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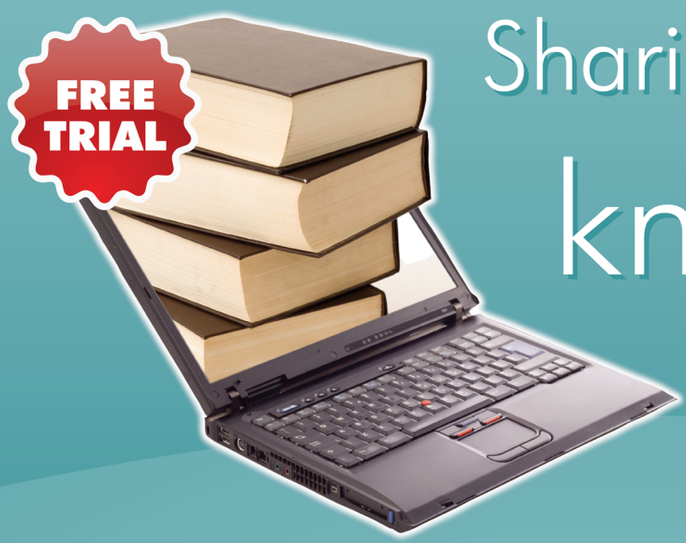

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Volume 8, Issue 5

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THE ACUTE DIABETIC FOOT

CM Amery

Abstract

Diabetic foot disease is a devastating complication of diabetes mellitus and may lead to prolonged disability, sepsis or death.

This article provides background information relating to diabetic foot disease followed by a practical guide to the management of the acutely infected diabetic foot.

Introduction

Diabetic foot disease is a major cause of disability and mortality in patients with diabetes mellitus. Diabetic foot disease comprises the complications derived from the presence of peripheral neuropathy with or without peripheral vascular disease in patients with diabetes.

Studies estimate that around 41% of patients with diabetes have peripheral sensorimotor neuropathy 10 years post diagnosis (1), whereas the prevalence of peripheral vascular disease in patients with diabetes has been quoted as 8.7% in type 1 diabetes up to 23.5% of patients with type 2 diabetes (2).

Diabetic foot disease includes a number of conditions precipitated by the presence of peripheral neuropathy and / or peripheral vascular disease. Such conditions include, foot ulceration, the Charcot foot and critical ischaemia with or without necrosis. This collection of conditions may result in both major and minor amputation, most often triggered by superadded infection (3).

The prevalence of major amputation in diabetes mellitus varies from country to country and from region to region in the United Kingdom (4). Major amputation is of course associated with a high economic cost, both in terms of burden on the NHS and personal cost due to unemployment (Williams & Airey, 2000, p.14), Prognosis post major amputation is poor; in Leeds of those who had a major amputation for diabetes-related problems during 2010, 25.8% were dead by the end of 2011 (5).

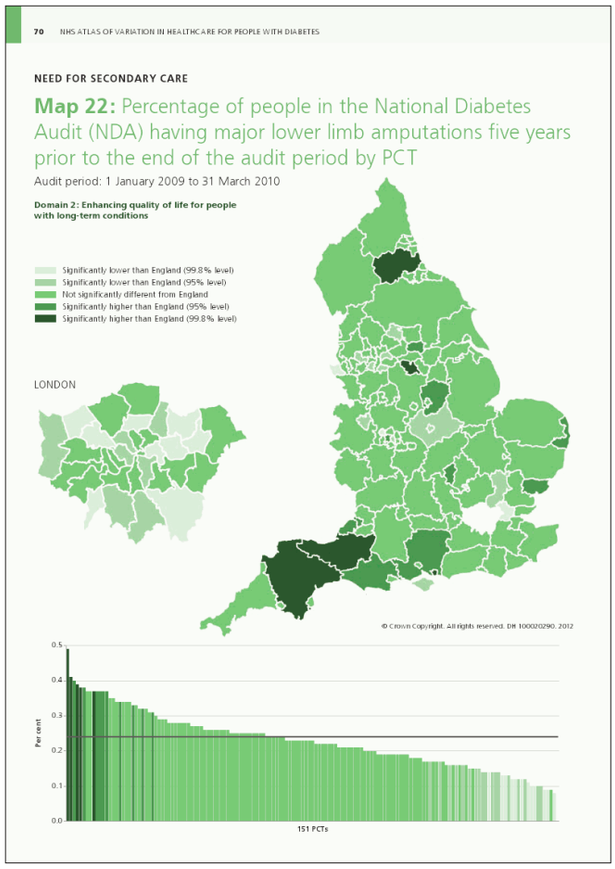

Figure1: Atlas of Variation: Map of Amputation Rates.

It is, therefore, very important to know how to assess the acute diabetic foot, to treat infection promptly and thus avoid complications such as sepsis, amputation and death.

THE ACUTE DIABETIC FOOT

CM Amery

Assessment Of The Patient With An Acute Diabetic Foot

Step 1: Is the patient sick?

There are a number of general features which suggest that the patient is unwell and will require urgent admission for intravenous antibiotics and specialist review.

These include:

- *Pyrexia*
- *Feeling generally unwell with "flu-like" symptoms*
- *Hyperglycaemia*
- *Vomiting*
- *Confusion*
- *Sepsis / Shock*
- *Presence of Diabetic Ketoacidosis (DKA)*

Step 2: Clinical Assessment of the Acute Diabetic Foot

- *Always remove all bandages / dressings to fully assess the foot*
- *Are there signs of cellulitis? (i.e. redness, induration, warmth, swelling, tenderness)*

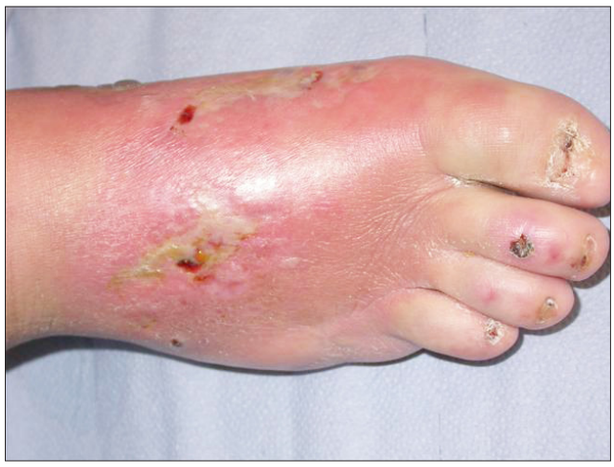

Figure 2: Cellulitis in a diabetic foot.

- *Is there evidence of ulceration / open wound?*
- *Is there pus?*
- *Does it smell bad?*
- *Is there obvious necrosis?*

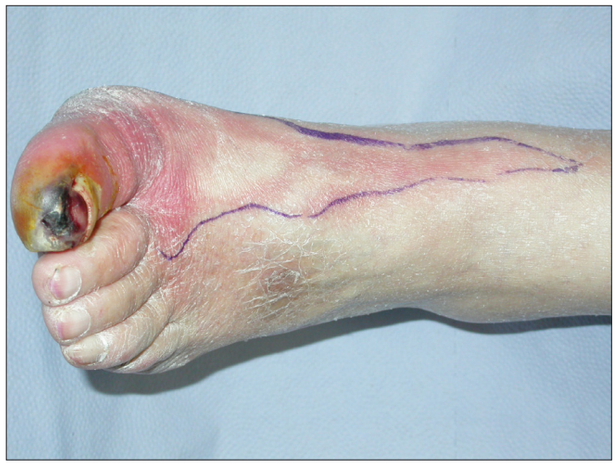

Figure 3: Necrosis of apex of first toe with ascending infection.

