Review Article:

Type 2 Diabetes and obesity: A review

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Abstract:

The article reviews the relationship between type 2 diabetes and obesity. This also includes types of obesity and its genetic predisposition. The modern generalization of sedentary life and caloric abundance has created new physiological conditions capable of changing the level of expression of a number of genes involved in fuel metabolism and body weight regulation. It is likely that the genetic variants or alleles of these genes have in the past participated in the adaptation of human physiology to its evolutionary constraints. In this article, we underscore the importance of obesity in relation to disorders of diverse etiologies characterized by disturbances of free fatty acids, visceral adiposity and insulin resistance. Further, we have investigated the role of selecting the traits to be subjected to quantitative genetic analysis in the occurrence of obesity

Key words: Diabetes, Obesity, Review

Introduction:

Diabetes mellitus (DM) and obesity have a complex relationship, with type 2 diabetes strongly associated with obesity [1]. Obesity stands out as a risk factor for Type 2 DM, but we see some lean type 2 diabetes subjects probably having Latent Autoimmune Diabetes in Adults (LADA). Thus obesity may be a precursor for Type 2 DM, following insulin resistance [2-3]. Most researchers consider that this relationship is different in different types of obesity and Type 2 DM [4]. Further studies are needed to fully understand this.

Causes of obesity are probably different for many types. Genetic disposition is clearly one [5-7]. Different demographic groups according to lifestyle and genetics must be studied in a comprehensive way in order to understand more of these patterns.

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For treatment and prevention of Type 2 DM, reduction of obesity is a key goal all over the world [6, 8, 9]. The main treatment of both conditions is reduced caloric intake and increased physical activity. Newly diagnosed cases of Type 2 DM and obesity are always treated in this way.

Free fatty acids and triglycerides in the development of Type 2 DM

Free fatty acids (FFA) are a major source of energy for liver, kidney and skeletal muscle and a key substrate for triglyceride production by the liver. In periods of prolonged fasting, FFA provide an alternative energy source to glucose, preserving glucose for cerebral requirements and also preserving body proteins, which can serve as substrates for gluconeogenesis. FFA are stored in the body in the form of triglycerides, the vast majority of which are located in white adipose tissue, and are released from triglycerides by the process of lipolysis. After transportation into the tissue, FFA are mainly oxidized in muscle cells to release energy, or converted into lipoproteins by the liver. The enzyme that controls the rate-limiting step for mobilization of triglycerides in adipose tissue is hormonally regulated. Insulin is one of the main hormones involved in this regulatory process [10], and the most potent antilipolytic hormone [11].

In insulin resistance, the insensitivity of adipocytes to insulin, results in elevated FFA [12-13] which is a characteristic feature of Type 2 DM [5, 6] and is strongly implicated in the development of insulin

resistance and beta-cell dysfunction. Thus, it is becoming increasingly apparent that reducing FFA levels is an important goal in the management of patients with Type 2 DM.

Prospective epidemiological studies have shown that an elevated FFA level is a risk marker for long-term development of glucose intolerance and progression to Type 2 DM [7], in addition to being associated with several other independent risk factors for cardiovascular diseases [1-3,8,14]. It is becoming increasingly clear that management of dyslipidaemia is of equal importance to control of hyperglycaemia and hypertension in the care of patients with Type 2 DM. The majority of these patients are obese and have elevated plasma FFA levels [5]. It has been suggested that FFA may be an important link between obesity, insulin resistance and Type 2 DM [4]. Insulin resistance might indeed originate in the adipose tissue [15] by mechanisms as suggested in Box 1 [16].

Box 1. Hypothesis: How Obesity Causes Insulin Resistance

The Adipokine Hypothesis

Obesity leads to an alteration in the profile of hormones secreted by adipose tissue

(adipokines). In the obese state, adipose tissue secretes proportionally more adipokines that cause insulin resistance and fewer that promote insulin sensitivity.

