Best practice in primary care pathology: review 11

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ABSTRACT

This eleventh best practice review examines two series of common primary care questions in laboratory medicine: (i) thyroid testing, and (ii) hypercalcaemia and hypocalcaemia. The review is presented in the same question–answer format as in the previous reviews. These questions and answers deal with common situations in men and non-pregnant women. The recommendations represent a précis of guidance found using a standardised literature search of national and international guidance notes, consensus statements, health policy documents and evidence-based medicine reviews, supplemented by Medline Embase searches to identify relevant primary research documents. In the case of the thyroid series, the recommendations are drawn from the 2006 guidelines published by the Association for Clinical Biochemistry, the British Thyroid Association and the British Thyroid Foundation. They are not standards but form a guide to be set in the clinical context. Most are consensus rather than evidence based. They will be updated periodically to take account of new information.

This is the eleventh in a planned series of reviews to answer a number of questions which arise in primary care use of pathology.

Each subject is introduced with a brief summary of the type of information found. While the individual subjects in the different reviews are not related, as they cover the disciplines of clinical biochemistry, microbiology, immunology, haematology and cellular pathology, they are designed once completed to form a resource which will be indexed and cover a wide range of the most common primary care laboratory issues, to be made available to users.

Where the new UK General Medical Services (GMS) contracts make specific reference to a laboratory test, the indicator or target is appended at the end of the answer.

THYROID TESTING (MPJV AND WSAS)

UK guidelines for the use of thyroid function tests were published in June 2006 jointly by the Association for Clinical Biochemistry, the British Thyroid Association and the British Thyroid Foundation.[1] These guidelines have provided a comprehensive literature review and evidence-based guidelines for the rational use of thyroid function tests for the diagnosis and management of thyroid disorders. They were written to encourage a greater understanding of thyroid function testing amongst all stakeholders including laboratory personnel, clinicians in primary and secondary care and patients and their carers. In drawing up these guidelines it was clear that there was a lack of high-quality evidence in clinical thyroid disease in the form of randomised controlled trials and meta-analyses. Consequently there was much reliance on second-level evidence such as cohort and case–control studies, with good practice points often used to plug the gaps where no real evidence existed. The guidelines, which contain over 200 recommendations, cover all aspects of thyroid disease including indications for thyroid function testing, hypothyroidism, hyperthyroidism, pregnancy, thyroid cancer and laboratory aspects of thyroid function testing. In order to illustrate the use of these guidelines, a common scenario presenting in primary care is described.

Which thyroid function test combination should a laboratory provide?

- Serum thyroid stimulating hormone (TSH) is considered a suitable screening test for primary hypothyroidism in most patients with additional tests (free thyroxine (FT4)) if outside the reference interval.
- If TSH is to be used alone, users and laboratories must identify patients thought to have possible pituitary hypothyroidism so that TSH and FT4 are measured in these cases.
- Serum TSH alone is sufficient in follow-up testing of patients at risk of developing hypothyroidism who are not being treated for thyroid disorders.

A strategy of first-line TSH may be cost effective for a wide range of clinical purposes including screening and case finding, but it may be inappropriate in patients being tested for the first time, and in some specific clinical settings. The guideline stresses that pituitary hypothyroidism can produce TSH concentrations within the reference interval but with low FT4. If laboratories are unable to identify those specimens that specifically require the measurement of serum TSH and FT4 then it would be prudent to measure serum TSH and FT4 on all specimens rather than embark on a first-line serum TSH strategy.

This would have considerable cost implications for primary care users, and we therefore recommend in the first instance that users should highlight cases in which any suspicion of hypothyroidism of pituitary origin are suspected. Measurement of serum TSH alone is appropriate after the first investigation in the sequential follow-up of individuals who have not been treated for thyroid disorders and who may be at risk of developing primary thyroid dysfunction.

In which patients should thyroid testing be performed systematically?

A 33-year-old woman presents to her family doctor complaining of gaining weight (5 kg in 6 months) and feeling tired all the time. There is no relevant family history and examination is normal.

Box 1: Examples of drugs that influence thyroid measurements either through a pharmacodynamic effect on thyroid function or by binding displacement[1 32 33]

Direct effect on thyroid function (mostly suppression)

- amiodarone[21]*
- lithium[22]
- corticosteroids
- iodinated contrast media*
- other iodine preparations* (eg, over-the-counter kelp preparations)
- interferon α*
- dopamine, levodopa.

Analytical interference: increased FT4 from displacement

- heparin, via an increase in free fatty acids
- non-steroidal anti-inflammatories
- high-dose aspirin (>2 g/day).

Drugs increasing thyroxine replacement requirements

- cytochrome P450 inducers: phenytoin, carbamazepine, ritonavir, rifampicin.

Intestinal absorbers

- sucralfate, colestyramine and colestipol, antacids containing aluminium
- ferrous sulphate
- proton pump inhibitors.