- *Is it painful? (Pain in a usually neuropathic foot suggests deep infection or fracture)*
- *Are the foot pulses present?*
- *Is it cool, pale and pulseless? (Critical Ischaemia)*

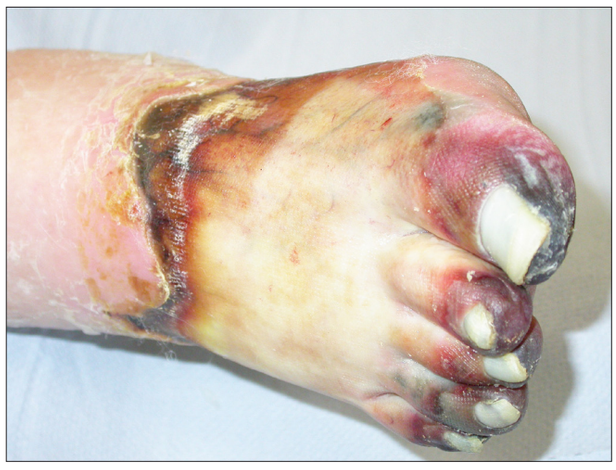

Figure 4: Critically ischaemic foot.

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Cellulitis suggests the need for urgent antibiotic treatment, the presence of malodour suggests the possibility of gas producing organisms and should prompt urgent surgical review.

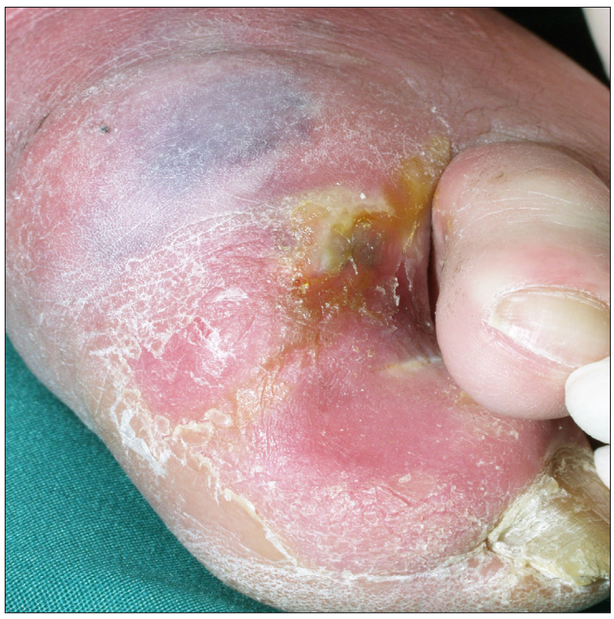

Figure 5: Gas under the skin in a patient with acute infection of the great toe.

The Acute Diabetic Foot
Patient Management

Step 3: Initial Investigations

- *Full Blood count / CRP / Glucose / Urea and Electrolytes*
- *Urinalysis for ketones*
- *Blood cultures*
- *Deep wound swab*
- *Plain Foot X ray - to look for gas in the tissues or obvious osteomyelitis.*

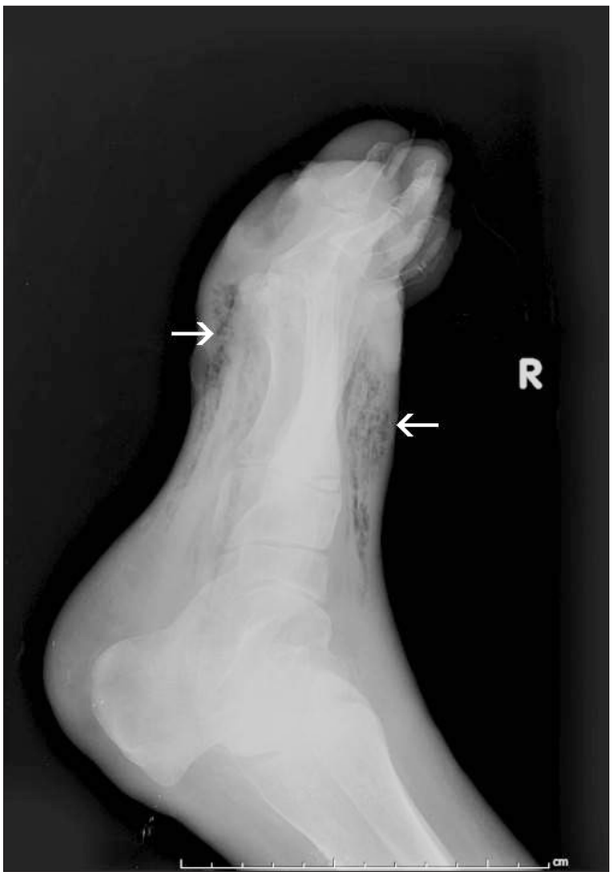

Figure 6: Gas in Tissues of Foot.

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Step 4: Management

The following should prompt urgent review by a vascular surgeon:

- *Septic patient with malodourous foot*
- *Evidence of abscess*
- *Extensive spreading soft tissue infection*
- *Evidence of gas on plain foot X ray*
- *Critical ischaemia / necrosis*

All other patients presenting with an acute diabetic foot should be seen by a member of a specialist diabetic foot team within 24 hours of admission (6,7).

- *Start intravenous antibiotics according to local guidance / antimicrobial policy. (N.B. The antimicrobial treatment of the infected diabetic foot is not the same as that for "cellulitis" as the pathogens involved are often different to those implicated in cellulitis. Often the diabetic foot infection is polymicrobial.)*
- *Treat any metabolic derangement, i.e. treat DKA if present, manage hyperglycaemia or acute kidney injury*
- *Start venous thromboembolism prophylaxis*
- *Appropriate non-occlusive dressings*

Summary

Diabetic foot infection is an emergency which may lead to sepsis, amputation or death. The recognition and prompt appropriate management of the diabetic foot is vitally important in order to reduce the catastrophic risks involved.

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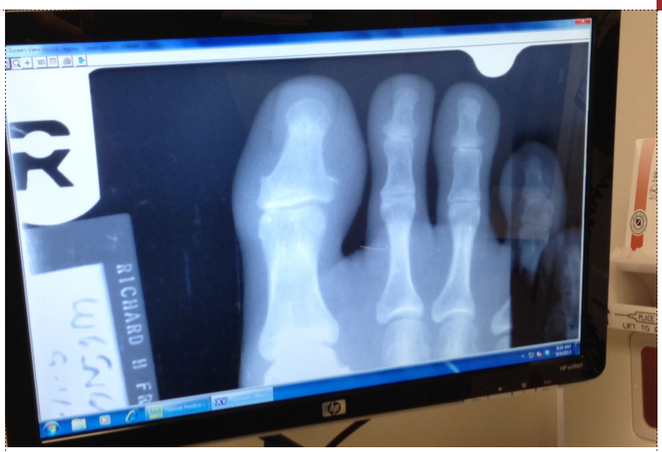
References

1) Boulton A. The Pathway to Ulceration: Aetiopathogenesis. In: Boulton AJM, Connor H and Cavanagh PR. The Foot in Diabetes, Chichester: Wiley 2000, p.22.
2) Williams R. and Airey M. The Size of the Problem: Epidemiological and Economic Aspects of Foot Problems in Diabetes. In: Boulton AJM, Connor H and Cavanagh PR. The Foot in Diabetes, Chichester: Wiley 2000, p.8.
3) Bowker JH and San Giovanni TP. Amputations in Diabetes Mellitus: Toes to Above Knee. In: Boulton AJM, Connor H and Cavanagh PR. The Foot in Diabetes, Chichester: Wiley 2000, p280.
4) NHS Atlas of Variation in Healthcare for People with Diabetes. Reducing unwanted variation to increase value and improve quality. 2012, p.70. http://www.rightcare.nhs.uk/index.php/atlas/diabetes.
5) Amery CM, Butland D, Dickie T, Patel I and Russell D. Amputation Facts, Leeds, (Unpublished data). 2011.
6) Putting Feet First Working Group, Diabetes UK. 2009. www.diabetes.org.uk
7) NICE guidelines – Diabetic Foot Problems: Inpatient Management 2013



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ADDISON'S DISEASE: AN ENDOCRINE EMERGENCY

R Hamblin, M Haq, D Barnes

Addison's Disease: An Endocrine Emergency
Patient Management

Abstract

Primary hypoadrenalism, also known as 'Addison's disease' is a rare condition, currently affecting around 8,400 individuals in the United Kingdom (1). Often insidious, it is potentially life-threatening if not recognised and treated promptly. This article aims to highlight the diagnosis, investigation and management of Addison's disease by focussing on a patient who presented acutely to our Emergency Department.

