fiberoptic bronchoscopic intubation, tracheotomy for unexpected difficult airway. [6] Obstructive sleep apnea syndrome (OSAS) is present in 70% of acromegalic patients. Cardiac complications such as left ventricule hyperthrophy, interstitial myocardial fibrosis, cardiomyopathy, coronary artery diseases, cardiac ryhthm disorders may occur in patients with untreated acromegaly. ST segment depression, T

wave abnormalities are common ECG findings in these patients. Diabetes mellitus and thyroid gland neoplasm may accompany acromegaly.

2.1.4. TSH Secreting Adenomes

Adenomas secreting TSH progress showing signs of hyperthyroidism. Detection of normal or high level of TSH when free thyroid hormones (fT3, fT4) are high, point out the cause of hyperthyroidism to be a lesion originating pituitary gland. Primary treatment is surgery.

2.1.5. Non-functional Adenomas

Symptoms often occur due to the mass effect of the adenome; increased ICP, headache, rhinorrhea, visual area defect, impaired sense of smell. The treatment of the tumors is surgical

2.1.6. Craniopharyngioma

Craniopharyngioma is an embryonal epithelial benign tumor of the hypothalomo-pituitary region. Signs of increased ICP, signs of hypopituitarism, diabetes incipidus, hyperphagia, impaired body temperature regulation, behavioral disorders, cognitive disorders, optic chiasm and optic nerve compression can be seen. The first option of treatment is surgery.

2.1.7. Hypopituitarism

Hypopituitarism is the clinical condition that occurs when one or more pituitary hormones are insufficient. The disease can be either genetical or aquired, from traumatic situations, benign or malign neoplasms, pregnancy, diabetes, hypotension, infective diseases, infiltrative diseases (sarcoidosis, histiocytosis X, Wegener granulomatosis, Takayasu disease). Its clinical findings develop due to the deficiency of the relevant pituitary hormone.

2.1.8. Central Diabetes Incipidus

Diabetes incipidus develops due to insufficient secretion of vasopressine, causing polyuria and polydipsia. The anesthesiologist should be careful in these patient about dehydratation and electrolyte imbalance. It may occur due to congenital disorder, trauma, post-surgical, ischemic/hemorrhagic cerebral disorders, neoplasm, infiltrative diseases. Desmopressine is the treatement of choice

2.2. Perioperative Steroid Replacement

In patients recieving glucocorticoid treatment (prednisolone 5mg/day and longer than 4 weeks term of treatment), the hypothalamo-pituitary-adrenal axis can be supressed. Further, all patients who will be opereted for elective pituitary surgery will require hydrocortison replacement during anesthesia

induction and 24 hours after surgery. The dose to be administrated may vary according to the clinician. The tbales below shows the racomentade dosage for steroids (Table 2,3)[7]:

Intraoperative Steroid Replacement	Postoperative Steroid Replacement
Hydrocortisone 100 mg iv on induction, followed by immidiate initiation of a continious infusion of hydrocortisone 200mg/24h	Hydrocortisone 200 mg/24 h by i.v. infusion while nil by mouth or for patients with postoperative vomiting (alternatively, hydrocortisone 50 mg every 6 h by i.m. injection) Resume enteral – double hydrocortisone doses for 48 h or for up to a week following major surgery With rapid recovery Resume enteral – double hydrocortisone doses for 24 h

Table 2: Recommended doses for intra and postoperative steroid cover in adults with primary and secondary adrenal insufficiency

	Intraoperative Steroid Replacement	Postoperative Steroid Replacement
Major surgery	Hydrocortisone 100 mg intravenously at induction, followed by immediate initiation of a continuous infusion of hydrocortisone at 200 mg/24 h; Alternatively, dexamethasone 6–8 mg intravenously, if used, will suffice for 24 h	Hydrocortisone 200 mg/24 h by i.v. infusion while nil by mouth (alternatively, hydrocortisone 50 mg every 6 h by i.m. injection) Resume enteral glucocorticoid at double the pre-surgical therapeutic dose for 48 h if recovery is uncomplicated. Otherwise continue double oral dose for up to a week
Intermediate Surgery	Hydrocortisone 100 mg, intravenously at induction, followed by immediate initiation of a continuous infusion of hydrocortisone 200 mg.24 h^{-1} Alternatively, dexamethasone 6–8 mg intravenously, if used, will suffice for 24 h	Double regular glucocorticoid dose for 48 h, then continue usual treatment dose if uncomplicated

Table 3: Recommended doses for intra and postoperative steroid cover in adults receiving adrenosuppresive doses of steroids (prednisolone equivalent ≥ 5 mg for 4 weeks or longer)

2.3. Preoperative Thyroid Hormone Control

Thyrotropic pituitary adenomes are invasive tumors with the potential for blood loss and respond to medical therapy. For these reasons, thyroid hormone abnormalities should be treated before the elective pituitary surgery.

3. INTRA-OPERATIVE MANAGEMENT

3.1. Surgical Procedure

3.1.1. Transsphenoidal Pituitary Surgery

Transsphenoidal surgery is the usually prefered methode to an extra-arachnoid approach. Microadenomes, macroadenomes that do not exceeding the sella limits, in patients who have rhinorrhea, with tumors growing trough the sphenoidal sinus are treated with this thechnique. The possible complications of this approach are hormonal abnormalities, secondary empty sella syndrome (visual disorders), hydrocephaly with coma, infection, cerebrospinal liquis leak, rhinorrhea, carotis artery rupture, nasal septal perforation.

3.1.2. Transcranial Pituitary Surgery

Although the transsphenoidal approach is often the prefered method of intervention, in some cases such as large suprasellar masses that enlarge the sella, with possible extrasellar extension to the middle fossa, conditions that may complicate transsphenoidal intervention such as parasellar aneurysm, ın the precence of a tumor that could not be completely removed by previous transsphenoidal surgery or in the case of recurrence; transcranial approaches may be preferred. The incidence of trauma in the adjacent structures, (frontal lobe ischemia, postoperative anosmia, and seizures) is higher in this approach.

3.2. Anesthetic Procedure

3.2.1. Airway Management

Patients undergoing pituitary surgery have the likelyhood of difficult airway. Both in Acromegaly and Cushing's disease, expanded soft tissue, large tongue and other upper airway structures, obesity can make airway management hard, or even fail[8,9]. The anesthesiologist should consider the awake fiberoptic bronchoscopic intubation option, in case of predictive difficult airway and be prepared for videoscopic laryngoscopic intubation or fiberoptic bronchoscopic intubation, tracheotomy for unexpected difficult airway.

Spiral endotracheal tubes may be preferred in order to prevent bending during the surgery. Preoperatively nasal decongestant spray and nasal

administration of lidocaine/cocaine/ epinephrine for surgical site preperation cna be used.

Before extubation, we should ensured that all blood that has accumulated in the surgical area is aspirated and that garses are removed.

3.2.2. Anesthetic Agents and Induction

There are no specific recommendations for the anesthetic manegement of patients with pituitary disease at induction. Etomidate can be preffered in Cushing's surgeries as it will block cortisol synthesis for anesthesia induction[10].

3.2.3. Monitoring

Non-invasive blood pressure, temperature, CO_2, pulse oximetry, ECG monitoring should be performed as standart monitoring. Large scale peripheric venousus accesses should be placed. In patients who have cardiovasculary disease or Cushing's disease invasive arterial blood pressure should be monitored. Central venous pressure should be monitored in patients who have cardiopulmonary comorbitities.

Invasive arterial blood pressure and intracranial pressure should be measured continuously during neuroendoscopies to detect early intraoperative cerebral ischemia instead of waiting for the appearance of bradycardia which may be late sign[11].

3.2.4. Anesthesia Maintenance

Both intravenous and volatile anesthetics may be preferred for anesthesia maintenance during pituitary surgery. However, the use of propofol has been shown to be more successful in providing hemodynamic stability compared to volatile anesthetics[12]. In the literature, there are studies in which dexmedetomidine infusion was applied to reduce hemodynamic instability in transsphenoidal pituitary surgeries. In these studies, it has been shown that the administration of dexmedetomidine infusion both provides stability in hemodynamics and contributes to early postoperative recovery by reducing the need for intraoperative propofol, fentanyl and sevoflurane. It has also been shown that there is a decrease in the need for postoperative analgesics[13]. Compared to fentanyl for intraoperative analgesia, remifentanil has been shown to provide better hemodynamic stability, reduce blood loss, and have more positive effects on recovery profiles[12]. The use of intravenous acetaminophen during the intraoperative period may also be considered by the anesthesiologist. The need for intraoperative opioids decreases with the use of intraoperative iv acetaminophen[14].

In the perioperative period, the anesthesiologist must deal with hemodynamic disturbances, volume overload and hypokalemia, glucose intolerance, and diabetes, maintaining the blood cortisol level and preventing the glucocorticoid deficiency in patients with Cushing's disease[8]. It is important to close follow-up of the ingested liquids and the excreted ones in relation to ADH.

3.2.5. Postoperative Neusea and Vomiting Prophilaxis

The use of droperidol and ondansetron reduces the incidance of nausea in the post-anesthesia care unit when used in prophilaxis. Since dexamethasone may cause suppression in the hypothalamis-pituitary-adrenal axis, the use of it in the prophilaxis of postoperative nausea-vomiting should be carefully[16].

4. POST-OPERATİVE CARE

The main goals in the postoperative period of the pituitary sugery, as in other surgeries, should be to relieve postoperative pain, early mobilization and respiratory exercises, and to prevent respiratory complications such as hypoxemia and atelectasis.

Diabetes incipidus is common after pituitary surgery and often does not require treatment. If necessary, rapid fluid administration and vasopressin analogue can be used. Steroid replacement therapy is necessary until the pituitary returns to normal function. It has been shown in some studies that an increase in postoperative pain and morphine need in patients with diabetes incipidus, and this possible relationship should be kept in mind.

The need for postoperative analgesic agents is less in patients undergoing transsphenoidal pituitary surgery compared to transcranial surgeries. These patients should be closely monitored for complications such as postoperative convulsions, hydrocephalus, bleeding or electrolyte imbalance.

Obstructive sleep apnea is a common condition in patients undergoing pituitary surgery. It is associated with postoperative respiratory complications. These patients sholud be monitored and treated in the intensive care unit. In these patients, the use of CPAP is characteristic to prevent complications. CPAP treatment may be difficult due to nasal tampons placed after surgery. In addition, the likelihood of developing pneumocephalus and meningitis increases following the use of CPAP. In patients with obstructive sleep apnea, high-flow oxygen therapy with face mask should be preferred, and CPAP use should be postponed rather than applied in the early postoperative period (postop day 0 and 1)[17,18].