Most commercial assays have now minimised assay interference per se, although users should refer to their local laboratory to discuss this possibility if unusual results are obtained. *Iodine, amiodarone and interferon can produce either hypo- or hyperthyroidism, although the more common effect is hypothyroidism in western countries.

We recommend the following.

- Thyroid testing (TSH and FT4 if TSH outside reference interval) is recommended in all patients presenting with goitre or thyroid nodule, atrial fibrillation, osteoporosis, subfertility or dyslipidaemia (particularly if total cholesterol >8 mmol/l).
- Thyroid testing (TSH, FT4 and anti-thyroperoxidase (anti-TPO) antibodies) is recommended pre-conception, at booking and at 3 months post partum in all women with type 1 diabetes.
- Patients with type 1 diabetes should have annual TSH testing, and those with type 2 diabetes should be tested at the time of diagnosis.
- Annual TSH screening (and screening before and 6–8 weeks after subsequent pregnancies) is recommended in all women who have suffered post-partum thyroiditis.
- Annual TSH screening is recommended in all patients with Down or Turner syndrome.
- Patients taking specific drugs (eg, amiodarone, lithium) should be tested according to established guidelines.

Targeted thyroid function testing is recommended on the basis of the relatively high prevalence of thyroid dysfunction in selected groups. In particular, thyroid function testing at diagnosis is considered to be cost-effective in type 2 diabetic patients. Routine testing in patients acutely admitted to hospital is not recommended because of the high prevalence of non-thyroidal illness, producing lowered or raised TSH concentrations in the absence of thyroid disease.

Should opportunistic population thyroid function testing be performed?

- Screening of the healthy population is not recommended.
- Opportunistic screening of adult women at menopause or presenting in primary care with non-specific symptoms may be considered.

Recommendations on population screening for thyroid disease, particularly subclinical hypothyroidism, vary. Targeted opportunistic screening in menopausal women or women with non-specific symptoms is recommended based principally on a cost-effectiveness analysis, suggesting that screening for hypothyroidism in this group compares well with other preventative practices and improves quality of life.

TSH within reference interval, low/"normal" FT4: does this patient have primary hypothyroidism and require treatment with thyroxine?

A GP receives the thyroid function test result FT4 10.0 pmol/l (reference interval 10–20 pmol/l) and TSH 4.4 mU/l (reference interval 0.4–4.5 mU/l) and contacts the laboratory for advice.

We recommend the following.

- The diagnosis of primary hypothyroidism requires the measurement of TSH and FT4.
- Primary hypothyroidism is excluded if the serum TSH is in the reference interval and the patient is not taking medication known to affect TSH.
- Consider secondary (pituitary or hypothalamic) causes if TSH is in the reference interval but FT4 is reduced.
- Note that reference intervals may differ in pregnant women depending on trimester of pregnancy.[2]

It is recognised that there is a growing distrust of thyroid function tests among a minority of patients because they have test results within the reference interval but have symptoms suggestive of hypothyroidism. It is accepted that the guidelines quote decision limits for TSH with the aim of simplifying, standardising and optimising clinical decisions. It is recognised that there can be variability in bias between the various commercial assays available. Nevertheless, large population surveys from the US using rigorous criteria for selecting a "healthy" reference population have failed to provide any evidence for narrowing the reference interval of TSH.

Box 2: National Institutes of Health consensus conference on primary hyperparathyroidism 2002: recommendations for surgery[16]

Presence of any one of

- serum adjusted calcium (ACa) >2.9–3.0 mmol/l (local laboratory dependent)
- urine calcium >10 mmol/24 h
- creatinine clearance reduced ⩾30%
- bone mineral densitometry Z score <−2.0 (forearm)
- age <50 years
- patient request; adequate follow up unlikely.

2002 changes/additions to 1990 recommendations

- serum ACa >0.25 mmol/l above the upper limit of local laboratory reference range
- bone mineral densitometry T score <−2.5 (at any site).

Box 3: Causes of hypocalcaemia (A Al-Bahrani, W D Fraser, Royal Liverpool Hospital data 2005)

Hypoparathyroidism (inherited and acquired) (22%)

- parathyroid or thyroid surgery
- autoimmune hyperparathyroidism
- hypomagnesaemia
- inherited (pseudohypoparathyroidism and others).

Vitamin D deficiency (73%)

- malnutrition and malabsorptive diseases
- low sun exposure/housebound/ethnicity
- liver disease
- renal disease
- hyperphosphataemia.

Drugs (3%)

- inhibiting bone resorption: bisphosphonates, calcitonin-cinacelet
- cytotoxics: cisplatin/cytosine/doxorubicin
- antimicrobials: ketoconazole
- furosemide
- anticonvulsants (phenytoin).

Extensive osteoblastic activity (osteoblastic metastases, "hungry bone syndrome") (2%).