Case History

A 66 year old gentleman was referred from his general practitioner with a 6 month history of increasing fatigue, weakness, dizziness and double vision. His past medical history included a thymoma, removed 5 years previously and complicated by a left phrenic nerve palsy. He had previously been treated with amlodipine for hypertension but at the time of presentation he was on no medication, stopping his anti-hypertensive one year previously due to resolution of his high blood pressure.

You are the clerking doctor. What additional questions are important to consider in the history?

Symptoms of hypoadrenalism are vague and non-specific, and therefore a low threshold for suspecting Addison's disease is crucial. Commonly reported symptoms include weakness, tiredness and fatigue. Anorexia is also common as well as non-specific gastrointestinal symptoms, including nausea, vomiting, constipation and abdominal pain. Any acute 'stress' event such as trauma or infection should be sought. Salt and sugar cravings may also occur in Addison's disease. Our patient reported cravings for liquorice which has some mineralocorticoid activity. In patients who are diagnosed with hypothyroidism but also have unrecognised Addison's disease, the introduction of thyroid hormone replacement may lead to a clinical deterioration or indeed an Addisonian crisis.

A personal or family history of autoimmune disease is particularly relevant as between 50-65% of patients with Addison's disease due to autoimmune disease will have one or more other autoimmune endocrine abnormalities (2,3) (Table 1). Our patient reported a history of thymoma, and coupled with a history of diplopia and fatigue, led us to consider a diagnosis of myasthenia gravis which may be associated with Addison's disease.

Type 1 Diabetes Mellitus
Autoimmune Thyroid Disease
Premature Ovarian Failure
Pernicious Anaemia
Vitiligo
Myasthenia Gravis
Hypoparathyroidism
Coeliac Disease
Sjogren's Syndrome

Table 1: Diseases associated with autoimmune adrenalitis.

Drug history is important when considering hypoadrenalism as prolonged steroid use is an important cause of this via suppression of ACTH. Rapid withdrawal of steroids in this situation can lead to secondary hypoadrenalism. Less commonly, drugs such as fluconazole, ketoconazole and metyraprone inhibit steroid biosynthesis (4-6). These alone are unlikely to cause hypoadrenalism, but can cause primary adrenal insufficiency in those with minimal reserve. In our patient, the development of Addison's disease led to a resolution of his previously treated hypertension and he no longer required anti-hypertensive medication.

Examination Findings

The patient was alert and orientated. He was apyrexial, had a pulse rate of 91 and BP of 121/85.

What other specific areas should be examined in this patient?

Firstly, it is important to assess whether the patient is haemodynamically stable. In an Addisonian 'crisis', the patient will be significantly volume depleted and will be in shock as indicated by hypotension and tachycardia. Underlying infection can often trigger a crisis in someone with Addison's disease and therefore evidence of sepsis should be looked for. Our patient had postural hypotension with a drop in blood pressure from 121/85 (lying) to 109/69 (standing).

ADDISON'S DISEASE: AN ENDOCRINE EMERGENCY

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This reflects a lack of mineralocorticoid activity. The patient's skin tone was tanned in appearance. There was also increased pigmentation within the palmar creases, buccal mucosa and most notably around his eyes (Figures 1-3). In primary hypoadrenalism ACTH levels are markedly raised in an attempt to stimulate cortisol production. ACTH from the anterior pituitary in turn leads to increased production of pro-opiomelanocortin – a precursor to ACTH which produces Melanocyte Stimulating Hormone, responsible for increased skin pigmentation.

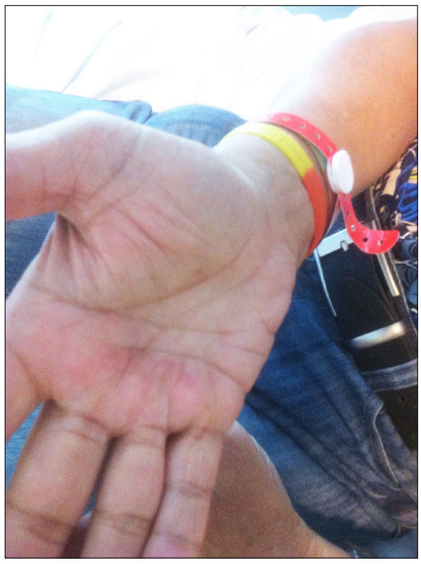

Figure 1: Dark palmar creases.

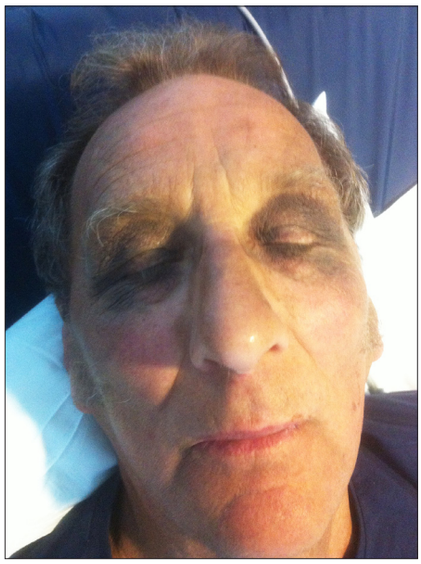

Figure 2: Increased pigmentation over both eyes.

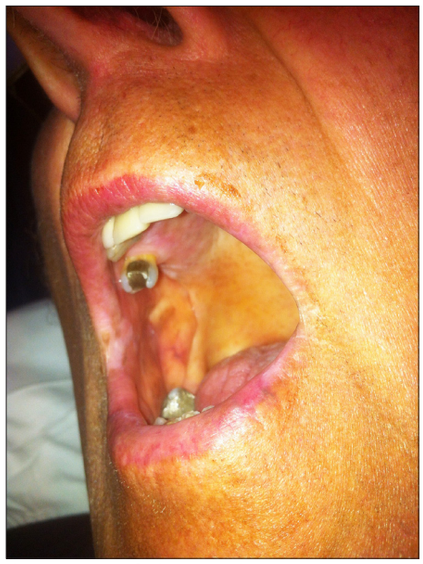

Figure 3: Buccal pigmentation.

Investigations

Full blood count was normal, sodium 134 mmol/l, potassium 4.3 mmol/l, creatinine 97 mcmol/l, and plasma glucose 6.7 mmol/l on admission.

What other investigations would you request prior to instigating specific treatment for this patient?

A chest X-ray should be requested as tuberculosis is a possible cause of primary hypoadrenalism if the adrenal glands are infected – this is more likely to be the case in the third world. Although a Short Synacthen test is the definitive test to confirm the presence of primary hypoadrenalism, it is inappropriate to delay the emergency management of this condition by organising the test and waiting for the results. In our patient, we elected to arrange a random cortisol and concomitant plasma ACTH level at the time of admission, and commenced treatment immediately afterwards. ACTH should be transported to the laboratory within 10 minutes of the sample being taken or put in ice if this is not feasible. The laboratory should be made aware that a sample is arriving so that it can be spun down straightaway. Although our patient had a normal plasma glucose on admission, unprovoked hypoglycaemia may be a feature of undiagnosed Addison's disease and requires further investigations.

Management

How would you manage this patient in the Emergency Department?

The patient requires intravenous fluid and high dose glucocorticoid replacement. He was given intravenous normal saline and hydrocortisone 100 mg six hourly. Some units prefer to give the first dose of hydrocortisone intravenously followed by 100 mg intramuscularly six hourly as the half life is longer when administered intramuscularly. Fludrocortisone is not usually necessary in the acute situation as hydrocortisone has some mineralocorticoid activity.

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Progress

The patient felt considerably better following 24 hours of intravenous fluid and hydrocortisone therapy. His cortisol level from admission returned at 11 nmol/l with a concomitant ACTH level of 753 ng/l (normal range for a 9 am sample is 5-46 ng/l).

What other investigations would you like to carry out and how would you manage the patient in the long term?

The blood tests on admission clearly confirm the presence of Addison's disease and there is little to be gained by organising a Short Synacthen test under such circumstances. In less clear-cut cases, this could be arranged by withholding the morning dose of hydrocortisone, taking a 9am cortisol blood sample, administering intramuscular or intravenous Synacthen (250 mcg) and then rechecking the serum cortisol 30 and 60 minutes after the injection.