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PART 20:

ANESTHESIA MANAGEMENT OF PATIENTS WITH ADRENAL DISORDERS

Gizem KURADA

The adrenal gland consists of the cortex and medulla. Androgens, mineralocorticoids, and glucocorticoids are secreted from the adrenal cortex. Catecholamines are secreted from the adrenal medulla. Adrenal androgens are of no importance in anesthesia practice.

Surgery in adrenal disorders requires a multidisciplinary approach. The endocrinologist, anesthesiologist and surgeon should work in cooperation. Before the procedure, attention should be paid to whether the mass is secretory or non-secretory.

MINERALOCORTICOIDS

A mineralocorticoid, aldosterone plays a role in fluid and electrolyte balance. It provides reabsorption of sodium and excretion of potassium and hydrogen from distal renal tubules. As a result, it increases the extracellular fluid, decreases the plasma potassium level and creates metabolic alkalosis. Its secretion is stimulated by the renin-angiotensin system, adrenocorticotropic hormone (ACTH) and hyperkalemia. Its secretion is suppressed in cases of hypovolemia, hypotension and congestive heart failure.

MINERALOCORTICOID EXCESS

Primary hyperaldosteronism is usually associated with Conn's syndrome. More rarely, it can be caused by bilateral adrenal hyperplasia or adrenal gland carcinoma. The most common causes of secondary hyperladesteronism include congestive heart failure, nephrotic syndrome, and cirrhosis. Clinically, hypokalemia and hypertension are seen. Hypertension results from aldosterone-induced sodium and water retention and is usually resistant to

medical therapy. Aldosterone increases the effect of catecholamines, due to noradrenaline re-uptake blocking effect, and it predisposes to myocardial fibrosis resulting in arrhythmias and myocardial ischemia [1] .

The main purpose of the anesthetic approach is to correct fluid and electrolyte imbalances. In the preoperative period, the patient's volume status should be carefully evaluated. Intraoperative hemodynamic instability and hypokalemia should be addressed. An aldosterone antagonist, spiranolactone, is used preoperatively to correct hypokalemia.

It should be checked preoperatively that there is sufficient cortisol level. Adrenal suppression can trigger hypotension, hyponatremia, and hypoglycemia. Etomidate should be avoided in induction because it interferes with cortisol synthesis.

Close hemodynamic control, potassium level and acid-base balance should be followed up in the intraoperative period. Hypokalemia and metabolic alkalosis may prolong the effect of neuromuscular blockers. Hypokalemia, together with sevoflurane-induced polyuria, can exacerbate respiratory alkalosis [2] . Hyperventilation must be avoided.

MINERALOCORTICOID DEFICIENCY

Isolated mineralocorticoid deficiency is rare. It is seen with glucocorticoid deficiency due to damage to both adrenal glands.

GLUCOCORTICOIDS

Glucocorticoids are essential steroid hormones for life. They are synthesized by ACTH stimulation under the control of the hypothalamic-pituitary-adrenal (HPA) axis according to the circadian rhythm. It regulates the stress response and metabolism, plays a role in gluconeogenesis, regulates inflammatory and immune functions. The most important of the glucocorticoids is cortisol. High cortisol levels increase blood glucose by stimulating gluconeogenesis in the liver. Glucocorticoids act as mineralocorticoids, increasing sodium retention and potassium excretion. It causes an increase in extracellular fluid as a net effect. Glucocorticoids are needed for vascular and bronchial smooth muscle to respond to catecholamines.

GLUKOCORTICOID EXCESS

Glucocorticoid excess may be due to administration of exogenous steroids, hyperfunction of the adrenal cortex, secretion of ACTH from an ectopic mass, or Cushing's disease. Cushing's syndrome, which is characterized by muscle weakness, osteoporosis, central obesity, glucose intolerance, hypertension and mental status changes, is seen in patients. Hypokalemic metabolic alkalosis is seen due to the mineralocorticoid effect of glucocorticoids. Fluid overload may occur in patients.

CUSHING SYNDROME

In Cushing's syndrome caused by exogenous steroids, the adrenal glands may not respond appropriately to the perioperative stress. Hypercrotisolism, hypertension, hyperglycemia and hypokalemia should be controlled in the preoperative period. Cortisol levels are controlled with adrenal enzyme inhibitors. Antihypertensive drugs should be continued until the morning of the operation. Spironolactone should be started to correct hypokalemia, and potassium should be added to the treatment if necessary. Hyperglycemia increases the risk of infection and mortality, delays wound healing. Therefore, blood sugar should be kept between 120-180 mg/dL by providing glycemic control [3] .

Central obesity can complicate airway management, and should be prepared for difficult airway. Since gastric emptying will be delayed, there is a risk of aspiration, rapid induction may be preferred. Because of thin skin and osteoporotic bones, position should be given carefully.

Adrenalectomy has complications of blood loss and pneumothorax. Arterial cannulation for close hemodynamic monitoring and wide central and peripheral vascular access for fluid therapy should be provided. In the intraoperative period, blood glucose, pH and electrolytes should be monitored. We recommend monitoring of neuromuscular block in order to prevent postoperative respiratory depression that can be caused by restrictive losses caused by difficult airway and obesity.

Epidural analgesia may be an appropriate choice for postoperative analgesia because of its suppressive effect on neurohumoral stress response [4].

GLUCOCORTICOID DEFICIENCY

ADDISON'S DISEASE

Primary adrenal insufficiency is called Addison's disease. Adrenal gland damage causes both glucocorticoid and mineralocorticoid deficiency. Due to

aldosterone deficiency, hyponatremia, hypovolemia, hypotension, hyperkalemia and metabolic acidosis are seen. Cortisol deficiency results in weakness, fatigue, hypotension, and weight loss.

Secondary adrenal insufficiency most commonly develops due to exogenous steroid therapy. ACTH secretion from the pituitary gland is insufficient. Mineralocorticoid secretion is not impaired, fluid and electrolyte imbalances are usually not observed. Stress situations can trigger an Addisonian crisis. Patients present with fever, abdominal pain, orthostatic hypotension, and hypovolemia unresponsive to fluid resuscitation. Adequate steroid replacement should be performed in the perioperative period in patients with glucocorticoid deficiency.

SURGICAL STEROID COVERAGE

Stress dose corticosteroid is required for two groups of patients; patients receiving replacement therapy for pituitary or adrenal insufficiency, patients receiving glucocorticoids for other indications and requiring surgical intervention. Patients using high-dose steroids for more than 4 weeks by any route in the one-year period prior to surgery may not respond appropriately to surgical stress [5] .

Adults normally secrete 20 mg/day of cortisol. It can increase to 300mg/day under maximum stress conditions.

Stress-dose steroid therapy is a highly controversial issue. The traditional recommendation is to give the patient 100 mg of hydrocortisone every 8 hours, starting the night before or the morning of the operation. An equivalent dose of another steroid can be used instead of hydrocortisone (Table 1).

Table 1. Steroid equivalency and potency

Steroid	Equivalent Dose	Glucocorticoid	Mineralocorticoid	Bioavailable half-life (hours)
Hydrocortisone	20 mg	1	1	8-12
Methylprednisolone	4 mg	5	0,1-0,2	18-36
Prednisolone	5 mg	4	1	12-36
Dexamethasone	0,75 mg	30	0,1	36-54

The preponderance of evidence points toward giving much smaller doses for coverage than has previously been thought to be safe [6] . Some clinicians argue that the dose to be administered should be based on the severity of surgical stress. Stress-dose steroid therapy is not required for every patient undergoing surgery. Stress-dose steroid therapy is decided according to duration and dose the patient heve been used glucocorticoid, the type and duration of the surgery (Table 2).

Table 2. Recommended stress hydrocortisone doses based on the severity of the surgery

Surgical stress	**Recommended hydrocortisone doses**
Low surgical interventions Inguinal hernia repair Colonoscopy	Before the procedure, 20-25 mg/m2/dose hydrocortisone is given intravenously, after the procedure the normal dose is given. The normal dose used is continued the next day.
Moderate surgical interventions Open cholecystectomy Segmental colon resection	Intravenous hydrocortisone 25 mg/m2 is injected. 50-75 mg/m2/day hydrocortisone is given parenterally at 8 hour intervals. The dose is reduced to the maintenance dose in 1-2 days.
Major surgical interventions Cardiothoracic surgery Whipple surgery Esophagogastrectomy	Intravenous hydrocortisone 50 mg/m2/dose is injected, Following this, hydrocortisone 100 mg/m2/day is given parenterally in three divided doses. In uncomplicated cases, the dose is reduced and the maintenance dose is started in 2-3 days.

Some studies show no adverse outcomes in surgical patients receiving their previous steroid dose while undergoing surgery [7, 8] . Avoiding large doses of steroids may prevent some of the adverse effects of steroids.

CATECHOLAMINES

Endogenous catecholamines are dopamine, adrenaline and noradrenaline. Catecholamine release is regulated by cholinergic preganglionic fibers of the sympathetic nervous system. Its release is stimulated by factors such as exercise, bleeding, hypotension, hypothermia, hypoglycemia, hypercapnia, and hypoxemia.

PHEOCHROMOCYTOMA

Pheochromocytoma arises from neurochromaffin cells and is a catecholamine-secreting tumor. Pheochromocytomas most often arise spontaneously, but some are associated with familial syndromes such as simple familial pheochromocytoma, multiple endocrine neoplasia (MEN) IIa and IIb, neurofibromatosis, tuberous sclerosis, von Hippel- Lindau disease and Sturge-Weber syndrome [9] . Because of the rarity of pheochromocytoma, most data on the anesthetic management and perioperative outcomes have been reported in small case series.

Symptoms are paroxysmal headache, hypertension, sweating and palpitations. Hypertension and tachycardia attacks may occur during manipulations of abdominal structures. Other, less common signs and symptoms include orthostatic hypotension, blurred vision, papilledema, weight loss, polyuria, polydipsia, and constipation. Catecholamine excess can result in volume depletion, postural hypotension, organ or limb ischemia, aortic dissection, angina, myocardial infarction, acute or chronic cardiomyopathy, congestive heart failure, and arrhythmias [10] .