Box 4: Summary of review 1[18]

Lipids monitoring

- How often should patients' lipids be tested after starting lipid lowering therapy?
- How often should cholesterol/lipids be tested once a patient has reached target/optimal cholesterol?
- How often and frequently should cholesterol/lipids be tested when assessing a patient's coronary risk.
- How often should liver enzymes (liver function tests (LFTs)) be routinely measured in patients taking statins?
- What if LFTs become elevated in a person taking a statin?
- How often should creatine kinase (CK) be measured in patients taking statins?
- What if CK becomes elevated in a person taking a statin?
- In which patients should vitamin B_{12} and folate concentrations be measured ?
- How should vitamin B_{12} or folate deficiency be monitored in patients who have or are receiving replacement?

Paraproteins/myeloma

- What are the uses of serum immunoglobulins and electrophoresis?
- What follow up is required once a patient has been found to have a paraprotein band?

Helicobacter pylori

- Who should I test for *H pylori*?
- Which non-invasive helicobacter test should I use?
- What do I do if I find my patient has *H pylori*?
- Do I retest for *H pylori* after treatment?
- Which test should I use if I need to retest?
- When should I refer patients for endoscopy to diagnose *H pylori*?

Raised TSH, low/"normal" FT4: when should evidence of thyroid failure be treated?

The GP decides to repeat the test 6 months later. The symptoms have persisted. The following thyroid function test results are now available: FT4 11.2 pmol/l (reference interval 10–20 pmol/l) and TSH 8.5 mU/l (reference interval 0.4–4.5 mU/l) and the GP contacts the laboratory for advice.

We recommend the following.

- If serum TSH on screening is mildly raised (5–10 mU/l), and the FT4 is within the reference interval:
  - exclude non-thyroidal illness and drug interference
  - repeat 3–6 months later, with measurement of serum FT4
  - measure serum anti-TPO antibodies.
- If the serum antibody measurement is positive:
  - measure serum TSH annually or earlier if symptoms
  - start thyroxine therapy if the serum TSH rises above 10 mU/l
  - consider possible trial of thyroxine if TSH over 5 mU/l on individual case basis.
- If the serum antibody measurement is negative:
  - repeat measurement of serum TSH approximately every 3 years.
- If the serum TSH is >10 mU/l and serum FT4 concentration is within the reference interval:
  - the person has overt hypothyroidism and should be treated with thyroxine.
- If the serum TSH concentration is >10 mU/l and serum FT4 concentration is within the reference interval:
  - treatment with thyroxine is recommended in most cases
  - further advice should be sought if FT4 well within normal range (eg, >15 pmol/l).
- If the serum TSH concentration is above the reference interval but <10 mU/l:
  - there is no evidence to support the benefit of routine early treatment with thyroxine in non-pregnant patients with a serum TSH above the reference interval but <10 mU/l. A therapeutic trial of thyroxine may be considered on an individual patient basis.

The guideline recommends that patients with a TSH greater than 10 mU/l and FT4 below the reference interval should be considered to have overt hypothyroidism. In those with TSH between 5 and 10 mU/l and FT4 within the reference interval, a further test in 3–6 months is recommended, combined with thyroid antibody (TPO antibody) measurement. Positive anti-TPO antibodies (above the positivity threshold for the laboratory method used) indicate a high likelihood of developing hypothyroidism. Treatment is recommended in patients with TSH greater than 10 mU/l but normal FT4 concentration. There is no clear statement on action in patients with TSH between 5 and 10 mU/l and low FT4 and it would appear reasonable to decide on an individual case basis whether to offer treatment or continue to monitor depending on symptoms and actual FT4 and TSH values. Patients with positive TPO antibody are recommended to have an annual thyroid function test. Those who are antibody negative are recommended to have a thyroid function test every 3 yeras.

What should be the target for TSH in those on thyroxine replacement?

The hypothyroid patient above is positive for TPO antibody. After 2 years the serum TSH has risen to 12 mU/l. She is

Box 5: Summary of review 2[19]

Allergy

- When should I request total IgE in general practice?
- When should I request allergen-specific IgE ("RAST" radioallergosorbent testing)?

Menopause

- When should I request tests for menopause?
- What tests are required to monitor women on hormone replacement therapy?
- When should I request an erythrocyte sedimentation rate?

Urine cytology

- When should I request urine cytology (particularly in the context of microscopic haematuria)?

Infection: urinary

- In children, when should I send a urine specimen in patients with possible urinary tract infection?
- In the elderly, when should I send a urine specimen in patients with possible urinary tract infection?
- In catheterised patients, when should I send a urine specimen in patients with possible urinary tract infection?
- When should I use urine dipsticks?
- How should I interpret urine dipstick results?
- How should I obtain a urine specimen?
- How should I interpret laboratory results?

Box 6: Summary of review 3[20]

Erythrocyte sedimentation rate

- What is the utility of the erythrocyte sedimentation rate?