In patients with normal adrenal reserve, cortisol rises to > 500 nmol/l at 30 or 60 minutes (7). 21-hydroxylase adrenal autoantibodies were positive in our patient consistent with an autoimmune adrenalitis; acetylcholine receptor autoantibodies were also positive suggestive of myasthenia gravis. We do not have information regarding whether he had been screened for this condition when he had presented with his thymoma previously. If the adrenal autoantibodies had turned out to be negative, a CT scan of the adrenals would have been considered to look for other pathologies such as TB, adrenal haemorrhage or tumour. Thyroid function was normal in our patient.

The patient was converted to oral hydrocortisone 20 mg tds, and this was tapered down to a replacement dose of 10 mg at breakfast, 5 mg at lunchtime and 5 mg in the late afternoon. He was reviewed in clinic a month post-discharge from hospital. Although he had felt generally well, he was symptomatic from postural hypotension. Electrolytes at that time showed a sodium of 136 mmol/l and potassium 5.7 mmol/l with an undetectably low aldosterone level. He was commenced on fludrocortisone 100 mcg a day.

The patient was strongly encouraged to wear a medical alert bracelet or necklace as information regarding long-term steroid usage is important in the event of an emergency to avoid abrupt discontinuation of therapy. Sick day rules were discussed with advice given to double up the dose of hydrocortisone in the event of a flu-like illness or fever for at least 2-3 days, and to taper the dose down to its maintenance dose as the infection subsides.

In more serious illnesses, especially ones associated with vomiting when hydrocortisone doses may not be kept down, it is important either for the patient or next-of-kin/carer to have access to an emergency intramuscular hydrocortisone kit. Education regarding the use of this should have previously been provided by the patient's Practice Nurse on request by the endocrinologist. Medical advice should be sought if severe vomiting occurs and/or the patient is not improving despite an increase in their hydrocortisone dose. Any patient on long-term steroids who is admitted to hospital with an acute illness is likely to require a temporary increase in their dose.

The patient should also have a flu vaccination every autumn as influenza itself can be a serious illness in the context of Addison's disease.

The importance of compliance with medication must be stressed. Patients often fear side-effects from long term use of steroids but in Addison's disease, steroids are given at doses to replace what should be produced by the adrenal glands and not at "high" dose for management of inflammatory disorders. The Addison's Disease Self Health Group has a website providing useful information (www.addisons.org.uk).

Key Learning Points

Addison's disease is a rare condition which is important not to miss as this could have devastating consequences. It is not usually clinically apparent until at least 90% of the adrenal cortex has been destroyed. Symptoms can be non-specific which can add to the difficulty in making a diagnosis. If the condition is suspected, and the patient is unwell, especially in the context of haemodynamic compromise, treatment should not be delayed while awaiting results to investigations. Certain "simple" blood tests can be taken in the acute setting even though the results may take a few days to return from the laboratory. Once confirmed, patient education is a vital component to help with self-management in the long term.

Multiple Choice Questions

1. A patient is admitted to the Emergency Department with a tachycardia and hypotension. Hypoadrenalism is thought to be a possible diagnosis. Which of the following statements represents the most appropriate course of action?

A. Fluid resuscitate the patient, organise a Short Synacthen test and only start intravenous glucocorticoids if the test suggests hypoadrenalism.
B. Fluid resuscitate the patient, organise a Short Synacthen test but commence intravenous glucocorticoids while awaiting result of test.
C. Fluid resuscitate the patient and commence intravenous antibiotics as sepsis is a much more likely diagnosis.
D. Fluid resuscitate the patient, request a random cortisol on admission but commence intravenous glucocorticoids while awaiting result of test.
E. Fluid resuscitate the patient, request a 9 am cortisol and commence intravenous glucocorticoids while awaiting result of test.

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2. The following biochemical findings are typical in a patient with undiagnosed Addison's disease:

A. Hypernatraemia, hypokalaemia, exaggerated cortisol response to Synacthen, high ACTH level.
B. Hyponatraemia, hyperkalaemia, flat cortisol response to Synacthen, low ACTH.
C. Hyponatraemia, hypokalaemia, flat cortisol response to Synacthen, high ACTH.
D. Hyponatraemia, hyperkalaemia, flat cortisol response to Synacthen, high ACTH.
E. Hyponatraemia, normal potassium, flat cortisol response to Synacthen, low ACTH.

Answers

1. D

Fluid resuscitation is vital for patients who present with shock. If hypoadrenalism is suspected, a random cortisol test can be taken on admission but intravenous glucorticoid treatment should not be delayed. Cortisol is not a blood test that will be analysed by the laboratory on an "emergency" or "urgent" basis – most laboratories will run this test in normal working hours during the week.

Although there is a Circadian rhythm of cortisol production which tends to peak in the morning (at around 9 am), one would normally expect a "high" cortisol in the context of stress such as in the case of a patient presenting with shock. A Short Synacthen test can be organised if necessary in patients who have been treated with glucocorticoids and are feeling better – this test can be performed in the morning by withholding the usual dose of glucocorticoid until after all the relevant blood samples have been taken.

In patients with an Addisonian crisis, a Short Synacthen test should not be performed as this delays vital treatment for at least an hour while the blood samples are collected.

2. D

The classical biochemical changes in Addison's disease are hyponatraemia and hyperkalaemia. Hyponatraemia is mediated by an increased release of antidiuretic hormone (ADH) which results in water retention. Furthermore cortisol deficiency results in increased production of corticotropin-releasing hormone (CRH), which is an ADH secretagogue. Mineralocorticoid deficiency contributes to this hyponatraemia but is the main reason for the hyperkalaemia.

In secondary causes of hypoadrenalism (ie due to pituitary pathology), hyperkalaemia does not classically occur as the renin-angiotensin-aldosterone pathway is still intact. In Addison's disease, the adrenal glands are unable to respond to synthetic ACTH (Synacthen) and therefore a flat response is typical of this condition. ACTH levels will be high as the pituitary gland tries to stimulate the adrenal glands to produce more cortisol.

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References

1. Wass J, Howlett T, Arlt W, et al. Diagnosing Addison's: a guide for GPs. Addison's Disease Self Help Group. 2009.
2. Zelissen PM, Bast EJ, Croughs RJ. Associated autoimmunity in Addison's disease. J Autoimmun 1995, 8(1):121-30.
3. Erichsen MM, Løvås K, Skinningsrud B, et al. Clinical, immunological, and genetic features of autoimmune primary adrenal insufficiency: observations from a Norwegian registry. J Clin Endocrinol Metab 2009, 94:4882-90.
4. Sonino N. The use of ketoconazole as an inhibitor of steroid production. N Engl J Med 1987, 317:812-8.
5. Riedl M, Maier C, Zettinig G, et al. Long term control of hypercortisolism with fluconazole: case report in vitro studies. Eur J Endocrinol 2006, 154:519-24.
6. Liddle GW, Island D, Lance EM, Harris AP. Alterations of adrenal steroid patterns in man resulting from treatment with a chemical inhibitor of 11 beta-hydroxylation. J Clin Endocrinol Metab 1958, 18:906-12
7. Addison's disease. NICE CKS, September 2010.

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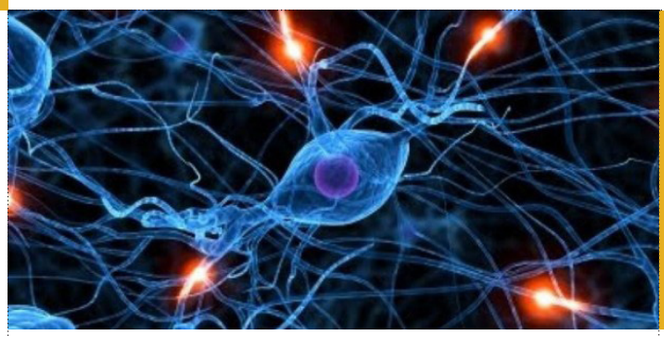
DISORDERS OF CALCIUM HOMEOSTASIS

M Asam, A Pawlak, G Matfin, R Quinton



Abstract

Calcium homeostasis is tightly regulated through multiple interactions between dietary intake of bone minerals and serum levels of homeostatic hormones (principally parathyroid hormone, vitamin D and phosphaturic agents such as osteocyte-secreted Fibroblast Growth Factor 23), acting principally on bone, intestine and kidneys. Both hypo- and hypercalcaemia represent a serious disruption of calcium homeostasis, wherein these homeostatic mechanisms have become overwhelmed by a specific pathological process.