Preoperative evaluation and medical management for pheochromocytoma resection should be multidisciplinary, including the surgeon, anesthesiologist, and endocrinologist. After confimation of the diagnosis, the patient must be evaluated for possible end organ damage caused by excess catecholamine secretion. There are three major complications expected in the perioperative period: hypertension, dysrhythmia, and hypotension. The adequacy of alpha adrenergic blockade and volume replacement should be considered in the preoperative evaluation.

Combined alpha- and beta-adrenergic blockade is the most commonly implemented strategy for intraoperative hemodynamic management. For patients with tachycardia or arrhythmias alpha blockade is initiated first. The beta-adrenergic blocker should never be started before the alpha blocker because blockade of vasodilatory peripheral beta-adrenergic receptors with unopposed alpha-adrenergic stimulation can lead to a further elevation in blood pressure. Calcium channel blockers (eg, nicardipine) are sometimes used to supplement combined alpha and beta blockade or as an alternative for patients with intolerable side effects from other regimens.

Premedication is important in these patients because of high catecholamine levels. Benzodiazepines and barbiturates are generally used for this purpose. Clonidine, an alpha-2 agonist, reduces central and peripheral

sympathetic tone. It reduces blood pressure without affecting blood catecholamine levels. It should be used with caution in patients with hypovolemia or use of beta-blockers. Dexmedetomidine, another alpha-2 agonist, may also be preferred for premedication.

Preoperative electrocardiogram (ECG) shoul be evaluated for possible ischemic changes and rhythm disturbances. Depending on the catecholamine discharge, supraventricular or ventricular arrhythmias can be seen at any stage.

Most agents and neuromuscular blockers are safe for induction of anesthesia. Ketamine is not preferred because of its hemodynamic effects. Succinylcholine causes significant increases in blood pressure. Agents that can potentially release histamine, such as atracurium, may cause hypotension due to histamine release or hypertension due to histamine inducing catecholamine release from tumor tissue. Tachycardia caused by pancuronium does not affect hemodynamics. Vecuronium and rocuronium are more preferred because they have fewer side effects. Lidocaine, high-dose opioids, intravenous esmolol, or magnesium sulfate can be used to control blood pressure change due to laryngoscopy and intubation. Invasive arterial monitoring should be performed from the beginning of the induction phase. Central venous pressure should be measured both to evaluate the volume status and to provide a wide vascular access.

Isoflurane, sevoflurane and desflurane can be used safely in the maintenance of anesthesia. The sympathetic stimulation effect of desflurane at increasing minimum alveolar concentration should not be forgotten. Total intravenous anesthesia can also be used safely. Analgesia is controlled by intravenous opioids. Anesthetic requirements may change during tumor manipulation due to changes in cardiac output, which can alter blood levels of both inhaled and intravenous anesthetics [11] . The main goal is to determine the appropriate depth of anesthesia. Bispectral analysis monitor could be helpfull during anesthesia.

Most patients with pheochromocytoma become hypertensive at some point during surgery. Nitroprusside, phentolamine, nicardipine, labetalol and esmolol are the drugs used to control hypertension during the surgery. Nitroprusside and esmolol are our first choices to control hypertensive crisis. Nitroprusside, an ultrashort-acting vasodilator, administered as an infusion at 0.5 to 5 mcg/kg/minute and adjusted every few minutes for target response. Esmolol is an ultrashort-acting selective beta1-adrenergic blocker. It can be administered by bolus (10 to 50 mg IV) or by infusion (25 to 250

mcg/kg/minute). When severe hypertension occurs, the surgeon should be alerted, surgery may need to be paused to allow for blood pressure control.

Magnesium sulfate reduces catecholamine release in the adrenal medulla and sympathetic nerve endings, blocks adrenergic receptors, has a direct vasodilator effect and is antiarrhythmic [12] . It is very effective in controlling intraoperative hypertension and arrhythmias. It can be used as a loading dose of 1-8 mg and a maintenance dose of 1-4 mg/h. Esmolol is a very short-acting selective beta-blocker. It is a safe choice, including conditions such as myocardial dysfunction.

Adrenalectomy for pheochromocytoma can be performed via laparotomy, laparoscopy, or robotically [13] . In laparoscopic surgery, excessive increases in blood pressure can be observed due to catecholamine release following pneumoperitoneum.

After vascular clamping during tumor resection, high circulating catecholamine levels are eliminated, resulting in reduced vasoconstriction and hypotension. Hypovolemia should be corrected with appropriate fluid therapy. Rarely, the use of vasopressors may be required. Drugs commonly used to support blood pressure are phenylephrine, ephedrine and norepinephrine. Norepinephrine is our first choice, is a combined alpha and beta agonist that is given by infusion (wide range of dosing; 2 to 20 mcg/minute IV), titrated to effect

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PART 21:

ANESTHESIA IN THYROID DISEASES

Semin TURHAN
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1. INTRODUCTION

The thyroid gland is located in the anterior part of the neck in front of the thyroid cartilage. Its approximate weight is 20 gr. It is vital for body metabolism. The word “thyroid”, which is a word of Latin origin, has taken this name, which means “shield” in Latin because it is likened to a war shield. It is controlled by the thyroid-stimulating hormone (TSH) secreted by the pituitary[1].

The thyroid gland mainly secretes hormones. Thyroid hormones increase metabolic rate, increase glycogenolysis, increase hepatic gluconeogenesis. Increases intestinal glucose absorption and cholesterol synthesis and degradation. It has positive inotropic and chronotropic effects on the heart. In addition, it increases gastrointestinal motility. Its effect on bone structures is to increase protein turnover. Thyroid hormones are critical to growth and brain development in children[2,3].

Thyroid hormones are produced from tyrosine. 3,5,3'-triiodothyronine is triiodized and T4 is four-iodized. It is synthesized and stored in the thyroid gland, bound to thyroglobulin protein. It circulates in the blood both free and bound to thyroglobulin. The active form is the free form. The functioning of the thyroid gland, and thus the secretion of thyroid hormone, is controlled by TSH secreted from the anterior pituitary (adenohypophysis) (thyroid-stimulating hormone). TSH is controlled by TRH secreted from the hypothalamus (thyrotropin-releasing hormone). TRH causes the release of TSH, and TSH causes the release of T3, T4. T3 and T4 suppress TSH and TRH release. This control mechanism is called the "hypothalamus-pituitary-thyroid axis"[4].

Hyperthyroidism is a clinical disease that occurs as a result of excessive secretion of thyroid hormones due to thyroid gland hyperactivity. It is more common in women than men. The most common causes are Basedow-Graves disease and toxic nodular goiter [5]. Clinical manifestations include weight loss,

heat intolerance, muscle weakness, sweating, diarrhea, hyperactive reflexes, nervousness, tremor, exophthalmos, goiter, and hypertension. Cardiac manifestations are sinus tachycardia, atrial fibrillation, and congestive heart failure. In laboratory findings, free T3 and free T4 levels are high and TSH levels are low. In the treatment of hyperthyroidism, it is aimed to reduce the increased hormone secretion both medically and surgically. Except in cases requiring emergency surgery, patients with hyperthyroidism should be medically brought to a euthyroid state before surgical interventions [6,7]. Otherwise, there is a risk of developing a thyroid crisis within 6-24 hours postoperatively. Thyroid crisis can also occur intraoperatively and the resulting clinical picture mimics malignant hyperthermia [8] .

Hypothyroidism is a serious co-health problem that adds characteristics to the perianesthetic period. Hypothyroidism is a syndrome that occurs with decreased thyroid hormone secretion from the thyroid gland. The prevalence of the subclinical and moderate forms is 15/1000. Hypothyroidism, which can vary from subclinical form to myxedema, is a clinical disease that develops due to the deficiency of thyroid hormones [9] . Hashimoto's thyroiditis may occur due to surgical excision, silent postpartum thyroiditis, Sheehan's syndrome, excessive radioactive iodine therapy, some antiarrhythmic drugs such as amiadoron. In addition, "low T3 syndrome" (euthyroid disease syndrome, nonthyroidal disease syndrome) may occur due to an unexplained decrease in T3 levels in tuberculosis, trauma, myocardial infarction, general surgery, bypass operations, and long-term fasting [10] .

2. PREOPERATIVE PERIOD

2.1. Hyperthyroidism: In the preoperative period, the patient should be made euthyroid if available. Some drugs can be used medicinally for this purpose. The most commonly used agents are; propylthiouracil, methimazole, and carbimazole. These drugs used for hyperthyroidism are called antithyroid drugs. It is usually started 2-4 weeks before surgery. In patients with severe hyperthyroidism, a heart rhythm-regulating beta-blocker is also added to the treatment (40-120 mg/day) [11]. Potassium iodide (0.5 ml, 3 times a day) can be added one week before the operation to prevent the blooding of the thyroid gland. Thyroid hormones may have caused cardiac hypertrophy and atrial fibrillation. High hormone levels can also cause tachyarrhythmias. B-blockers inhibit T4-T3 conversion in the peripheral area as well as adrenergic antagonism [12].

2.2. Hypothyroidism: Typical complaints of hypothyroid patients are fatigue, increased need for sleep, depression, chills, weight gain despite the same diet, constipation, forgetfulness, prolonged time required to complete a task, and decreased exercise tolerance. The face is pale and apathetic, with swelling around the eyes and shedding on the lateral eyebrows [13]. The skin is cold, dry, rough and mixed oedema. This condition, called myxedema coma, which is characterized by extreme symptoms of hypothyroidism and has a mortality of 30%, is not a true coma. Edema is due to intradermal protein deposition, not interstitial edema fluid accumulation. The diagnosis of myxedema is made on clinical grounds with laboratory data. Cardiovascular effects are cardiac contractility disorder manifested by decreased cardiac output, increased peripheral vascular resistance, decreased systolic blood pressure, increased diastolic blood pressure, and bradycardia. It can be seen in pericardial effusion and Torsades de pointes. There may be symptoms of angina due to anemia. Breathing becomes shallow and slow. Hypoxic and hypercapneic ventilatory management is impaired [14] . As drug metabolism slows down, sensitivity to sedatives and anesthetics increases and respiratory failure may develop. Great care should be taken during premedication and premedication should be avoided if necessary. Care should be taken in terms of hypotension, aspiration, hypoglycemia and bleeding. Since gastric emptying times are slowed down, H2 receptor antagonist and metoclopramide can be applied for premedication [15] .