Blood count abnormal (1)

- When and how should I investigate a low platelet count?
- What is the significance of a high platelet count?
- What is the significance of high haemoglobin?

Anaemia: iron-deficient

- In which patients with anaemia should iron deficiency be assessed and what tests should be used?
- How should iron deficiency be monitored in patients who have received replacement treatment?

Lipids: secondary hyperlipidaemia

- When should I screen for secondary hyperlipidaemia and what investigations are required?
- When and why should I measure triglycerides at the same time as I measure cholesterol?

Lipids: triglycerides

- What triglyceride levels are associated with a risk of pancreatitis and require treatment on this basis?

Diabetes monitoring

- How frequently should HbA_{1c} be measured in diabetic patients?
- When should HbA_{1c} be used in the diagnosis of diabetes or in non-diabetic patients?
- How often should microalbumin be measured in patients with diabetes?
- How are HbA_{1c} values interpreted?

commenced on thyroxine replacement and stabilised on a dose of 100 μg daily. Her symptoms have persisted. When tested 8 weeks later, the following thyroid function test result is available: FT4 19.4 pmol/l (reference interval 10–20 pmol/l) and TSH 0.5 mU/l (reference interval 0.4–4.5 mU/l).

We recommend the following.

- Annual measurement of thyroid function (minimum of TSH) is recommended in all patients receiving long-term replacement thyroxine.
- Measurement of TSH and FT4 is usually recommended to assess thyroid replacement with thyroxine. TSH alone may be all that is required and measurement of FT4 may only be required if TSH is outside of the reference interval.
- Replacement should be assessed from clinical well-being and thyroid testing.
- A minimum interval of 2 months is recommended before measuring thyroid function after changing thyroxine dose.
- Thyroid measurement may be appropriate 2 months after starting drugs which influence thyroxine requirements (box 1).
- Recommended aims in thyroid replacement are for TSH within and FT4 within (or slightly above) the population reference interval.
- Not all patients will be clinically optimally controlled within this range.

The guidance is based on observational studies indicating high rates of subclinical hypo- and hyperthyroidism in patients taking long-term thyroxine, and on the potential effect of some commonly prescribed drugs (iron salts, oestrogens, phenytoin, carbamazepine) to alter thyroxine requirements. This could suggest benefit from monitoring after starting such drugs. The guideline recommended that variations in dosage requirement due to concomitant drugs be taken into account. After changing dose, thyroid function should not normally be measured within 2 months, the period required to reach thyroid steady state. The recommended target range is based on TSH, for which most evidence is available. This target is a TSH which is within the reference interval. If below it should be at least detectable (ie' not suppressed below the limit of detection of the method). To achieve this, the FT4 will normally lie within or slightly above the reference interval. Different TSH methods have different limits of detection although there is inadequate evidence to discriminate between different levels of TSH suppression at these limits. We therefore use the term "detectable by the method".

This strategy will prevent over-replacement in patients and decrease possible adverse effects noted in terms of cardiovascular outcome and loss of bone density. It has been suggested that in a minority of patients clinical well-being can only be achieved if the serum TSH is subnormal or suppressed and that this is of no detriment to the patient as long as the serum FT3 is unequivocally normal. However, no evidence could be found to support such a recommendation that in non-pregnant patients titrating the serum TSH to the lower half of the reference interval results in improved outcomes.

Low TSH, "normal" FT4: does this patient have hyperthyroidism?

A GP receives the following thyroid function test result: FT4 16.2 pmol/l (reference interval 10–20 pmol/l) and TSH 0.1 mU/l (reference interval 0.4–4.5 mU/l) and contacts the laboratory for advice.

If the serum TSH is below the reference interval but above the limit of detection of the laboratory method:

Box 7: Summary of review 4[21]

Drugs: antithyroid

- What safety monitoring is required in a patient receiving carbimazole or propylthiouracil in primary care?

Drugs: digoxin

- What safety monitoring is required in a patient receiving digoxin in primary care?

Drugs: amiodarone

- What safety monitoring is required in a patient receiving amiodarone in primary care?

Prostate cancer

- Should prostate-specific antigen (PSA) be measured in asymptomatic men?
- What action should be taken in a patient with a raised PSA?
- How often PSA should be measured in patients who have been diagnosed as suffering from prostate cancer?

Infection: vaginal

- When should I send a vaginal swab in a woman with abnormal vaginal discharge or vaginitis?
- When should I take an endocervical swab for chlamydia?
- Do I need to retest for chlamydia after treatment?
- How do I obtain a vaginal swab?

Fertility

- Who should be investigated for subfertility?
- What tests should be used to investigate subfertility in men?
- When should primary amenorrhoea be investigated and what tests are used?
- What tests should be used to investigate primary amenorrhoea?
- When should secondary amenorrhoea be investigated?