Acute disorders of calcium homeostasis are associated with measurable morbidity and mortality and therefore prompt recognition and treatment is crucial. Primary hyperparathyroidism and malignancy are the most important causes of hypercalcaemia, with the former predominating in the outpatient setting and the latter among hospital inpatients. Vitamin D deficiency has the greatest contribution to hypocalcaemia in the community, with surgical hypoparathyroidism being the most significant cause of acute hypocalcaemia in the hospital setting.

However, multiple other drugs and aetiologies can interplay to amplify the impact of any principal pathological process. In this review article we describe the pathophysiology, aetiology, clinical presentations, investigation and treatment of both hypo- and hypercalcaemia, focusing first on common management pathways and, second, on situation-specific pathways depending on the outcome of the initial diagnostics.

Introduction

Hypo- and hypercalcaemia are common electrolyte disorders. The prevalence of hypercalcaemia among hospital inpatients is 0.5%, though it is only transient in about 19% of these. Hypocalcaemia is seen in approximately 26% of hospital admissions and in up to 88% of patients admitted to an intensive care unit (ICU) (Zivin et al., 2001). Although there are multiple, overlapping causes of calcium imbalance, much of the acute management is generic, logical and intuitive. However, making a correct diagnosis remains important for the quality of management and long-term outcomes (Murphy and Williams, 2009; Schafer and Shoback, 2013).

Severe hypercalcaemia usually presents as an emergency and should be treated immediately, as delay carries significant morbidity and mortality, as should any degree of acute hypocalcaemia associated with neurological, muscular or cardiac signs. However, patients with chronic hypocalcaemia can remain surprisingly asymptomatic even at very low serum calcium levels.

Calcium homeostasis

Calcium is one of the major divalent cations in the body (Favus and Goltzman, 2013). Calcium levels are regulated within a narrow range by vitamin D and parathyroid hormone (PTH) through their actions on the bowel, skeleton and kidneys.

Vitamin D

Vitamin D is structurally similar to steroid and retinoid hormones and, functionally, is also more of a prohormone than a classical "vitamin" (Holick, 2007; Pearce and Cheetham, 2010; National Osteoporosis Society, 2013). It regulates the plasma levels of calcium and phosphate by increasing their absorption from the bowel and plays a crucial role in the normal bone formation by promoting mineralisation of the osteoid.

Unless specified otherwise in the text, we use the term vitamin D (calciferol) to encompass both its D3 (colecalciferol) and D2 (ergocalciferol) forms, which undergo similar metabolism to 25(0H)D (calcidiol) and 1,25-(OH)D (calcitriol), respectively, but differ in their side-chains.

Determination of circulating vitamin D status refers to plasma levels of the 25-hydroxylated forms of both vitamins, 25-(OH)D3 and 25-(OH)D2 (ie. the cole- and ergo- forms of calcidiol, respectively). This is presently the best biochemical marker of somatic vitamin D sufficiency, although different expert panels continue to recommend different arbitrary plasma calcidol cut-offs to indicate deficiency.

D3 is mainly synthesized by ultraviolet (UV) irradiation of 7-dehydrocholesterol in the skin, with a typically much smaller dietary contribution, whereas circulating D2 (photosynthesised by UV irradiation of sterol precursors by algae, fungi, or marine plankton), derives exclusively from consumption of oily fish or food supplements. It is probably slightly less bioactive than D3 by a factor of, perhaps, 25%. Once vitamin D enters circulation from the skin or intestine, it is concentrated in the liver and 25-hydroxylated to calcidiol. Calcidiol is then transported to the kidney, where it undergoes 1-, alpha hydroxylation to the biologically most active form, calcitriol (see figure 1). Some hydroxylation also occurs in a paracrine manner in peripheral tissues.

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The main role of calcitriol is to increase the absorption of calcium from the intestine, but it also sensitizes bone to the action of PTH, suppresses the synthesis and secretion of PTH, and restricts parathyroid gland growth. A discussion of its non-bone-related functions lies beyond the scope of this article. Calcitriol formation is regulated by plasma levels of calcium, phosphate, fibroblast growth factor 23 (FGF23) and by levels of calcitriol itself. As plasma levels increase, so the balance between cutaneous UV-mediated photosynthesis and UV-mediated photo-destruction shifts towards the latter function.

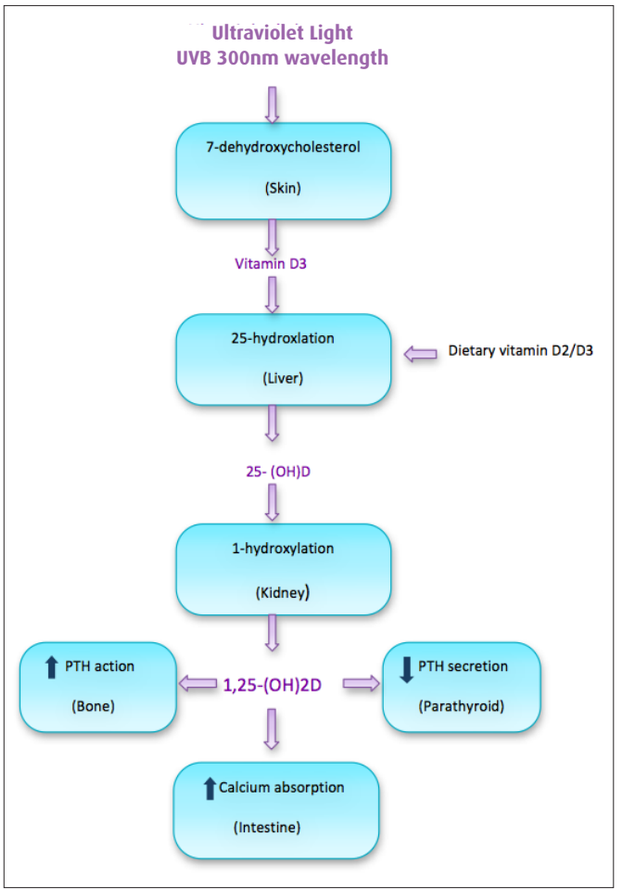

Figure 1: Metabolism of vitamin D.

Parathyroid Hormone

PTH is secreted by the four parathyroid glands classically located on the posterior surface of the thyroid gland. Secretion is regulated by the serum calcium concentration which is detected by calcium-sensing receptors (CaSR) present on the parathyroid cell membrane (Egbuna and Brown, 2008). PTH maintains normal serum calcium levels promoting the activation of vitamin D, enhancing release of calcium from bone and its resorption from renal tubular filtrate, whilst promoting renal phosphate excretion (which prevents calcium phosphate salt formation in the extracellular fluid [ECF]). When the plasma calcium concentration is high, PTH secretion is inhibited and vice versa, but calcitriol also inhibits PTH secretion independently of plasma calcium levels (Juppner, 2011).

Aetiology

The causes of hypercalcaemia can be broadly divided into those associated with high or inappropriately normal PTH levels and those with low or suppressed PTH levels (Endres, 2012) (see table 1), and the mechanisms leading to hypocalcaemia involve either decreased entry of calcium into circulation or increased movement of calcium out of circulation (see table 2).

Hypercalcaemia

Common causes

The two most common causes of hypercalcaemia are primary hyperparathyroidism (PHPT) and malignancy, which together make up approximately 90% of all cases. PHPT tends to be more common in outpatient settings, whereas malignancy is most commonly seen in inpatients (Fenech and Turner, 2013). PHPT affects more women than men and can be caused either by a single parathyroid adenoma, or by hyperplasia of two or more glands. Nowadays, it is increasingly detected as an incidental finding on blood testing. Hypercalcaemia occurs at some point in 10%-30% of all patients with malignancies and usually signals advanced malignancy and poor prognosis. Recognising the non-specific signs of hypercalcaemia and identifying the underlying pathology can make a significant difference to the patient outcome (Rosner and Dalkin, 2012).