3. INTRAOPERATIVE PERIOD

3.1. Hyperthyroidism: For ineligible patients with hyperthyroidism, regional anesthesia can be an outstanding alternative. Ephedrine solutions should be avoided. Local anesthesia (Cervical plexus block +/- sedation) may be used infrequently in patients with the poor general condition for whom general anesthesia is not indicated. Bilateral cervical plexus block can be performed for video-assisted thyroidectomy (VAT), hemithyroidectomy, or total thyroidectomy, the operation time of which will not exceed 2 hours, in patients who are inconvenient to use general anesthesia. Bilateral deep cervical plexus block should be avoided because of the possibility of a loss of phrenic nerve function [14] . Complications of a bilateral superficial cervical block are toxicity by injection into the thyroid veins, internal jugular vein, or carotid, and thyroid hematoma. In addition, the vagal injection may cause recurrent laryngeal nerve palsy, voice hoarseness, and swallowing difficulties, and may require

conversion to general anesthesia. After the block is in place, it is recommended to provide oxygen support and mild conscious sedation with midazolam, fentanyl, and/or propofol. Thyroidectomy can also be performed with acupuncture and hypnosis using additional analgesics [5,15] . Difficult airway preparation should be considered, as intubation difficulties are encountered at a rate of 6% during thyroid surgery. The use of a spiral tube ensures that the airway is not affected by tracheal deviation, especially in patients with retrosternal and large goiter. General anesthesia with the laryngeal mask is not recommended because of airway anatomy changes such as tracheal narrowing and deviation, and surgical manipulations. Since the risk of corneal abrasion and ulceration increases in patients with proptosis, the eyes of the patients should be well protected. Hyperextension of the head should be avoided. Although it increases the risk of air embolism to provide venous drainage and reduce blood loss, the patient's head can be raised 15-20 degrees. The risk of embolism is reduced by keeping the intrathoracic pressure high. Metabolic rate and oxygen consumption are increased in hyperthyroidism. Tachycardia, high cardiac output, tachyarrhythmia, atrial fibrillation, left ventricular hypertrophy, congestive heart failure may develop. To avoid tachycardia, hypertension, and ventricular arrhythmias, adequate depth of anesthesia should be provided before laryngoscopy and surgical simulation. Thiopental may be chosen for induction because it produces some antithyroid activity at high doses [11,16] . Ketamine, pancuronium, indirect-acting adrenergic agonists, and drugs that stimulate the sympathetic nervous system should be avoided, which will increase blood pressure and heart rate. As muscle relaxants, more cardiovascularly stable drugs such as vecuronium or atracurium should be used instead of pancuronium. It should be considered that anticholinergics may increase sympathetic responses in reversing muscle relaxation. Therefore, glycopyrrolate may be preferred due to its less chronotropic effect. Since the incidence of myasthenia gravis is higher in hyperthyroid patients (2-17.5%), it is useful to reduce the initial dose of muscle relaxants and to perform neuromuscular monitoring(17). TIVA with propofol and short-acting opioids is recommended for rapid onset of anesthesia, early recovery, good control of postoperative nausea and vomiting, and safe in terms of malignant hyperthermia. Induction with volatile anesthetics is slow due to increased cardiac output. Resistance appears to develop due to increased drug metabolism. Since the minimal alveolar concentration does not change, the need for an anesthetic drug does not increase. Hyperthermia caused by

hyperthyroidism indirectly increases MAC [18] . If a surgery other than thyroidectomy is to be performed in these patients, regional anesthesia may be preferred. Spinal, epidural anesthesia reduces the release of catecholamines and alleviates the symptoms of hyperthyroidism [11].

3.2. Hypothyroidism: Although it is ideal for patients to be euthyroid, mild to moderate hypothyroidism is not an absolute contraindication for surgery. Patients with uncorrected severe hypothyroidism or myxedema coma should not undergo elective surgery and should be treated with thyroid hormone before emergency surgery. Because of the high mortality risk in emergency surgery, aggressive supportive therapy, hormone replacement, and close monitoring are required to monitor response to therapy. Thyroid hormone therapy should be performed with caution in patients with coronary artery disease, as it may cause myocardial ischemia. Myocardial function is depressed. Cardiac output, heart rate, and stroke volume decrease. Impairment of baroreceptor reflexes and pericardial effusion may accompany hypothyroidism. Enlarged tongue, loosening of oropharyngeal tissues, large goiter, and obesity can cause difficulty in airway control. Intubation may be difficult due to the large tongue. Sensitivity to the hypotensive effect of anesthetic agents used in induction increases, severe hypotension and cardiac arrest may develop [19,20] . Therefore, ketamine is often recommended for anesthesia induction. Decreased cardiac output increases the rate of induction with inhalation anesthetic, but does not decrease the MAC value. Since gastric emptying is delayed, rapid serial intubation with succinylcholine or use of fast-acting nondepolarizing muscle relaxants is recommended. Since the sensitivity of the hypothyroid patient to anesthetics increases, it would be appropriate to reduce anesthetic drug doses and use bispectral index monitoring. It is prone to per-postoperative hypothermia due to low basal metabolic rate and decreased heat production. Hypertonic solutions should be used as hyponatremia may be present. In addition, anemia, hypoglycemia, coagulation disorder, decreased hepatic and renal clearance of drugs may ocur [21,22] .

4. POSTOPERATIVE PERIOD

4.1. Hyperthyroidism: Nonsteroidal anti-inflammatories and tramadol are sufficient for postoperative pain. Thyroidectomy leads to various surgical complications. Respiratory complications are the most common postoperative complication in subtotal thyroidectomies. If recurrent laryngeal nerve injury is

suspected, the vocal cords can be examined with a laryngeal mask and fiberoptic endoscope. Hoarseness, aphonia due to unilateral paralysis of the recurrent laryngeal nerve; Stridor may develop due to bilateral paralysis. During close follow-up in the recovery room, hoarseness in the voice and failure to pronounce the letter "i" may be an early warning for unilateral nerve palsy [23] . Monitored anesthesia care tried with laryngeal mask and propofol-remifentanil in Thyroplasty Type I surgery performed in unilateral vocal cord paralysis was found to be very effective because it provides an excellent surgical field and the airway is safe [24] . Voice changes and swallowing difficulties may occur due to superior laryngeal nerve damage. After deep extubation, vocal cords are evaluated by laryngoscopy, reintubation of the patient or wound exploration may be required. Cough and nausea-vomiting should be avoided during and after extubation. For this purpose, deep extubation, dexmedetomidine, intravenous, topical or intracuff lidocaine and remifentanil are recommended. Tracheomalacia may occur due to erosion of the tracheal cartilages due to goiter, malignancy or collapse of the trachea due to hematoma. If the anesthetist does not hear a leak sound when the cuff of the endotracheal tube is deflated, he should suspect tracheomalacia.[25,26] In case of hematoma formation, the clot should be drained by opening the suture on the neck of the patient, and the necessity of reintubation should be evaluated. Postoperative 12-72. Parathyroidectomy, which causes laryngospasm and progresses with hypocalcemia, may have been performed unintentionally. Pneumothorax may develop during neck dissection [27] .

4.2. Hypothyroidism: Recovery from general anesthesia may be delayed in hypothyroid patients as drug biotransformation is slow. There may be a need for prolonged mechanical ventilation support due to respiratory depression. Nonopioid agents should be chosen because agents used in the postoperative pain treatment of hypothyroid patients increase the susceptibility to respiratory depression. Since patients are prone to hypothermia, they should be intubated until normothermia is achieved [28,29] .

5. THYROID CRISIS

The most serious postoperative event in patients with hyperthyroidism is thyroid crisis. Thyrotoxicosis is a medical emergency that is characterized by extreme manifestations and requires aggressive treatment. Usually 6-18 weeks postoperatively. appears on the hour. It is characterized by hyperpyrexia,

tachycardia, altered consciousness, and fluctuating blood pressure. If it occurs in the intraoperative period, it can be confused with malignant hyperthermia. Muscle rigidity, increase in creatinine kinase, absence of metabolic and respiratory acidosis are guiding in the differential diagnosis. Differential diagnosis from sepsis, neuroleptic malignant syndrome and pheochromocytoma should be made. The mortality rate in thyroid crisis is 20-30% [30] . It usually occurs suddenly in a patient with thyrotoxicosis after an acute infection, operation, acute medical illness, stress or trauma. In some cases, it may develop spontaneously or after I131 treatment, after discontinuation of antithyroid drugs. Human chorionic gonadotropin hormone (hCG) has an alpha subunit structurally very similar to TSH [31] , and thyrotoxicosis may occur in pregnancies and malignancies with hydatidiform moles. There are two important groups of facilitating factors that lead to the crisis. One of them is increased peripheral effects of thyroid hormones due to comorbidities. In the second group, as during thyroid surgery, the secretion of thyroid hormones increased. The diagnosis of thyroid crisis is made with suspicion, but clinical findings are not specific. Desiring laboratory confirmation of elevated thyroid hormone levels leads to critical delays in treatment. Mild to moderate hyperglycemia may be seen in patients in thyrotoxicosis crisis due to increased glycogenolysis and impaired insulin secretion due to catecholamines. The key clinical manifestations of thyroid storm are fever above 38.5°C, tachycardia (more than expected from fever), central nervous system findings (anxiety, agitation, delirium, acute psychosis, and coma), and gastrointestinal (nausea, vomiting, abdominal pain, diarrhea, jaundice) findings. . Accurate and timely diagnosis and treatment are essential to prevent potentially fatal consequences [32,33] .

5.1. Thyroid Storm Treatment & Management

There are five main steps. These are prevention of production (propylthiouracil, methimazole) and release (sodium iodide, potassium iodide, Lugol solution) of thyroid hormones, blockade of their peripheral effects (propranolol, esmolol, diltiazem), treatment of systemic decompensation and underlying disease, and finally permanent treatment [34] .

1-Prevention of the production of thyroid hormones: It is almost completely stopping the synthesis of hormones with propylthiouracil (PTU) or methimazole (MM). Since these drugs do not have parenteral forms, they can be given by nasogastric tube or rectally to patients with poor consciousness. For

PTU, it is necessary to give 1200-1500 mg daily, 6x1 200-250 mg after a 600 or 1000 mg loading dose. For MM, this dose is 120 mg daily, 6x1 20 mg. PTU has superiority over MM as it also blocks peripheral conversion above 600 mg [35] .