Box 8: Summary of review 5[22]

Liver function test: abnormal

- How should I investigate an isolated slightly raised alkaline phosphatase in an asymptomatic adult?
- How should I investigate an isolated "slightly raised" bilirubin in an asymptomatic adult?
- How should I investigate abnormal transaminases in asymptomatic patients without risk factors for or clinical features of liver disease?
- How should I investigate abnormal transaminases in patients with risk factors for, or clinical features of liver disease?
- How should I investigate abnormal gamma glutamyl transpeptidase in an asymptomatic patients without risk factors for or clinical features of liver disease?
- When should I refer for secondary assessment and possible liver biopsy?

Drugs: lithium

- When should I measure blood lithium concentrations and what additional testing is recommended?
- When should I measure blood lithium concentrations after a change in dose or after starting treatment?
- What is the target range for lithium, and what action should I take for raised lithium concentration?

Deep vein thrombosis

- In which patients with suspected deep vein thrombosis should a D-dimer test be performed in a primary care setting?

- exclude non-thyroidal illness and drug effects (eg, patients on corticosteroid or dopamine therapy)
  - repeat 1 or 2 months later together with serum FT4 and FT3
  - continue to monitor if FT4/FT3 rising.

If the serum TSH is below the limit of detection of the laboratory method:

- measure serum FT4 and FT3 to exclude overt hyperthyroidism
- FT3 or FT4 above reference interval indicated hyperthyroidism.

If treatment is not undertaken, serum TSH should be measured every 6–12 months, and serum FT4 and FT3 measured if the serum TSH result is below 0.1 mU/l.

Patients with low TSH but normal FT4 and FT3 (free triiodothyronine) concentrations are deemed to have subclinical hyperthyroidism. Antibody testing is not recommended in these patients unless the clinical context is suggestive of hyperthyroidism, but those in which results are not explained by non-thyroidal illness or drug therapy should have tests repeated and if not treated, should be followed up with thyroid testing every 6–12 months. Endocrine referral is recommended for persistent subclinical hyperthyroidism. Free T3 measurement is require to identify cases of T3 toxicosis.

A drug history is important to identify patients taking pharmacological agents which may influence TSH or FT4 concentrations either because of their pharmacological activity (dopamine, corticosteroids, amiodarone) or assay interference (displaced protein binding with heparin, increasing FT4 concentrations).

GMS Contract indicator: percentage of hypothyroid patients with record of thyroid function tests performed in previous 15 months.

HYPERCALCAEMIA AND HYPOCALCAEMIA (WSAS AND WDF)

In many situations hypercalcaemia will develop in a context of known disease and the cause may be apparent. In this situation practitioners may be more concerned with action limits for treatment and/or referral. In others, the cause may not be apparent and the guidance below is designed to elucidate the more common causes. As with other biochemical electrolyte disorders, the "action limits" offered are only approximate guidance, as rate of change and clinical signs and symptoms are more important than absolute values.

Most laboratories report total calcium concentration in serum. This is influenced in particular by serum albumin concentration, and for most primary care purposes the relevant parameter is the "adjusted calcium" concentration (with the exception of rare patients with congenital dysalbuminaemic states). While ionised calcium can be measured, this is not used in routine primary care testing. The questions and answers therefore relate only to the serum calcium concentration adjusted for the serum albumin concentration.

What should I do about an unexplained raised serum adjusted calcium (ACa)?

We recommend the following.

- Assess symptoms:

Box 9: Summary of review 6[23]

Drugs: diuretics/ACE inhibitors (AECIs)

- How often should renal function (creatinine and electrolytes) be monitored in heart failure patients receiving diuretics, ACEI or angiotensin receptor blocker (ARB)
- How often should renal function tests be monitored in hypertensive patients receiving, ACEI or ARB?
- How often should electrolytes/renal function tests be measured in hypertensive patients receiving diuretics?
- What level of rise in creatinine/electrolytes is acceptable when a patient is started on a diuretic or ACEI/ARB in heart failure or hypertension.

Joint disease

- What information does rheumatoid factor (RhF) measurement provide in the investigation of multiple small joint disease and in whom should I measure it?
- Should I repeat RhF measurement to obtain information in the monitoring of rheumatoid disease?
- When should I test for HLA B27 in a patient with back pain?

Diarrhoea: adult/child

- What initial screening investigations are used to investigate chronic adult diarrhoea in primary care in the UK?
- What initial screening investigations are used to investigate chronic childhood diarrhoea in primary care in the UK?

Viral infections

- What tests should I do if a pregnant woman has been in contact with chicken pox or shingles?
- When should I test for mumps, and should I notify mumps infection?

Box 10: Summary of review 7[24]

Blood count: abnormal (2)

- When should I refer an adult patient with a lymphocytosis ($>5\times10^9$/l)?
- When should I refer a patient with a low neutrophil count?
- How should I interpret a raised eosinophil count?