Hypercalcaemia may arise as a result of one or a combination of the following mechanisms:

- **Increased bone resorption**
- **Increased calcium absorption from bowel or kidneys**
- **Reduced renal excretion.**

Raised PTH levels in primary hyperparathyroidism lead to increased hydroxylation of vitamin D to its active form in the kidneys and increased bone resorption resulting in hypercalcaemia. All other forms of clinically-significant hypercalcaemia are associated with suppressed PTH levels.

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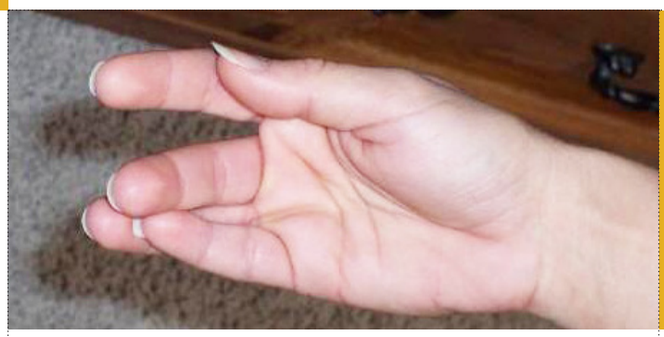

Hypercalcaemia in malignant disease is principally due to systemic tumorous secretion of PTH-related peptide (PTHrP), which activates the PTH receptor, with paracrine secretion of PTHrP by bone metastases causing local osteolysis; exceptionally rarely, the tumour itself may release PTH. Increased 1-alpha hydroxylation of 25(OH)D in granulomatous diseases and lymphoma (Li et al., 2013) results in markedly supraphysiological production of calcitriol (1,25(OH)2D3). Both hyperthyroidism and prolonged immobilisation can result in uncoupling of osteoclastic and osteoblastic activities, causing hypercalcaemia through net calcium release from bone.

Drugs cause hypercalcemia through different mechanisms. For example, thiazide diuretics and lithium lead to retention of calcium by the kidney, whereas lithium also raises PTH levels. Calcium absorption is increased in milk alkali syndrome (Singh and Ashraf, 2012).

Rare causes

Familial hypocalciuric hypercalcaemia (FHH) is a rare disease caused by an inactivating mutation in the calcium sensing receptor. Reduced sensing of extracellular calcium leads to a rise in PTH levels, resulting in hypercalcaemia without hypercalciuria. Biochemically, it can look very similar to PHPT, distinguished only by a lower fractional excretion of urine calcium (FeCA) and the absence of clinical complications. Other genetic causes include multiple endocrine neoplasia (MEN) syndromes type 1 and type 2, both of which cause hypercalcaemia through PHPT. Parathyroid carcinoma is a rare malignancy and it may occur sporadically or as a part of a genetic syndrome. It accounts for approximately 1% of patients with PHPT (Wei and Harari, 2012).

PTH-mediated	*Independent of PTH*
• Primary hyperparathyroidism • Tertiary hyperparathyroidism • Parathyroid cancer • Lithium • FHH (familial hypocalciuric hypercalcaemia)	• Non-parathyroid malignancy • Drug-induced (thiazide diuretics, theophylline, antacids, vitamin D, vitamin A, aluminium) • Thyrotoxicosis • Adrenal insufficiency • Immobilisation • Granulomatous diseases (e.g. sarcoidosis, TB) • Recovery phase of rhabdomyolysis

Table 1: Causes of hypercalcaemia.

Hypocalcaemia

Common causes

The most common cause of chronic hypocalcaemia in the general population is vitamin D deficiency. However, in hospital setting, the most common cause of acute symptomatic hypocalcaemia is post-operative hypoparathyroidism following recent head and neck surgery (Bilezikian et al., 2011). In practice, most cases are multifactorial with two or more risk factors such as recent total thyroidectomy and unrecognised vitamin D deficiency being responsible (Pearce and Cheetham, 2010). Reversible hypoparathyroidism seen in severe hypomagnesaemia (common in patients on diuretics and proton pump inhibitors [PPI]) may also predispose to hypocalcaemia.

The term "hungry bone syndrome" is used to describe excessive movement of ECF calcium into bone. It can occur with osteoblastic bone disease including metastatic cancer, following correction of longstanding hypercalcaemia due to hyperparathyroidism and occasionally with treatment of hyperthyroidism and osteomalacia due to rapid bone remineralization (Brasier et al., 1988).

Hyperphosphataemia, encountered in renal impairment, tumour lysis syndrome and rhabdomyolysis cause hypocalcaemia through sequestration and formation of complexes with ionized calcium. In acute pancreatitis, calcium complexes form within the abdominal cavity. Calcium chelation can be achieved with ethylenediaminetetraacetic acid (EDTA), or citrate transfusion, but they are rarely used in patients with normal renal and hepatic function. Some of the factors contributing to hypocalcaemia seen in sepsis are renal impairment, magnesium abnormalities, release of inflammatory cytokines and frequent transfusions. Mortality rates are higher in septic patients with hypocalcaemia than in septic patients without hypocalcaemia (Desai et al., 1988). Finally, there are a number of drugs associated with hypocalcaemia (reviewed elsewhere, Liamis et al., 2009).

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Rare causes

Rare causes of hypocalcaemia include genetic/epigenetic, autoimmune and infiltrative conditions (Shoback, 2008) (see table 2).

Reduced entry of calcium into circulation	*Increased movement of calcium out of circulation*
Parathyroid dysfunction: • Hypoparathyroidism – Autoimmune – Autoimmune polyglandular syndrome – Postoperative – Infiltrative (e.g. haemochromatosis, amyloidosis) • Hypomagnesaemia • Hypermagnesaemia • Congenital disorders of the parathyroid glands – Di George syndrome – Defects in calcium-sensing receptor • Pseudohypoparathyroidism secondary to G-protein defects • Drugs (including cinacalcet) **Vitamin D deficiency:** • Dietary or malabsorption • Lack of sunlight exposure • Renal impairment **Reduced bone resorption:** • Drugs (including bisphosphonates and denosumab)	**Movement into bone stores:** • 'Hungry bone' syndrome • Osteoblastic metastases (e.g. prostate, breast cancer) **Chelation of ionized calcium:** • Acute pancreatitis • Hyperphosphataemia – Renal impairment – Tumour lysis syndrome – Rhabdomyolysis • Citrate or EDTA in context of transfusions • Phlebotomy **Miscellaneous:** • Sepsis • Drugs (including chemotherapeutic agents and foscarnet)

Table 2: Causes of hypocalcaemia.

Clinical presentation

Thorough medical history and examination are crucial in the initial assessment and help to set priorities for the diagnostic workup. It is important to identify the clinical manifestations of hypo- and hypercalcaemia as the patients may require urgent corrective measures. The severity of signs and symptoms depends on calcium levels and the speed of onset.

Hypercalcaemia

Medical history

Most patients with mild hypercalcaemia are asymptomatic and hypercalcaemia is an incidental finding on blood testing. However, severe hypercalcaemia is usually symptomatic and symptoms can vary from malaise to severe dehydration and coma (Table 3). In practice, most cases of severe, acute hypercalcaemia are due to cancer, though excess intake of calcium-containing products elicits a similar biochemical picture with suppressed PTH and biochemical alkalosis.

Features of hypercalcaemia	*Features of the underlying cause*
• Malaise, fatigue, lethargy • Anorexia, nausea, vomiting, weight loss • Mental status change: depression, confusion, coma • Bone pain • Polydypsia and polyuria • Abdominal pain suggestive of pancreatitis/peptic ulcer • Features of bowel distension due to faecal impaction (constipation) • Fracture due to osteoporosis in PHPT • Metastatic calcification • ECG changes: short QT interval	• Lymphadenopathy - lymphoma or tuberculosis • Clubbing, chest dullness, haemoptysis - lung cancer • Abdominal masses, visceromegaly – solid organ malignancy or lymphoma • Neck mass – cancer or goitre • Tachycardia, goitre, sweating - thyrotoxicosis • Hyperpigmentation and hypotension - Addison's disease • End-stage chronic kidney disease/dialysis - tertiary hyperparathyroidism

Table 3: Assessment of the hypercalcaemic patient.