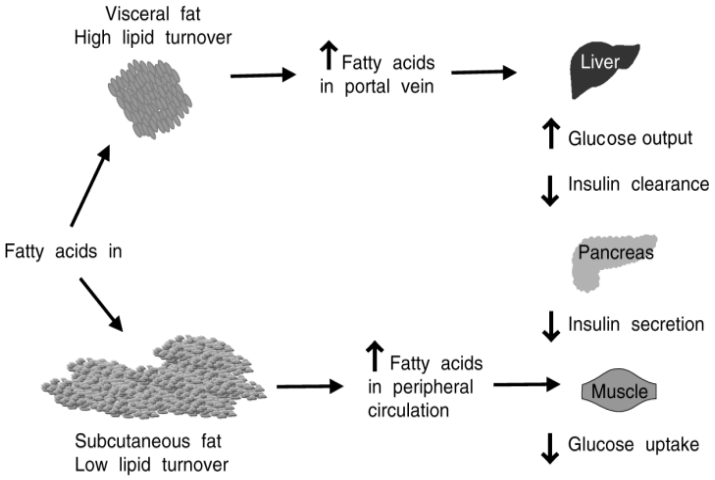
The Inflammation Hypothesis

Obesity is associated with an increase in adipocyte secretion of chemokines, which promote macrophage infiltration [17]. In addition to increased macrophage infiltration, obesity is also associated with increased macrophage activation. Activated macrophages produce cytokines that can negatively impact insulin sensitivity [17].

Interplay between central obesity and free fatty acids

Central obesity, i.e. fat accumulation in the subcutaneous abdominal and visceral depots, is most strongly associated with the risk of metabolic and cardiovascular complications [18-20]. Upper-body obesity results in an increased mass effect in the visceral region coupled with increased mobilization of FFA from the individual fat cells in the visceral depot into the portal vein [21]. The combination of these factors produces markedly elevated 'portal' FFA levels in obese subjects, resulting in hyperglycaemia, hyperinsulinaemia, and hepatic insulin resistance (Figure 1). In addition, although the effect is less marked, the increase in upper-body subcutaneous fat in obese subjects generate an excess of FFA in the peripheral circulation, which is likely to inhibit insulin-stimulated glucose uptake in muscle and, maybe, impaired insulin secretion by the pancreas (10).

Figure 1: FFA turnover in visceral and subcutaneous adipose tissues From: Arner P. Diabetes obesity and Metabolism 3 (s1) 11-19, 2001.



Visceral obesity and Adipocytokines

Several studies have investigated the biological characteristics of both visceral and subcutaneous adipose tissue by analysis of the gene-expression profile to establish a molecular basis of visceral fat related disease. Approximately 20% of all genes in subcutaneous adipose tissue and about 30% in the visceral adipose tissue have been identified. These bioactive substances are classified as 'adipocytokines', and are subdivided into adipocytokines which are adipose tissue-specific bioactive substances (i.e. leptin and adiponectin) and adipocytokines abundantly secreted from adipose tissue, but which are nonspecific for adipose tissue (i.e. PAI-1, tumor necrosis factor-alpha, interleukins, etc.) [22].

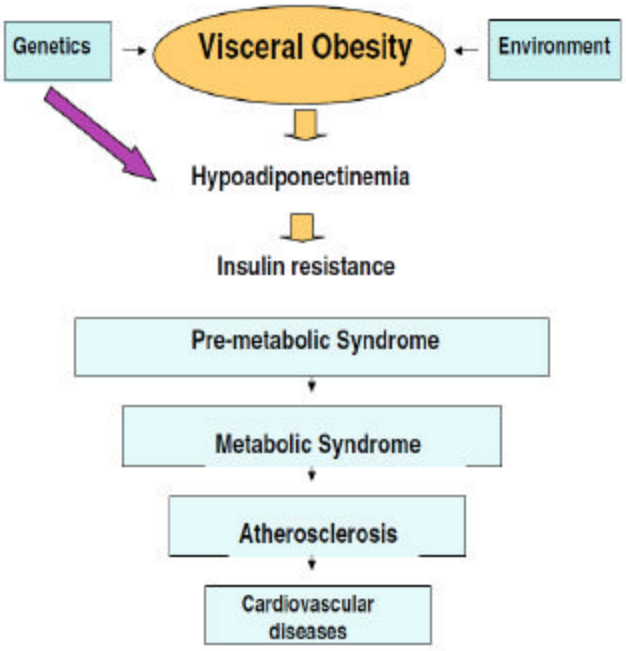
Adipocytokines are involved both in regulation of glucose and lipid metabolism, control of oxidative stress and in maintenance of the vascular wall integrity. For example, TNF- a, IL-6 and leptin are able to induce insulin resistance, whereas adiponectin improves insulin sensitivity.