2-Preventing the release of thyroid hormones: The release is blocked by iodine and lithium carbonate. Iodine should be given at least 1 hour after the blockade of hormone synthesis with antithyroid drugs. It should be kept in mind that antithyroid drugs should not be discontinued after starting iodine. The recommended dose of iodine is 4x1 8 drops of Lugol's solution or 4x1 5 drops of potassium iodide. The contrast agent, one of the iodine preparations, is propanoic acid. It blocks both thyroid hormone release and T4 and T3 conversion. Another drug is Lithium carbonate. Lithium dose should be started with 300 mg every 6 hours and adjusted to a Lithium level of 1 mEq/L. The use of lithium is recommended only for those who are inconvenient to use iodine and antithyroid drugs due to its renal and neurological toxicity [36] .

3-Block of peripheral effects β-Blockers Propranolol: Oral or parenteral forms are available. In the treatment of tachycardia and neuromuscular findings, 20-40 mg orally is used every 4-6 hours, IV 1-2 mg 2-5 minutes. It is given within, then 2-3 mg IV dose can be repeated every 2-4 hours in 5-10 minutes if necessary. Esmolol: It is an alternative β-blocker to propranolol. The starting dose of Esmolol is 0.5 mg kg-1. If necessary, esmolol perfusion can be continued at 50-100 μg kg-1 min-1 [37] . Since ACTH and cortisol cannot be secreted, it is recommended to administer 50mg hydrocortisone or 2mg dexamethasone intravenously every 8 hours. It binds thyroid hormones and causes a decrease in circulating thyroid hormone levels. If there is no response despite treatment, this treatment may be considered.

4-Treatment of systemic decompensation Benzodiazepines and barbiturates can be used for the treatment of hyperkinesia. Aspirin should not be used as an antipyretic because it increases the release of T4. General cooling can be applied, dehydration should be corrected. Nutrition and vitamins, if necessary, oxygen and mechanical ventilation therapy are applied. Congestive heart failure should be treated.

5-Treatment of the underlying disease in the etiology, the treatment of the causative disease is important.

6-Permanent treatment after emergency treatment of thyroid storm is performed, standard medical treatment of thyroid diseases should be continued. If necessary, radioactive iodine therapy and surgical thyroidectomy can be applied [38].

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PART 22:

NEUROLOGICAL CLINICAL PRESENTATION OF FERRITIN HORMONE DEFICIENCY: RESTLESS LEGS SYNDROME

Meltem KARACAN GÖLEN

1. INTRODUCTION and HISTORY

Restless legs syndrome (RLS) is a sensorimotor, chronic disorder characterized by abnormal sensations accompanied by pain and restlessness, which causes an uncomfortable, unpleasant, irresistible urge to move the legs. It can be observed usually in the legs, less frequently anywhere in the body. It is characteristic of RLS that the symptoms are usually more pronounced in the evening and at night, occur and increase at rest, and cause sleep disturbances.[1-2] The symptoms of the patients begin at night with rest and usually disappear during the day. Patients state that their symptoms of sensations such as uncomfortable paresthesia regress by moving their legs, shaking them, getting out of bed, and walking.[3]

Thomas Willis was the first to describe these symptoms, which were considered disease-related, in 1685. RLS was first clinically described by Karl-Axel Ekbom in 1945, and this syndrome, also known as Ekbom syndrome, was named "restless legs". This definition has been used to describe sensory symptoms and motor discomfort in the extremities, especially during rest.[3,4]

While studies on RLS were continuing, in 1950, Norlander reported that serum ferritin levels were low in patients with RLS.[5] There upon, the role of ferritin levels in the pathophysiology of RLS was emphasized in later studies.

The prevalence of RLS in the general population is known to be between 5-15% and it is more common in women than in men. Symptoms often begin in the fourth and fifth decades.[6] In a population-based study conducted in Turkey, the prevalence of RLS was found as 3.2%.[7]

2. ETIOPATHOGENESIS

The causative agent of the disease has not been definitively revealed, but it is suggested that there is more than one mechanism responsible for the pathophysiology. In the pathophysiology of RLS, dopaminergic system disorder and iron deficiency and genetic predisposition are held responsible. Ekbom was the first to suggest that iron was responsible for the pathophysiology.[8] Dopaminergic hypofunction was brought to the agenda by Şevket Akpınar in 1982 when the symptoms disappeared with levodapa (L-DOPA) treatment.[9] Dopaminergic activity increases in the morning and decreases in the early hours of the night. The period of decreased dopaminergic activity is similar to the symptoms of RLS. In clinical studies of RLS, a positive family history with autosomal dominant inheritance was detected. In genome studies, findings explaining the clinical symptoms were found in chromosomes 9, 12, and 14, and it was reported that advanced studies were needed to identify the relevant genes.[10,11,12] In gene studies, the home box gene MEIS1, and MAP2K5, and LBXCOR1, which carried genetic risk, were held responsible.[13,14]

There are primary (idiopathic) and secondary forms of RLS. In the primary (idiopathic) form, there is no obvious cause other than possible genetic predisposition, and it usually starts at an earlier age with a positive family history. In the secondary form, the age of onset is higher and RLS symptoms secondary to diseases such as end-stage chronic renal failure, anemia, ferritin deficiency, diabetes mellitus, pregnancy, rheumatoid arthritis, Parkinson's disease, and polyneuropathy can be observed.

In the pathophysiology, dopamine dysfunction and ferritin deficiency are emphasized most frequently. Dopaminergic hypofunction was supported by imaging studies, and single-photon emission computed tomography (SPECT) studies showed that the number and affinity of post-synaptic D2 receptors decreased. The diurnal change in dopamine activity is similar to the increase in RLS symptoms and the benefit from dopaminergic treatment confirms this mechanism.

Iron deficiency plays an important role in the pathophysiology of secondary RLS. Although systemic iron levels are normal, it is known that iron deficiency may occur in the central nervous system. In studies on RLS and iron metabolism, it is known that iron concentrations play a key role in dopamine levels. Iron is a co-factor of tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis. Iron is required for the conversion of tyrosine to L-DOPA. Iron deficiency affects adenosine and dopamine in the spinal system and brain.

Iron deficiency plays a role in pathophysiology by indirectly affecting dopaminergic release. It was also reported that it increased the level of tyrosine hydroxylase and increased extracellular dopamine, which might cause a decrease in dopamine transporter on the cell surface, and in some patients, a decrease in the number of D2 receptors.[15,16] Iron concentrations were found to be low in the substantia nigra and putamen, correlated with the severity of RLS in the brain.[17] Recently, the role of serum iron in the pathophysiology, as well as the effect of ferritin, has been emphasized. In post-mortem immuno-histochemical studies, iron and ferritin levels were found to be low in the brain.[18] Several studies found low levels of ferritin in the cerebrospinal fluid (CSF) in patients with RLS.[19,20] Iron deficiency was detected in 43% of patients with RLS. In another study, the severity of RLS symptoms was found to be correlated with serum ferritin levels. In clinical practice, it is known that if the ferritin level is below 20 µ/L, RLS symptoms may occur (normal range for women 12-150 ng/mL, for men 15-200 ng/mL).[21, 22]

In another study, it was reported that up to 75% of patients with secondary RLS had iron deficiency. In addition, it was reported that RLS symptoms might occur if the serum ferritin concentration was <50 ng/mL, even within the normal range.[23] The same study also reported that serum iron levels showed a circadian rhythm and were 50-60% lower at nighttime. It was determined that nocturnal ferritin levels in the CSF of patients with RLS were quite low.

3. CLINICAL FINDINGS AND DIAGNOSTIC CRITERIA

After the definition of RLS, the diagnostic criteria were published by the International Restless Legs Society Study Group (IRLSSG) in 1995. Later, as a result of ongoing research, it was revised in light of new information and new criteria were published by the American National Health Institute in 2003.[24]

(Table 1)

Patients usually describe unpleasant abnormal sensations in both legs, sometimes in one extremity. They describe their symptoms with analogies such as tingling, a desire to move, electric current, chills, and tension. They state that their symptoms are relieved or reduced when they move their extremities. In addition to moving their extremities, they may prefer relaxation methods such as rubbing their legs, washing them with hot or cold water. Although it is mostly seen in the legs, it has been reported that the symptoms can also spread to the

arms. Although the symptoms are known to occur after long inactivity at night, symptoms can be observed during the day in severe RLS. [24]

The diagnosis of RLS is based on careful anamnesis and neurologic examinations, which may be normal in idiopathic and secondary forms. For a definitive diagnosis, four of the essential diagnostic criteria must be met. Supportive features are helpful in patients with an indefinite diagnosis but are not necessary.[24] (Table 1)

There is no objective test for definitive diagnosis. Laboratory tests (fasting blood sugar, glucose tolerance test, hemogram, ferritin, vitamin B12 levels, ferritin, folate, thyroid-stimulating hormone [TSH], cholesterol level, magnesium, blood urea nitrogen [BUN], and creatine), electrophysiologic examinations (electromyography [EMG] for polyneuropathy), polysomnography, suggested immobilization test (SIT) and actigraphy, and spinal imaging are the preferred tests for diagnosis and differential diagnosis in primary and secondary RLS. In patients with late-onset RLS, peripheral neuropathy and radiculopathy findings may be observed.[25]

Severity classification of patients is made according to the disease severity scale developed by the International Restless Legs Society Working Group in 2003. According to this scale, treatment selection can be made and post-treatment response can be evaluated numerically. [26]

Table 1: Restless Legs Syndrome Diagnostic Criteria

Essential Diagnostic Criteria
1. An urge to move the legs accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs
2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.
5. The occurrence of the above features are not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping)
Supporting Clinical Features
1. Family history in first-degree relatives
2. Response to dopaminergic therapy
3. Periodic leg movements (while awake or asleep)
4. Absence of severe daytime sleepiness
Specifiers for Clinical Course

A. Chronic-persistent RLS: Symptoms, when not treated, would occur on average at least twice weekly for the past year. B. Intermittent RLS: symptoms, when not treated, would occur on average < 2/week for the past year, with at least five lifetime events
Specifier for Clinical Significance The symptoms of RLS cause significant distress or impairment in social, occupational, educational or other important areas of functioning by the impact on sleep, energy/vitality, daily activities, behavior, cognition or mood.

4. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of RLS should be carefully reviewed and should be taken into account when planning an examination for the etiology. Some diseases may present with symptoms similar to those of RLS. In particular, akathisia, nocturnal leg cramps, peripheral neuropathy, radiculopathy, myelopathy, painful legs-moving toes syndrome, nocturnal dyskinesia, leg edema, and venous stasis should be considered. Periodic limb movements are a movement disorder with similar features to RLS and are usually observed in the NREM stage of sleep. Patients with peripheral neuropathy state that they have a burning sensation in the feet, which is relieved with a cold shower. The diagnosis is made by detecting the presence of polyneuropathy with electrophysiologic examinations. In the anamnesis of patients with radiculopathy or spinal stenosis, unlike RLS, clinical and imaging findings consistent with radicular pain that restrict the patient's movements are detected, independent of the circadian rhythm, and the diagnosis of RLS is not considered. Akathisia develops secondary to neuroleptic drugs and causes involuntary movements. Its difference from RLS is that it is independent of the circadian rhythm. In addition, neuroleptic use should be questioned. Painful legs and moving toes syndrome is characterized by abnormal flexion and extension of the toes originating from the spinal cord. [15,27] (Table 2)

Table 2. Differential Diagnosis

Nocturnal Leg Cramp
Painful legs and moving toes syndrome
Peripheral Neuropathy
Lower extremity venous/vascular abnormalities
Lumbosacral radiculopathy- Spinal stenosis
Periodic leg movements during sleep
Akathisia

5. TREATMENT

Restless legs syndrome is a disease that affects daily living activities and sleep patterns. If there are mild symptoms, they may not require treatment or non-pharmacologic methods may be preferred. Relaxing practices such as stretching exercises, hot bath and massage before sleep are some of them. Apart from this, it is recommended to avoid known factors that affect the sleep pattern of the person. Caffeine, antihistaminic drugs with an antidopaminergic effect, alcohol, antipsychotics and antidepressants are known to increase RLS symptoms because they affect the dopaminergic activity and their use should be avoided.

Treatment planning is made according to the algorithm created by the IRLSSG in 2004. [28]

1- Intermittent RLS: When the first symptoms occur in the patient, the symptoms are severe but the frequency is rare. If there is a factor that triggers RLS (e.g. travel), treatment may be preferred before these factors.

2- Daily RLS: Due to the frequency and severity of RLS symptoms, daily treatment is required.

3- Resistant RLS: Patients who need daily dopamine agonists and patients who have inadequate treatment response despite an appropriate dose or dose increase are in this group.

RLS treatment should be treated with a multidisciplinary approach. A treatment plan for secondary causes determined according to their assessment forms the basis of treatment. Before moving on to advanced pharmacologic treatments, iron replacement therapy should be applied to eliminate the secondary cause of iron deficiency, which is frequently encountered in clinical practice. Treatment should aim to increase the serum ferritin value above 50 µ/L.[2,29] Intravenous iron therapy is effective in RLS.[30] Studies have shown that patients with low ferritin plasma levels (<45 µg/L) have regression in symptoms after iron supplementation.[31-32-33]

Considering the evidence-based medicine criteria, dopaminergic therapy is the first-line treatment in RLS. L-DOPA and dopamine agonists, pramipexole and ropinirole can be preferred in dopaminergic treatment. L-DOPA is short-acting and may be preferred between doses of 100-300 mg in the treatment of patients with intermittent symptoms. Treatment can be planned as a single dose administered at night or with a repeat dose after 3 hours, depending on the symptoms. In long-term use, augmentation, which is called the earlier onset of

symptoms, may develop. It is known that augmentation increases if there is a concomitant decrease in ferritin value.[34-35]

Among the dopamine agonists, bromocriptine, pergolide, cabergoline, ropinirole, pramipexole, and rotigotine can be preferred. There is no superiority of drugs to each other. Randomized control studies of dopamine agonists have shown that it reduces RLS symptoms and is effective in long-term treatment. Ropinirole is recommended as a single dose of 2 mg (0.25-4 mg) 1-3 hours before bedtime, and pramipexole is recommended as a single dose of 0.5 mg (0.25-0.75 mg) approximately 2 hours before bedtime. It is generally recommended to be used before going to bed at night.[2,33]

Opioids may be preferred in addition to dopaminergic treatment in unresponsive patients. Opioids, oxycodone and propoxyphene, are not available in our country. Clonazepam, one of the benzodiazepines, is known to affect insomnia symptoms rather than RLS symptoms. It is preferred because of its adverse effects. Due to the lack of adequate studies of clonazepam in the treatment of RLS, there is insufficient evidence for its effectiveness.[33]

It has been suggested that antiepileptics in RLS are effective in the treatment because of their effect on increased excitability. Pregabalin and gabapentin enacarbil can be considered effective in the short-term treatment of primary RLS. Gabapentin and pregabalin may be preferred for add-on therapy in patients using dopamine agonists. Antiepileptics for the treatment of RLS are not yet the United States Food and Drug Administration (FDA) approved.[2] There is insufficient evidence to conclude the efficacy of antiepileptics, levetiracetam, and lamotrigine.

6. CONCLUSION

Restless Legs Syndrome is a chronic disorder that should be followed up with a multidisciplinary approach from diagnosis to treatment. It is very important to recognize the disease and to make a treatment plan by distinguishing the primary and secondary causes because it affects daily life activities and sleep patterns. Detecting and treating secondary causes, especially ferritin deficiency, is a simple and effective option that is easy to obtain and use for patient treatment, and will also contribute positively in terms of treatment costs.

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PART 23:

OUR NURSING APPROACHES IN METABOLIC SYNDROME MANAGEMENT

Ecem ÖZDEMİR

1. Description

Metabolic syndrome (MS) is a serious health problem with high morbidity and mortality, spreading globally with cardiometabolic complications[1]. MS, also known as "insulin resistance" syndrome, is a combination of many risk conditions that include each other; It is an endocrinopathy with high mortality, in which many systemic conditions such as abdominal obesity, lack of glucose tolerance or diabetes mellitus (DM), cholesterol disorders (hyperlipidemia, etc.), hypertension and coronary artery disease (CAD) are present[2,3]. MS is also associated with insulin resistance syndrome, syndrome X, polymetabolic syndrome, fatal quartet, civilization syndrome, etc. definitions are also available[4].

2. Etiology and Diagnostic Criteria

MS, atherosclerotic diseases and type 2 DM are among the most critical and most prevalent causes. These factors are; abdominal obesity, cholesterol disorders (dyslipidemia, etc.), hypertension and hyperglycemia[5]. The prevalence varies from country to country due to the inability to reach a common denominator regarding its definition.

- Abdominal obesity,
- Dyslipidemia,
- Insulin resistance and
- It is hypertension. In addition, since there is an increase in fibrinogen and C-reactive protein (CRP) in these people, the risks of infection and clot formation are higher[6].

MS causes can be divided into 3 different groups: Obesity/adipose tissue disorder, insulin resistance, non-dependent parameters (vascular, hepatic,

immunological origin molecules, etc.). Although it is mentioned that it is a condition determined by more than one gene, the sedentary lifestyle caused by new city life, the high calories in the diet can worsen the general course of MS. The National Cholesterol Education Program Expert Panel prepared the report (ATP III) of the detection, assessment, and treatment of high blood cholesterol in adults in 2001. In the content of the report, it was stated that the presence of 3 of the 5 factors in the table was sufficient for the diagnosis of MS (Table 1).[7]

Components	Presence of ≥3 components
Glucose	≥100 mg/dL
HDL-c	<40 mg/dL for men <50 mg/dL for women
Triglycerides	≥150 mg/dL
WC	≥102 cm for men or ≥88 cm for women
Systemic arterial hypertension	≥130 × 85 mmHg

HDL-c: high-density lipoprotein cholesterol; WC: waist circumference.

Table 1: ATP III-MS Diagnostic Parameters[7]

ATP III, IDF and Altered ATP III criteria for MS are given in Table 2. The graphs also show female-male-age prevalences according to ATP III, IDF and Modified ATP III.

MetS component	ATP III criteria [19,20]	IDF criteria [21,22]	Modified ATP III criteria [23]
To be identified as Mets	Any three or more of the following five components	Central obesity plus any two other factors	Any three or more of the following five components
Waist circumference			
Men	>102 cm	≥90 cm for Chinese men	≥90 cm for Asian men
Women	>88 cm	≥80 cm for Chinese women	≥80 cm for Asian women
TG	≥1.70 mmol/L (150 mg/dL)	≥1.70 mmol/L (150 mg/dL) mg/dL or specific treatment for this lipid abnormality	≥1.70 mmol/L (150 mg/dL) or drug treatment for elevated TG
HDL-C			
Men	<1.03 mmol/L (40 mg/dL)	<1.03 mmol/L (40 mg/dL) in males or specific treatment for this lipid abnormality	<1.03 mmol/L (40 mg/dL) in men or drug treatment for reduced HDL-C
Women	<1.30 mmol/L (50 mg/dL)	<1.30 mmol/L (50 mg/dL) in women, or specific treatment for this lipid abnormality	<1.30 mmol/L (50 mg/dL) in women or drug treatment for reduced HDL-C
Blood pressure	≥130/85 mm Hg	SBP ≥130 or DBP ≥85 mm Hg, or treatment of previously diagnosed hypertension	≥130 mm Hg SBP or ≥85 mm Hg DBP or on antihypertensive drug treatment in a patient with a history of hypertension
Fasting glucose	≥6.1 mmol/L (110 mg/dL)	≥5.6 mmol/L (100 mg/dL), or previously diagnosed type 2 diabetes	≥5.6 mmol/L (100 mg/dL) or drug treatment for elevated glucose

MetS: metabolic syndrome; TG: triglycerides; HDL-C: high-density lipid cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure.
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Table 2: MS Components and Changing Criteria[8]