A history of smoking, persistent cough, haemoptysis and weight loss make squamous cell lung cancer the most likely underlying diagnosis. Back pain can be due to bone metastases, myeloma, osteoporotic fracture, vitamin D deficiency or, rarely, Paget's disease, but can also be unrelated e.g. due to degenerative disease. Night sweats and lymphadenopathy may be suggestive of lymphoma or tuberculosis. If the patient is known to have cancer then hypercalcaemia is most likely malignancy-related, but other causes, particularly PHPT, should be ruled out. Longstanding, relatively asymptomatic hypercalcaemia is usually most likely due to PHPT, but the diagnosis should always be confirmed. Family history may indicate rare genetic causes such as FHH, MEN syndromes or familial hyperparathyroidism-jaw tumour syndrome. Thiazide diuretics, lithium, calcium supplements (including antacids) and high-dose vitamin A supplements may promote hypercalcaemia that is typically reversible on stopping the medication.

Examination

Examination of patients with hypercalcaemia should explore the effects of hypercalcaemia itself as well as search for the underlying cause. Features of severe hypercalcaemia usually affect multiple organ systems as shown in table 3. Patients with chronic hypercalcaemia may present with renal failure, renal stones or osteoporotic fractures.

Palpable masses, enlarged lymph nodes or visceromegaly on abdominal examination point towards malignancy as a likely cause. Finger clubbing, cough, haemoptysis and pleural effusions suggest lung cancer. Back pain, leg weakness and spinal tenderness indicate spinal disease which can be either a primary tumour or metastases from a different site. If features of thyrotoxicosis or adrenal insufficiency are present, they should be considered as a possible aetiology. Granulomatous diseases usually produce signs in the chest or bowel, but other organ systems may also be affected.

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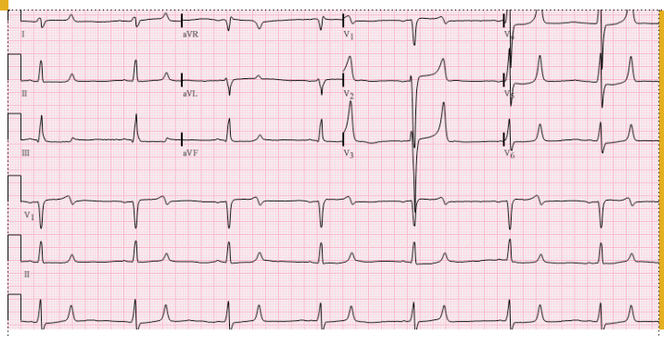

Hypocalcaemia

Medical history

Most clinical manifestations of hypocalcaemia relate to neuromuscular dysfunction. Perioral and acral paraesthesia are the earliest symptoms and are almost always present in symptomatic patients. Other frequently reported features include muscle stiffness, myalgia and confusion (Table 4). Neurological manifestations of acute hypocalcaemia include irritability, confusion and seizures. Hypocalcaemia lowers the threshold for seizure activity in epileptic patients. Chronic hypocalcaemia may present with depression, dementia, extrapyramidal features, hair and nail changes, cataracts and papilloedema. Patients with acute-on-chronic hypocalcaemia may exhibit both sets of features.

Onset in childhood would point to a congenital aetiology, but environmental factors should also be taken into consideration. Family history may flag up conditions such as autosomal dominant hypocalcaemia/hypercalciuria or autoimmune polyglandular syndrome type 1 as a possible cause. Abdominal pain and/or jaundice suggest pancreatitis, whereas history of massive or multiple transfusions might point to transfusion-related hypocalcaemia. Recent thyroidectomy or parathyroidectomy suggests acute post-operative hypoparathyroidism as a likely cause. A history of renal disease, liver disease and/or anticonvulsant therapy may indicate a defect in vitamin D metabolism. Certain malignancies such as breast or prostate cancer are likely to give osteoblastic metastases. Risk factors for malabsorption of calcium, vitamin D and/or magnesium should also be identified (e.g. Crohn's disease, coeliac disease, chronic pancreatitis, bariatric surgery and bacterial overgrowth).

Hyperventilation may cause a fall in ionized calcium due to induced respiratory alkalosis. Recent contrast-magnetic resonance imaging (MRI) may indicate gadolinium-induced pseudohypocalcaemia due to assay interference. Measurement of ionised calcium becomes important in hypoalbuminaemia associated with malnutrition and chronic illness, where even the albumin-adjusted calcium level may appear artifactually-low. Drug history is also important, with the magnesium-wasting effects of loop diuretics, proton-pump inhibitors and alcohol abuse (particularly in combination) potentially causing resistant secondary hypocalcaemia. A history of prior head and neck radiotherapy points towards hypoparathyroidism.

Examination

Hypocalcaemia is associated with a number of specific signs. Chvostek's sign describes ipsilateral twitching of the facial muscle groups when the facial nerve is tapped 2 cm anterior to the earlobe beneath the zygomatic bone. However, it may be positive in up to 25% of normal individuals and negative in approximately 30% of patients with hypocalcaemia (Hoffman, 1958). Trousseau's sign describes flexion of the wrist and metacarpophalangeal joints and hyperextension of the fingers and flexion of the thumb elicited by occluding the brachial artery 20 mmHg above systolic pressure for 3 minutes. It is more sensitive (94%) and specific for hypocalcaemia as it is positive in only 1% of normocalcaemic patients (Jesus and Landry, 2012).

Hypocalcaemia may lead to electrocardiographic (ECG) changes and cardiac failure (Hurley and Baggs, 2005). Prolongation of the corrected QT interval can lead to torsade de pointes arrhythmia. If untreated, it can progress to ventricular fibrillation and cardiac arrest.

Features of acute hypocalcaemia	*Features of chronic hypocalcaemia*	*Features of the underlying cause*
• Arrhythmias - check pulse and electrocardiogram (ECG) • Tetany • Chvostek's sign – less specific (present in 25% normocalcaemic subjects) • Trousseau's sign - more specific (present in 1% normocalcaemic subjects) • Shortness of breath, stridor • Seizure (partial or generalized) • Acute confusion • Cardiac failure	• Features of parkinsonism or other movement disorders • Dementia • Nail dystrophy • Hair loss • Dry skin • Papilloedema	• Evidence of neck surgery • Abdominal tenderness (pancreatitis) • Previous abdominal surgery – malabsorption • Hepatic failure - haemochromatosis • Proximal muscle weakness - osteomalacia • Syndromic features suggestive of genetic cause • Evidence of malignancy like breast, prostate cancer • Features of infiltrative diseases like skin discolouration (haemochromatosis), Kayser-Fleischer rings (Wilson's disease) • Features of Addison's disease, mucocutaneous candidiasis – autoimmune polyglandular syndrome type 1

Table 4: Assessment of the hypocalcaemic patient.

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Investigations

Investigations should measure calcium levels and target the potential underlying cause. Serum calcium is normally maintained within a narrow reference range (2.1-2.6 mmol/L; 8.5-10.5 mg/dl). 40% of total serum calcium is bound to protein, mainly albumin, whilst 50% is in the active ionized form. Alkalosis increases binding to albumin and therefore decreases ionised calcium levels. Albumin levels should thus always be considered when assessing calcium status and, indeed, most laboratories now automatically provide corrected (adjusted) calcium (ACa). However, in sepsis or other states of acute albumin fluctuation measurement of ionised calcium is more reliable.

It is important to perform an ECG in patients with major calcium disorders as disturbances in calcium homeostasis can cause arrhythmias.