Several studies suggest that leptin may be considered an important link between central obesity, hypertension and Metabolic Syndrome. Results from an Italian prospective study emphasize that higher circulating plasma leptin levels are a significant predictor of the risk of Metabolic Syndrome and, in particular, of higher blood pressure and IFG components [23].

Insulin resistance

Visceral obesity may play an important role in developing Insulin resistance, through certain inflammatory cytokines, such as IL-6, TNF-alpha, TGF b1 and monocyte chemotactic protein-1, produced by the resident fat macrophages (Box 1). These inflammatory cytokines are involved in the increased cardiovascular risk of the obese patient, independent of their role in insulin resistance (Figure 2).

Figure 2: Role of visceral obesity in the pathogenesis of metabolic syndrome. * From Kadowachi et al (24)



Visceral obesity is often associated with the endothelial up-regulation of the adhesion molecules, hypercoagulability. The inflammatory background is also probably promoted by a concomitant deficit of nitric oxide, which also appears to decrease the vasodilator properties of perivascular adipose tissue (PVAT) leading to hypoxia, inflammation, and oxidative stress. (25-28). Nevertheless, genetic factors play a role in the genesis of insulin resistance. Visceral obesity and hyperinsulinemia contribute also to the arterial hypertension. Accordingly, a vicious circle possibly develops between sympathetic activation, hyperinsulinemia and weight gain in patients with visceral obesity. Clinical and experimental studies in obese subjects demonstrate sympathetic hyperactivity, accelerated regional kinetics of catecholamines, excited neuromuscular activity, dysregulation in sodium-modulator hormones and pre-clinical left ventricular dysfunction (29-32).

The biological effects of adiponectin in humans

The first indication that adiponectin might have a role in human obesity derives from the report of Hu et al., indicating that the expression of adiponectin using Northern blots is reduced in the adipose tissue of obese mice and humans (33,34). Adiponectin is the only fat protein that is down regulated with weight gain, and it is possible that an accumulation of visceral fat might produce inhibiting factors for adiponectin synthesis or secretion, such as TNF-alpha (35, 36). Plasma adiponectin levels are higher in women than in men, and in non-obese compared to obese subjects [37]. Lower plasma levels of adiponectin are predictive of type 2 DM and are found in diabetic subjects, and in patients with hypertriglyceridemia, low HDL-cholesterol and hypertension (22, 37-39).

In fact, antiatherogenic effects of adiponectin have also been demonstrated in some clinical studies, indicating that higher adiponectin levels are associated with a reduced risk of acute myocardial infarction in men (40). However, other prospective studies (41,42) have not reported a significant cardioprotective effect of adiponectin. These conflicting results raise the possibility that adiponectin may have different prognostic implications in populations with different risk for vascular disease.

Link between Adiponectin, obesity and insulin resistance

Animal experiments using an injection of recombinant adiponectin proteins and studies on adiponectin KO mice have demonstrated that adiponectin produces effects on both body weight and insulin sensitivity in the liver and muscle (37). In a prospective human study hypoadiponectinemia did not predict obesity but did predict the development of type 2 DM.

Interestingly, significant body weight reduction in humans is shown to raise plasma adiponectin levels and improve insulin sensitivity (43).