Viral disease (2)

- When should I investigate a patient for possible infectious mononucleosis (IM) due to Epstein–Barr virus?
- What tests should I use to investigate a patient for possible IM?
- What tests should I do for a pregnant woman in contact with a child with a macular rash?

Lipids: high density lipoprotein (HDL)

- When and how often should HDL-cholesterol (HDL-C) be measured together with total cholesterol (TC) and LDL-cholesterol (LDL-C)?
- When and how often should HDL-cholesterol (HDL-C) be measured together with total cholesterol (TC) and LDL-cholesterol (LDL-C)?
- What is a low HDL-C and how can it be treated?

Myocardial infarction: troponin

- When should I measure cardiac troponin in someone who comes to the surgery with chest pain?
  - lethargy/weakness
  - confusion/impaired mentation
  - anorexia
  - nausea/vomiting
  - constipation
  - polyuria/polydipsia
  - bone pain.
- Repeat to confirm unless patient acutely unwell and immediate referral considered.
- Consider more common causes in primary care depending on clinical presentation:
  - primary hyperparathyroidism
  - hypercalcaemia of malignancy
  - kidney disease (vitamin D treatment)
  - calcium + vitamin D treatment
  - immobilisation
  - effect of low albumin concentration on calcium adjustment.
- Ensure phosphate, alkaline phosphatase and renal function requested if not already available.
- Assess urgency
  - ACa 2.65–3.0 mmol/l.
- Request parathyroid hormone (PTH) with repeat ACa measurement to classify as parathyroid or non-parathyroid cause.
- For non-parathyroid causes, add erythrocyte sedimentation rate (ESR), serum electrophoresis and targeted imaging investigations depending on clinical presentation pending specialist assessment
  - ACa 3–3.4 mmol/l and symptomatic, or >3.4 mmol/l: hospital admission usually required.

Hypercalcaemia can be defined as serum calcium adjusted for the serum albumin concentration above the upper limit of the population reference interval 2.62 mmol/l.[3 4] Different ranges are published depending on method and population studies although a threshold of 2.65 mmol/l (at the upper end of quoted adult ranges) appears reasonable to trigger investigation. Minor variations with age and sex have been described.[3] In view of analytical imprecision and method differences influencing the albumin adjustment (particularly albumin concentrations outside of the reference interval, when the adjustment becomes increasingly less valid), values above 2.65 mmol/l should be confirmed before further investigation unless a patient's clinical state merits immediate referral. Values more than 3 SD outside of the population mean (approximately 2.70 mmol/l) are statistically very unlikely to be findings due to variation.

Total calcium is adjusted for the serum albumin concentration ACa (mmol/l) = serum total Ca (mmol/l) + (0.02×Alb(g/l)),[3 4] although equations can vary depending on the "normal" albumin concentration adopted.[5] The adjustment is however an approximation that may be inaccurate particularly at extreme albumin concentrations, and inter-individual differences exist.

Hypercalcaemia can be classified as mild (up to 3.00 mmol/l), moderate (up to 3.40 mmol/l) or severe (over 3.40 mmol/l).[4–8] The threshold for severe of 3.40 mmol/l corresponds to 13.6 mg/l. One guidance quoted lower thresholds for severe hypercalcaemia.[9] Primary care investigation of hypercalcaemia would usually be limited to mild and asymptomatic moderate hypercalcaemia, as acute management of severe or symptomatic hypercalcaemia combined with its subsequent investigation would usually be indicated in secondary care. As for other electrolyte abnormalities,

Box 11: Summary of review 8[25]

Faecal occult blood

- When should I do a faecal occult blood test in an adult with lower gastrointestinal (GI) symptoms?
- What faecal occult test type should I use and how many samples are required?
- How do I interpret faecal occult blood test results in adult patients with lower GI symptoms?

Anticoagulation

- What international normalised ratio (INR) monitoring is required for a patient on warfarin therapy?
- What additional monitoring is required if a patient starts a drug which can interfere with warfarin?

Sputum cytology/lung cancer

- When should I request sputum cytology?

Sodium

- How should I investigate a patient with raised serum sodium concentration?
- How should I investigate a patient with low serum sodium concentration?

rate of change is more important than absolute values in influencing the onset or severity of symptoms.

Values are also increased by additional calcium binding by certain paraproteins.[10] Prolonged venous stasis for a tourniquet is cited as a reason for increased calcium[3] producing changes of 0.12–0.25 mmol/l or +1.6 to +3.6% between 1 and 3 min after application,[11] although some authors believe the change to be of minimal significance in practical circumstances,[12] and the advice that blood should be taken without prolonged tourniquet use would seem reasonable

Various sample-related changes (haemolysis, lipaemia) may interfere with calcium measurement. Local laboratories should be aware of method specific interferences as these vary qualitatively and quantitatively.