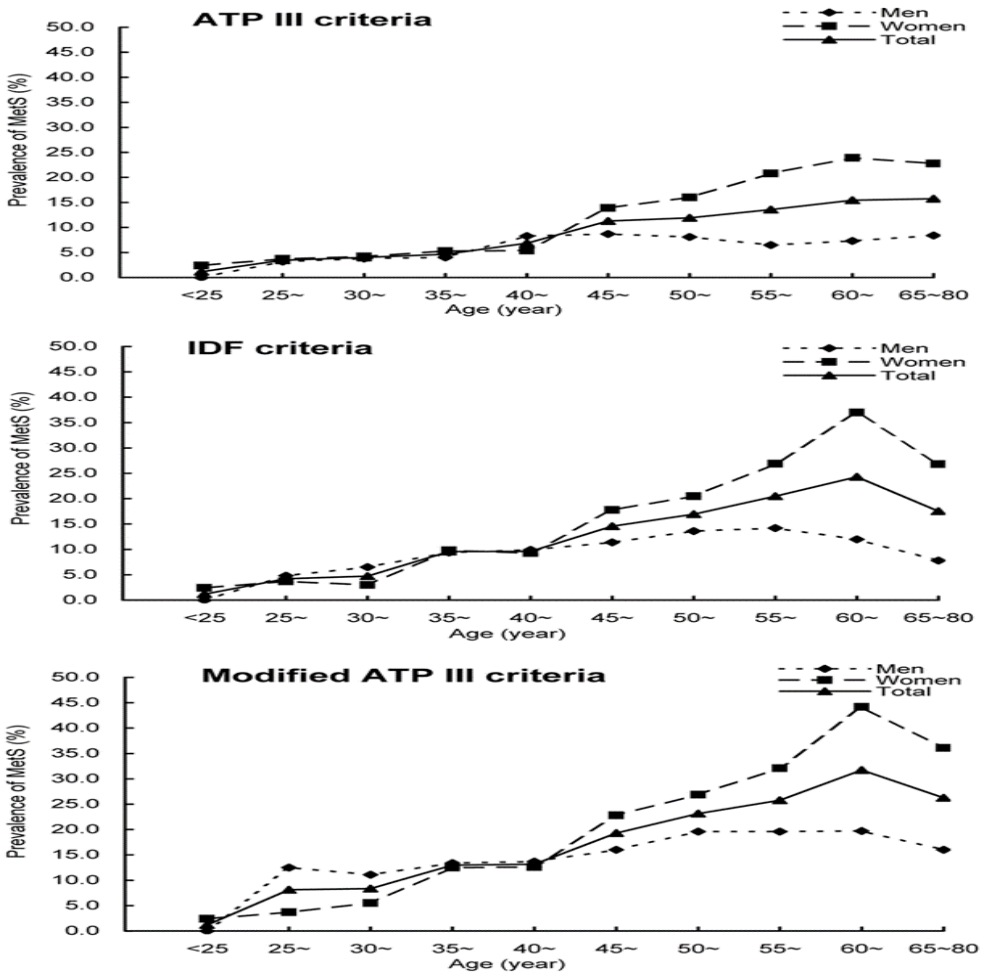

Table 3: Female-Male-Age Prevalences by ATP III, IDF, and Modified ATP III[8]

3. Frequency of MS

MS, which is a major public health problem in nearly all countries, is a global problem affecting 20% to 30% of the adult population in most of the countries, although the frequency of MS varies according to the changing geography and national conditions, the definitions used, age and gender characteristics of the population. seen as a problem[9,10].

The prevalence of MS in the population is around 22% in adults. In the MS Society Turkey Health Study conducted in 2010, 4057 people were included in the study, and waist circumference >94 cm for men and >80 cm for women was

accepted as criteria; MS prevalence was 43.5% in women and 41.4% in men. In addition, with the increase in the prevalence of MS as people get older, the prevalence of MS in the 60-64 age range was 57.7%. Another striking aspect of the study is that 63.6% of women and 34.5% of men were obese[11].

While its incidence increases as age and body mass index increase; decreases as education level and exercise level increase. In Turkey, as in other western countries, the incidence of abdominal obesity and MS is increasing. According to the study conducted by the Metabolic Syndrome Association; In Turkey, the incidence of MS is thirty-four percent, forty percent of women and twenty-eight percent of men are under the influence of MS. Its incidence is 6.7 percent in the 20-29 age group, and 43.5 percent in the 60-65 age group[12].

4. Medical Treatment

Apart from hereditary factors, the primary thing to do in MS, which can occur with many variables that affect the environment, is lifestyle examination and, if necessary, making changes. Our aim here is to prevent diabetes, cardiovascular diseases in particular. It is possible to prevent all the problems seen in MS by losing weight with a personalized diet and exercise plan. Apart from lifestyle change, there is no single factor that can cure MS[13]. The most appropriate treatment method is lifestyle change for weight loss and regular exercise, healthy eating and smoking cessation.

MS is an endocrinopathy with high morbidity and mortality. Evaluation of patients with a multidisciplinary perspective; Physician, dietitian, physiotherapist, nurse should be treated and cared for[14]. The treatment plan is formed under four headings in accordance with the risk factors:

- Improvement of atherogenic dyslipidemia
- Controlling hypertensive conditions
- Healing of prothrombotic diseases
- It is all of the treatments for the correction of insulin resistance[14].

Metformin, which is used in medical treatment, is the first drug to be applied. Metformin is a drug of the biguanide group, it suppresses hepatic glucose production, increases insulin receptors and HDL levels, decreases the amount of fat in the internal organs, and the FDA has approved its use in adolescents. However, if Type 2 DM develops, another treatment is required to keep it under control. Another drug is glitazone. Glitazones have efficacy against insulin resistance.

For the correction of prothrombotic conditions, aspirin should be used[12,15].

In addition to these treatments, an important and difficult treatment for MS is to create a "lifestyle change" in people.

5. Nursing Approaches

There is no better method or drug that can provide treatment for MS other than lifestyle changes. The first step to make a change in lifestyle is to lose weight. Therefore, first of all, moderate calorie restriction will be appropriate. Five to ten percent of the weight should be lost in the first year. After weight loss, other issues should be focused on. These; planned physical activity, regular food planning, quitting smoking and alcohol habits[14].

In studies, MS, obesity, HT, DM etc. Lifestyle change in diseases has been described as “therapeutic lifestyle change” (TYD). Changes in lifestyle are a critical and important part of the treatment plan. The nurse's individualized care principle is very important at this point[16].

BLS has been proposed for the management of MS within the NCEP ATP-III plan. In the ATP-III plan, planned physical activity, a regular nutritional planning, pharmacotherapy, family support, etc. concepts are available. Pharmacotherapy in MS is mostly applied to reduce cardiometabolic risk[17].

Regular exercise plan in one's life with lifestyle change; It helps to have a positive effect on the person's DM, HT control and CAH.

As nurses, we should approach individuals with the principle of personalized care from many points, verbally and in writing, and use healing aspects in providing life change. It is very important for healthcare professionals, especially us nurses, to know what stage their patients are at in terms of lifestyle change[18].

There is a model used to bring about lifestyle change. It is the LEARN model developed by Brownell in 2004. With the model, it is aimed to increase the quality of life of people and make a lifestyle change. The content of the model includes Lifestyle, Physical Activity (Exercise), Attitudes, Relationships, Nutrition (Nutrition) titles[19].

When applying the model:

- Related to Eating
- Nutritional Stimulus Control
- Regular Exercise Program
- Education

- Changing self-defeating thoughts and associated negative emotions with diet and body image
- Setting realistic goals
- Relationships
- Weight maintenance and maintenance, etc. topics are addressed.

The nurse should put the patient at the center of the treatment system; should motivate patients in a way that will gain their self-esteem. Individuals should be taken to group trainings, and joint studies should be carried out to find solutions to them by communicating with people who have the same problems. In these group therapies, the individual's feeling of belonging to a place is very valuable in terms of the psychological process. In therapies, the nurse should take on the role of a participant from time to time, from time to time. These trainings should not be for one time only, they should be continued until the patient finds individual strength in himself. Because the individual needs to feel that they can have a say in their medical treatment.

With the training of nurses; providing individuals with therapeutic lifestyle changes with the right techniques in line with the principles of individualized care; Psychologically, individuals need to use techniques that eliminate social isolation and stress.

It should be ensured that the nursing profession, which is present in all areas of society, is intertwined with the society in MS, and nurses should be included at every step in all local, national and international practices. In addition, nurses should not only be involved in planned projects, but should also engage in practices that will ensure the health and welfare of the society by taking initiatives[20].

MS should be included in the curriculum, and the ways of caring for the patient and MS with a multidisciplinary perspective should be tried to be conveyed to the students.

Nursing diagnoses in MS can be listed as follows:

- Anxiety and Fear
- Lack of Knowledge
- Social Isolation
- Disruption in Thought Processes
- Immobility-Related Constipation
- Inability to Cope.

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PART 24:

USE OF ALTERNATIVE AND COMPLEMENTARY TREATMENTS FOR METABOLIC SYNDROME

Berna AKSOY

1. Description and Diagnostic Criteria

Complementary and alternative medicine (CAM) can be defined as "techniques to improve quality of life and health, which have historical origins outside of traditional medical care and include various alternative treatments used together with them".[1] While CAM is defined by the World Health Organization as "a broad set of healthcare practices that are not part of that country's own tradition and not integrated into the dominant healthcare system".[2] The National Center for Complementary and Integrative Health defines it as "a diverse group of medical and health care systems, practices, and products that are not considered part of conventional or allopathic medicine."[3]

Complementary and alternative medicine therapies include alternative medical systems, the mind-body approach or techniques, biologically-based systems, manipulative and body-based methods, and energy therapies.[4] The use of CAM in The *United States* of America increased rapidly during the 1990s and remained stable from 1997 to 2002 as 39% [5], 49% of the France populations and 46% of the Germany populations having used some form of CAM in 1992. [6] Today, popular CAM therapies are acupuncture, homeopathy, and chiropractics in western societies.[7]

Complementary and alternative medicine therapies are used for hard-to-treat chronic diseases as supplements to the conventional therapy[8] and many patients suffering from chronic diseases prefere alternative therapies.[9] Complementary and alternative medicine therapies are also used by individuals with metabolic syndrome.[10] Metabolic syndrome (MS) is a complex disorder and can be diagnosed if at least three of the five cardio-metabolic abnormalities consisting of abdominal obesity, hyperglycemia, hypertension, and hyperlipidemia which are met.[11-12] (Table 1).