Patterns of genetic investigation of Obesity and Type 2 Diabetes

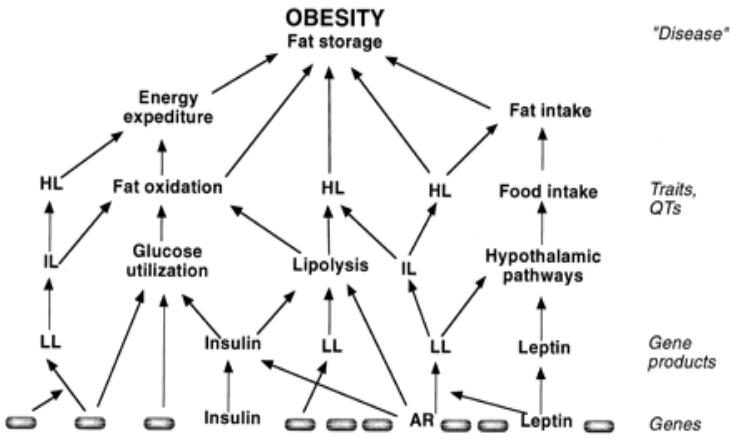
It is difficult to identify a genetic influence on continuous traits in humans, because it is difficult to separate environmental factors from genetic effects. This "multiple-factor hypothesis" (a large number of genes, each with a small effect, producing quantitative variation) is known as quantitative genetics. Obesity may be dissected into several partial phenotypes, which may be called "descriptive traits" (DT) for genetic analyses. This approach has been widely used in genome scan research for new loci. Traits can be anthropometric or body composition parameters. For example, instead of being defined as obese, a young individual can be characterized as having a BMI of 39 kg/m2, a fat mass of 49 kg, a subcutaneous depot of 41 kg, a waist-to-hip ratio of 1.21, etc. The status of obesity can also be characterized biologically in such patients with fasting serum levels of leptin at 45 pmol/l, insulin at 33 µU/ml, FFAs at 0.73 mmol/l, etc., with the hope that these DT's could partially reflect disease pathogenesis. The difficulty is that most physiological systems have hierarchical components, leading from the gene to its product, to intermediate phenotypes of greater complexity, to the ultimate phenotypes used to diagnose disease, in this case obesity as shown in figure 3. Thus high leptin, insulin, or FFA levels can be implicated in both the causal mechanisms and the consequences of the obese status (Figure 3).

Measuring "thrifty" pathogenic traits during youth

The study of young subjects is generally recommended for the genetic study of complex diseases (44). There are several reasons why this could be particularly important in the obesity-diabetes field.

First, evolutionary forces may have shaped the human genome according to mechanisms that are now directly involved in the pathophysiology of juvenile obesity and associated changes in insulin-fuel homeostasis, such as the fact that these physiological functions were of major importance for our ancestors. It is likely that prehistoric metabolic genes welcomed new mutations that favoured storage of calories (fat storage and mobilization, insulin secretion and sensitivity, leptin signalling, weight and body composition regulation, availability of glucose to the brain) (9, 45-46).

Figure 3. Schematic diagram of the relationships of genes and their products to intermediate phenotypes concurring with weight regulation and body adiposity AR: adrenergic receptor; HL, high-level phenotypes; IL, intermediate phenotypes; LL, low-level phenotypes. From: Pierre Bougnères Diabetes.



Now these genes are exerting deleterious effects on modern subjects because of an unexpected caloric richness and sedentary environment. Similarly, it is possible that insulin sensitivity underwent evolutionary changes toward increased channeling of glucose to the large human brain rather than to the insulin-sensitive muscle mass. Measuring these phenomena early in life rather than in adulthood may more closely reflect their evolutionary tendencies. In addition, the life span of early humans was limited, and evolution may have mostly worked on the physiology of young people.

Studying young individuals meets the goals of predictive genetic epidemiology because it allows the follow-up of genotyped patients through later phenotype evolution as well as conducting clinical trials. It has also been observed that the motivation and sampling of siblings and parents for genetic analysis are facilitated when medical traits, such as obesity, are detected in children and adolescents. The study of nuclear families with young sib-ships favours the analysis of sibling pairs in a comparable environment, as well as transmission disequilibrium tests (47).

Conclusion

Visceral obesity plays an important role in the development of diabetes by mobilizing free fatty acids and certain inflammatory cytokines promoting insulin resistance. Studies on molecular mechanism for visceral fat support this notion. Adiponectin which is secreted from adipose tissues is inversely correlated with weight gain. To study the genetics of obesity and diabetes, it has been suggested that a systematic approach to common juvenile obesity or Type 2 DM genetics based on measurement of related traits in a pathogenic rather than descriptive perspective may be more appropriate. To do so, individuals should be studied long before the disease starts, in a situation when traits can be measured "intact". Further investigations are needed to study the molecular mechanism of obesity for insulin resistance and diabetes in different populations since genetic predisposition plays an important role in the genesis of insulin resistance.

Physician, Jean de Meyer, who in 1909 isolated glucose lowering hormone from the pancreas and gave it the name insulin (Latin, insula= Island, as it was produced by islet cells [14].

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