Box 12: Summary of review 9[26]

Potassium

- What is a high serum potassium?
- How should I treat a severely increased or rapidly rising potassium?
- What should I do if I suspect a high potassium result is spurious:
- What should I do about a low serum potassium?
- How should I investigate a low serum potassium?
- How should I treat a low serum potassium?

Infection/leg ulcer

- What can a microbiological sample from a venous leg ulcer tell me?
- When should I sample a venous leg ulcer?
- How should I sample a venous leg ulcer for microbiology investigation?
- How do I interpret the laboratory report?
- How do I treat a wound that is clinically infected?

Table 1 Causes of hypercalcaemia in hospital practice 2005 (A Al-Bahrani, WD Fraser, Royal Liverpool Hospital data, 2005)

Cause of hypercalcaemia	No. of patients (%)
Chronic kidney disease	53
Renal transplant	21
Hypercalcaemia of malignancy	11
Osteoporosis	7
Primary hyperparathyroidism	4
Diabetes, liver disease, Paget disease	3
Granulomatous disease	0.5

PTH provides discrimination between the leading causes of hyperparathyroidism and is recommended as an initial test.[4 6 7 9]

Prior to taking samples for PTH in a primary care setting, users are recommended to check local guidance as some PTH methods require specific collection tubes or rapid sample separation, and therefore the sample to be taken close to the laboratory.

The clinical filter will identify predisposing situations including drug-induced causes, particularly thiazide diuretics and hypercalcaemia occurring in specific clinical contexts (table 1 shows a recent audit of causes in a hospital population).

While other tests may provide supporting information none offer sufficient specificity to establish a diagnosis. While serum phosphate is frequently low in primary hyperparathyroidism, this neither confirms nor excludes the diagnosis. The alkaline phosphatase may be raised in primary hyperparathyroidism, but it may also be raised in metastatic malignancy and Paget disease, although hypercalcaemia is uncommon in the latter in the absence of either prolonged immobilisation or co-existent hyperparathyroidism.[13] Indications for surgery in hyperparathyroidism are shown for reference in box 2.

In the absence of consumption of vitamin D or vitamin D analogues, suppressed PTH indicates a probable non-parathyroid cause due to lung, breast or haematological malignancy (74%) head and neck, renal or prostate malignancy (11%) or other/unknown primary malignancy (15%).[14] This would normally prompt secondary care referral, although useful information in the absence of clinical pointers can be obtained from a full blood count, renal and hepatic profiles, plasma ESR (or viscosity) and serum and urine protein electrophoresis.

One rare diagnosis that may produce a similar presentation to hyperparathyroidism is familial hypocalciuric hypercalcaemia (FHH), in which PTH may not be suppressed, but in which urinary calcium is reduced, whereas this is raised in primary hyperparathyroidism[6] (table 2).

What should I do about a low serum ACa?

We recommend the following.

- Repeat within a week to confirm unless patient acutely unwell and immediate referral considered.
- Rapidly falling values or values under 1.9 mmol/l may require immediate referral.
- Assess symptoms and refer immediately if symptomatic:
  - peripheral paraesthesiae
  - cramps
  - psychological changes
  - seizures
  - bronchospasm
  - tetany

Table 2 Comparison of clinical and biochemical findings in familial hypocalciuric hypercalcaemia and primary hyperparathyroidism[17]

Sign, symptom or measurement	FHH	Primary HPT
Age/gender	<40/equal	>50/majority female
Symptoms	Unrelated to Ca	Ca related
Plasma ACa, mmol/l	2.55–3.5	2.55–4.5
Intact PTH (range, median), pmol/l	Majority within reference range (0.9–11.0, 3.0)	Majority above reference range (2.5–84.5, 8.2)
Plasma Mg (range, median), mmol/l	Trend higher (0.78–1.18, 0.94)	Trend lower (0.34–1.03, 0.84)
Plasma 1,25-$(OH)_2$-vitamin D (range, median), pmol/l	Within reference range (54–134, 87)	Often elevated (62–212, 105)
Ca_{Cl}/Cr_{Cl} (range, median)	Majority <0.01 (0.001–0.018, 0.005)	Majority >0.015 (0.001–0.060, 0.019)

FHH, familial hypocalciuric hypercalcaemia; HPT, hyperparathyroidism; ACa, adjusted Ca; Ca_{Cl}/Cr_{Cl}, ratio of calcium clearance to creatinine clearance.

  - dystonic movements, Chvostek or Trousseau signs
  - ECG: long QT interval or arrhythmia
  - cataract.
- Consider:
  - possible spurious result (mainly EDTA but also citrate/oxalate contamination)
  - effect of high albumin concentration on calcium adjustment
  - values changing rapidly or below 1.9 mmol/l may require urgent advice from secondary care.
- Consider causes related to patient history:
  - renal/hepatic disease
  - parathyroid/thyroid surgery
  - drug history
  - predisposing factors for vitamin D deficiency: malnutrition/housebound/malabsorption.
- Ensure phosphate, alkaline phosphatase and renal function requested if not already available.