Table 1. Definitions of Metabolic syndrome[13]

Clinical and biochemical features	WHO(1998)	AACE (2003)	Consensus (AHA/NHLBI + IDF) (2009)
Insulin resistance	Impaired glucose tolerance, impaired fasting glucose, T2DM, or lowered insulin sensitivity plus any two of the following	Impaired glucose tolerance or impaired fasting glucose, plus any of the following	Any three of the following
Obesity	Abdominal obesity (waist-to-hip ratio >0.9inmen or >0.85 in women, or BMI >30 kg/m2)	BMI ≥25 kg/m2	Raised WC (population-and country-spe
Plasma glucose concentration	Impaired glucose tolerance, impaired fasting glucose, or T2DM	Impaired fasting glucose, or Impaired glucose tolerance	FPG ≥100 mg/dL or on diabetes treatment
Hypertension	BP ≥140/90 mm Hg	BP≥130/85 mm Hg	BP ≥130/85 mm Hg, or on antihypertensive treatment
Triglycerides (TG)	TG ≥150 mg/dL	TG ≥150 mg/dL	TG ≥150 mg/dL or on treatment
HDL-cholesterol (HDLC)	HDLC<40 mg/dL in men and <50 mg/dL in women	HDLC<40 mg/dL in men and <50 mg/dL in women	HDL<40 mg/dL in men and <50 mg/dL in women
Other	Urinary albumin excretion ≥20 μg/min, or ACR ≥30 mg/g		

AACE, American Association of Clinical Endocrinologists; ACR, albumin-creatinine ratio; AHA, American Heart Association; BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose concentration; HDLC, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; NHLBI, National Heart, Lung, and Blood Institute; T2DM, type 2 diabetes mellitus; TG, triglycerides; WC, waist circumference; WHO, World Health Organization.

Due to the lack of adequate health system support and the lack of complex and expense pharmacological treatment regimens, patients have difficulty in managing the MS. individuals with MS turn to nutritional interventions use to managing of this complex disorder. They use safe, effective, and cheap dietary supplementation which include chromium or cinnamon. Studies regarding CAM therapies are showed that individuals with MS turn to nutritional interventions use to managing of this complex disorder and they used safe, effective, and cheap dietary supplementation which include chromium or cinnamon.[14] Akilen et al. (2014) reported that over third of individuals with MS were used CAM such as nutritional supplements, massage therapy, acupuncture, yoga, aromatherapy and herbal supplements in the past 12 months.[10]

This chapter will focus on alternatıve and complementary treatments for metabolıc syndrome.

2. Complementary and alternative medicine metods

2.1. Yoga

Yoga which is rooted in Indian philosophy, one type of mind-body therapy and spiritual practice.[15] Studies have shown that yoga has positive effects on physical function, obesity, glycemic index, lipid profile and cardiovascular

parameters.[16,17] Cramer et al. (2014) reported that yoga practice had a positive effect on individuals' waist circumference, systolic and diastolic blood pressure, cholesterol and triglycerides (TG), glycosylated haemoglobin (HbA1c) and insulin resistance[18], (Figure 1).

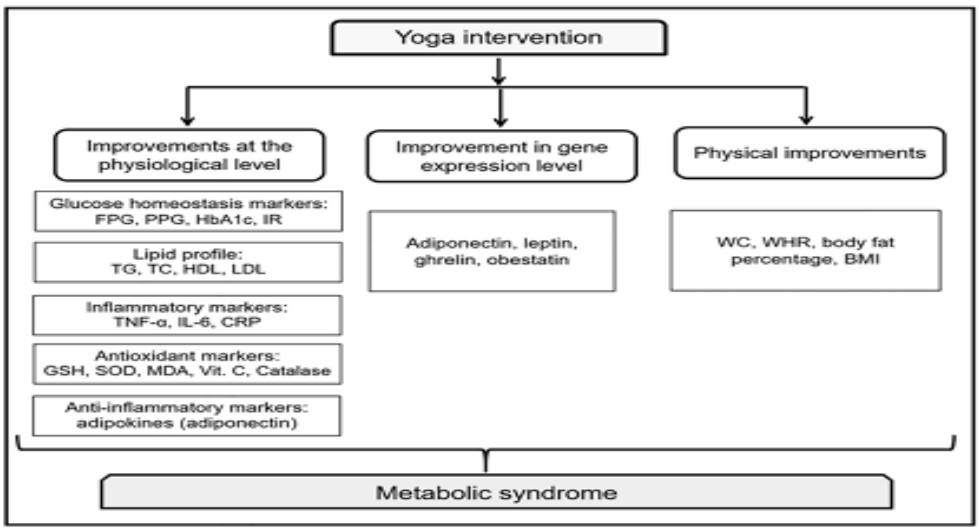

Figure 1. Effects of yoga on metabolic syndrome [19]

2.2. n-3 Polyunsaturated Fatty Acids

Cold water fish are a rich source of nutrients of n-3 fatty acids which effectively and safely lower triglycerides. A study condected by Harris et al. reported that individuals who used n-3 fatty acid had lower triglyceride, very-low density lipoproteins cholesterol (VLDL-C) and total cholesterol levels.[20] Venturini et al. (2015) reported that fish and olive oil reduced the total cholesterol and low-density lipoprotein cholesterol (LDL-C) concentrations.[21] A meta-analysis study was reported that a higher circulating n-3 PUFAs is associated with reduction in MS risk.[22]

2.3. Soy Protein

The literature shows that soy protein supplementation effective in reducing LDL-C level while raising high-density lipoprotein cholesterol (HDL-C) level.[23] In the meta-analysis by Zhang et. al (2016) showed that soy protein improved glycemic control.[24] Moderate intake of soy protein is recommended by expert and the evidence supports it.[23]

2.4. Dark Chocolate

In the literature, it has been reported that many studies have been conducted on the prevention between diet and MS. [25] They showed that high intake of fruits and vegetables rich in flavonoids was associated with a reduced risk of MS. Fruits, vegetables, and beverages, including coffee, tea, and wine are contain dietary flavonoids.[26] Studies reported that intake flavonoid-rich foods decrease triglyceride, total cholesterol, LDL-C and increase HDL-C.[25] Cocoa products contain flavonoids. Cocoa has positive effects on blood lipid levels by reducing LDL and TG and increasing HDL.[27] Also, the consumption of dark chocolate have blood pressure lowering effects.

2.5. Wine

It has been reported in the literature that light to moderate consumption of alcohol reduces the risk of developing MS. A systematic meta analysis which was conducted by Howard et al (2004) showed that the relationship between alcohol consumption and the incidence of type 2 diabetes. According to this study, moderate alcohol consumption reduced the risk and incidence of type 2 diabetes.[28] Tresserra-Rimbau (2015) reported that moderate red wine consumption was found to be associated with a decreased prevalence of the MS, by reducing the risk of having an abnormal waist circumference, high blood pressure, low HDL-C concentrations and high fasting plasma glucose concentrations.[29]

2.6. Chromium

Chromium which is an essential element, is found in seafood, meat, green vegetables, cheese, whole grains, and fruits. It playing a important role in alleviating diabetes, insulin resistance and lipid anomalies.[30-32] In the study of Bai et al (2015), it is reported that an inverse association between chromium and incidence of MS (blood lipids) in American young adults.[33] Chen et al (2017) reported that plasma chromium concentrations were inversely associated with type 2 diabetes mellitus and pre-diabetes mellitus.[34] In the randomized and double-blind study of San Mauro-Martin et al (2016), it is reported that chromium picolinate demonstrated significant improvement in insulin sensitivity. [35]

2.7. Dietary Approaches to Stop Hypertension (DASH) Diet

Dietary modification is recommended as the safest and most effective strategy for preventing the incidence of MS. Dietary Approaches to Stop Hypertension (DASH) which has similarities with the Mediterranean diet, is a dietary pattern which was initially proposed for the treatment of hypertension and encouraged high-fiber foods. It is rich in fruits, vegetables, whole grains and limiting meat.[36] (Table 2). The DASH diet has effective on glucose and insulin levels [37] and decreased total cholesterol, LDL-C[38]. In the study of Azadbakht et al (2005), it is reported that the reduction in triglycerides, systolic and diastolic blood pressure, weight, and increase in HDL-C was higher in the DASH group than control diet.[39]

Table 2. The DASH Eating Plan[40]

The DASH eating plan shown below is based on **2,000 calories a day.** The number of daily servings in a food group may vary from those listed, depending upon your caloric needs.		
Food Group	**Daily Servings Food Group (except as noted)**	**Daily Servings Food Group (except as noted)**
Grains and grain products	7–8	1 slice bread 1 cup ready-to-eat cereal* 1/2 cup cooked rice, pasta, or cereal
Vegetables	7–8	1 cup raw leafy vegetable 1/2 cup cooked vegetable 6 ounces vegetable juice
Fruits	4–5	medium fruit 1/4 cup dried fruit 1/2 cup fresh, frozen, or canned fruit 6 ounces fruit juice
Lowfat or fat free dairy foods	2-3	8 ounces milk 1 cup yogurt 1 1/2 ounces cheese
Lean meats, poultry, and fish	2 or fewer	3 ounces cooked lean meat, skinless poultry, or fish
Nuts, seeds, and dry beans	4–5 per week	1/3 cup or 1 1/2 ounces nuts 1 tablespoon or 1/2 ounce seeds 1/2 cup cooked dry beans
Fats and oils†	2–3	1 teaspoon soft margarine 1 tablespoon lowfat mayonnaise 2 tablespoons light salad dressing 1 teaspoon vegetable oil
Sweets	5 per week	1 tablespoon sugar 1 tablespoon jelly or jam 1/2 ounce jelly beans 8 ounces lemonade
* Serving sizes vary between 1/2 cup and 1 1/4 cups. Check the product's nutrition label. † Fat content changes serving counts for fats and oils: For example, 1 tablespoon of regular salad dressing equals 1 serving, 1 tablespoon of lowfat salad dressing equals 1/2 serving, and 1 tablespoon of fat free salad dressing equals 0 servings.		

2.8. Green tea

Green tea is made from the leaves of Cammellia sinensis and widely consumed the world. It has polyphenolic compounds and caffeine.[41] Green tea have beneficial effects on human health. It is effective in decreasing sugar and cholesterol, antioxidant activity and prevention of cardiovascular disease.[42]

Studies have shown that green tea has antihyperglycemic effects, prevention of liver gluconeogenesis, increasing insulin sensitivity.[43] In a study by Wang et al. (2010) reported that using consumption of green tea extract decrease in abdominal fat, waist circumference and body weight. [44] In the meta-analysis study of Liu et al. (2013), it is reported that green tea consumption significantly reduces the fasting blood glucose and HbA1C levels of people with MS.[45]

2.9. Cinnamon

Cinnamon has polyphenol compounds which display insulin-potentiating, antioxidant. It has positive effect in improving insulin sensitivity[46], reducing fasting blood glucose[47], HbA1C [48], total cholesterol, serum triglycerides, LDL-C [49], systolic blood pressure and percent body fat [47].

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