Hypocalcaemia can be defined as a serum calcium adjusted for the serum albumin concentration below the population reference interval 2.15 mmol/l (adult male <60 years old).[3] Different ranges are published depending on method and population, although a threshold of 2.15 mmol/l (at the lower end of quoted adult ranges) appears reasonable to trigger investigation. Threshold values of hypocalcaemia are described as those above which symptoms generally do not appear (1.75 mmol/l[4] and 1.80–1.87 mmol/l[7]), although rate of change is more important than absolute values. In the absence of clear guidance we have suggested the upper of these figures (rounded off to 1.9 mmol/l) as a threshold at which secondary care advice should be considered even if a patient is asymptomatic, unless the cause is apparent.

Minor variations with age and sex are also described.[3] Five per cent of the healthy population will have values outside of this range, and in view of additional analytical imprecision and approximation introduced by the albumin adjustment equation, particularly at extreme albumin concentrations, it would be prudent to recheck an out-of-range value, and consider the possibility of statistical outliers in patients with serum calcium concentrations less than 5% outside of the range. Values more than 3 SD outside of the mean (approximately 2.1 mmol/l) are statistically very unlikely to be findings due to variation. Symptoms of hypocalcaemia are shown in table 2.

No consensus on severity stratification was found, probably because rate of change is more important than absolute values in influencing the onset or severity of symptoms.

Spurious results may arise from cross-contamination with certain anticoagulants used to collect plasma samples (potassium EDTA, citrate, oxalate) from assay interference in gross lipaemia and in patients with markedly elevated globulins,[15] although the reverse may also occur.[10]

Causes of true hypocalcaemia are grouped into three categories.

The causes of hypoparathyroidism may be obvious – such as parathyroid or thyroid surgery – or require further investigation (autoimmune or more rarely amyloid or granulomatous parathyroid disease). Various inherited hypoparathyroid syndromes exist, including pseudohypoparathyroidism, that present firstly in adolescence or early adulthood. These may be suggested by a family history of calcium or endocrine disorders, although, as the modes of inheritance vary, a history may not be found.

Vitamin D deficiency may be suspected from the clinical context: malnutrition or limited sun exposure (particularly combined with dark skin colour), malabsorption or other known gastrointestinal, liver or renal disease.

Finally, a range of drugs may lower calcium either as intentional therapeutic use or by a range of different effects (see box 3).

GMS Contract indicator: none.

Box 13: Summary of review 10[27]

Diabetes (2)

- When should a glucose tolerance test (GTT) be performed in patients and if abnormal how often should it be repeated?
- What is more appropriate, interval fasting blood glucose or GTT in patients with impaired fasting glycaemia?
- When can blood BM measurements usefully be measured in primary care rather than a laboratory sample?
- When should a laboratory glucose sample be tested in diabetic patients?

Estimated glomerular filtration rate (eGFR)

- How should I calculate eGFR?
- How often should I measure eGFR?

Antenatal testing

- What antenatal tests should I perform on a newly pregnant woman (first and subsequent pregnancies)?

Drugs: methotrexate

- What safety monitoring is required for methotrexate used in non-malignant disease?

CONCLUSION

This eleventh review brings a running total of approximately 122 question and answer sets written in order to provide an overview of current advice in the use of laboratory tests in primary care. Answers to the first 10 question and answer sets can be found in reviews 1–10.[18–27] They have all used a common

Box 14: Summary of review 11

Thyroid testing

- In which patients should thyroid testing be performed systematically?
- Should opportunistic population thyroid function testing be performed?
- Which thyroid function test combination should a laboratory provide?
- "Normal" thyroid stimulating hormone (TSH), low/"normal" free thyroxine (FT4). Does this patient have primary hypothyroidism and require treatment with thyroxine?
- Raised TSH, low/"normal" FT4. When should evidence of thyroid failure be treated?
- What should be the target for TSH in those on thyroxine replacement?
- Low TSH, 'normal' FT4. Does this patient have hyperthyroidism?

Calcium

- What should I do about a raised serum adjusted calcium (ACa)?
- What should I do about a low serum ACa?

search methodology[28] although where recent systematic reviews have been performed, the guidance relies heavily also on the findings of these reviews. For authors wishing to consult the UK GMS Contract and related quality and outcomes framework, these can be found in[29–31] respectively.

Summaries of the content of the 11 reviews is provided for reference in boxes 4–14. These answers are currently in the process of being updated as the first now date from 2005, and it is intended that they will be revised on a biannual basis. We are also in the process of indexing these for a website to allow a more logical means of accessing the individual subjects than was necessarily imposed by the constraints of authoring a large body of topics in a relatively short period of time. Details of this will be published shortly.

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