Hypercalcaemia

The usual investigations are a bone profile with albumin to give the corrected calcium level. PTH levels are measured to differentiate between different causes of hypercalcaemia. Renal function should be checked as it may be abnormal due to dehydration or indicate tertiary hyperparathyroidism. Vitamin D level is typically low in both primary hyperparathyroidism and malignancy. Raised alkaline phosphatase is associated with osteoblastic bone metastases, but also with vitamin D deficiency and acute fracture. Full blood count may point to haematological disorders such as lymphoma, whereas serum electrophoresis is used to diagnose myeloma. Different imaging modalities can be used if cancer or granulomatous disease are suspected. Levels of blood markers such as calcitriol and angiotensin converting enzyme (ACE) may be raised in sarcoidosis. Thyroid disease and Addison's disease should be investigated if clinical manifestations are present (see table 5).

FeCa (fractional excretion of calcium) is used to differentiate between PHPT and FHH, but the definitive diagnosis of FHH requires sequencing of the CASR gene.

Routine investigations	*Specific investigations*
• Corrected calcium, phosphate - low phosphate suggests PHPT • Urea/creatinine - raised due to dehydration or suggest tertiary hyperparathyroidism • Alkaline phosphatase (ALP) - raised with bone metastases • PTH • Vitamin D levels -raised in toxicity • Urine calcium excretion	• Blood film/markers - lymphoma • Serum electrophoresis - myeloma • CXR/chest CT scan – lung cancer or granulomatous disease • Bone scan/MRI – bone metastases • Imaging/scopes/biopsy/calcitriol/ACE – granulomatous diseases • PTHrP - malignancy • Ultrasound kidney - kidney stones/renal cancer • Ultrasound parathyroid/sestamibi scan - parathyroid adenoma • Thyroid function tests - thyrotoxicosis • Cortisol level/Short synacthen test (SST) - adrenal insufficiency • Genetic tests - FHH and MEN syndromes • X-ray hands – periosteal calcification due to vitamin A toxicity • Vitamin A /theophylline level - toxicity

Table 5: Investigation of hypercalcaemia.

Hypocalcaemia

Performing investigations should not delay treatment of acute hypocalcaemia. Biochemical testing should aim to elicit the cause and include renal function, PTH, phosphate, alkaline phosphatase (ALP), magnesium, bicarbonate and vitamin D levels (Table 6). Measurement of PTH level is crucial in identifying the underlying cause. Inappropriately low levels suggest hypoparathyroidism, whereas high levels show a physiological response to hypocalcaemia due to another cause. However, both hypo- and hypermagnesaemia can be associated with hypocalcaemia due to inhibition of PTH release.

Calcidiol (25OHD) level measurement should be a part of the routine diagnostic workup as vitamin D deficiency is one of the commonest causes of hypocalcaemia Measurement of serum calcitriol tends to be unhelpful, perhaps due to a predominantly paracrine mechanism of action. In vitamin D deficiency, both hypocalcaemia and hypophosphataemia may be present, whereas patients with hypoparathyroidism, tumour lysis syndrome and renal failure tend to present with hypocalcaemia with hyperphosphataemia.

Acid base balance should be assessed as alkalosis can lead to increased protein binding and reduction in ionised calcium levels. Apparent hypocalcaemia after gadolinium-based MRI contrasts is due to assay interference and is transient as the contrast is excreted in urine where there is normal renal function (Doorenbos et al., 2003).

Routine investigations	*Specific investigations*
• Corrected calcium, phosphate • PTH (parathyroid hormone) • ALP (alkaline phosphatase) • Magnesium • Vitamin D level • Blood urea nitrogen/creatinine • Liver function tests • Bicarbonate level • ECG - looking for prolonged QT interval or arrhythmia	• Amylase/lipase - pancreatitis • Faecal elastase/bowel investigation/ breath testing - malabsorption/ bacterial overgrowth • Urinary magnesium - urinary magnesium loss • X -rays - osteomalacia due to vitamin D deficiency • Bone scan and other imaging - malignancy • Genetic tests - genetic causes • c-AMP in urine - pseudohypoparathyroidism

Table 6: Investigation of hypocalcaemia.

Management

Hypercalcaemia

There are two aims in management of hypercalcaemia: reduction of calcium levels and treatment of the underlying cause. Hypercalcaemia causes nephrogenic diabetes insipidus, anorexia, nausea and vomiting, all of which contribute to a negative fluid balance and exacerbate dehydration. The patient becomes progressively worse until hypercalcaemia is treated and the vicious cycle is broken (figure 2).

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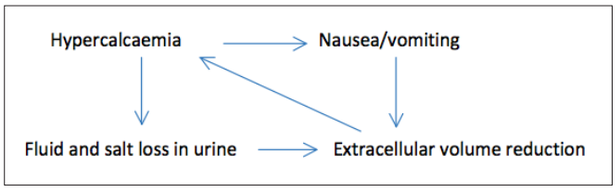

Figure 2

If it is suspected that hypercalcaemia may be drug-induced, the medication should always be stopped if possible. Rehydration therapy and bisphosphonates are the mainstay of treatment of hypercalcaemia. However, depending on the cause, other specific treatment may be required (see figure 3 for acute treatment of hypercalcaemia).

Rehydration

Intravenous (IV) normal saline should be given immediately, usually 4-6 litres/day (Society for Endocrinology, 2013a). Patient symptoms and urine output should be monitored and drip rate adjusted accordingly. Patient's renal function should also be monitored as dialysis may be required in severe renal failure or resistant hypercalcaemia with renal failure. Fluid overload may become a problem in elderly patients or patients with renal or heart failure so fluids should be given with caution. Loop diuretics are only useful in patients who remain hypercalcaemic and have become fluid overloaded following over-enthusiastic rehydration, and are otherwise no longer routinely recommended in treatment of hypercalcaemia.

Bisphosphonates

Bisphosphonates should be used soon after IV saline has commenced as they take a few days to take effect. They decrease calcium levels by reducing bone resorption and the dose is dependent on severity of hypercalcaemia. Most commonly used bisphosphonates are zoledronic acid and pamidronate. Pamidronate is given IV as a dose of 90 mg over a few hours. Zoledronic acid is given as a dose of 4 mg over 15 minutes and is more potent and much longer-acting than pamidronate, though very significantly more expensive (Body et al., 1999). Repeated doses may be needed to control hypercalcaemia, particularly in malignancy.

Renal function should be monitored as bisphosphonates may precipitate renal failure in the dehydrated patient and dose reduction is advised in patients with renal impairment. Other side effects include flu-like symptoms and rarely osteonecrosis of the jaw (Tanvetyanon and Stiff, 2006). Calcium level should also be monitored as bisphosphonates can cause hypocalcaemia in patients with uncorrected vitamin D deficiency (Society for Endocrinology, 2013a), though ideally patient would have been rendered vitamin D replete (>30nmol/L) beforehand. See below in "oral therapies" section.

Steroids

Steroids are used to treat hypercalcaemia resulting from granulomatous disease as they inhibit 1-alpha hydoxylase activity and 1,25 OH)2D3 (calcitriol) production in granulomatous tissue. They are also effective in intravenous treatment of hypercalcaemia due to vitamin A toxicity. Steroids are also helpful in treatment of vitamin D poisoning as they inhibit action of vitamin D. The usual starting dose of prednisolone is 40 mg once daily or the equivalent dose of IV hydrocortisone. Steroid use also has a place in treatment of hypercalcaemia due to haematological malignancies such as multiple myeloma and lymphoma (Percival et al., 1984). Management plan should be established in liaison with a haematologist.

Calcimimetics

Calcimimetics, such as cinacalcet, activate CaSR, reduced PTH secretion and, subsequently, a decrease in calcium levels (Shoback et al., 2003). They can precipitate hypocalcaemia in patients with uncorrected vitamin D deficiency. At present they are licensed for use in primary parathyroid cancer, primary hyperparathyroidism in patients unfit for surgery and in secondary, or tertiary hyperparathyroidism of end-stage chronic kidney disease (CKD), but have only limited outcome data in respect of bone density and fracture prevention.

Parathyroidectomy

Parathyroidectomy is the definitive treatment for primary and tertiary hyperparathyroidism and it is curative in most cases of PHPT. Surgery is recommended in all symptomatic patients, asymptomatic patients with hypercalcaemia above the upper limit of the reference range by more than 0.25 mmol/litre, evidence of end-organ damage, reduced bone mineral density and patients under 50 years of age (Fenech and Turner, 2013). Emergency parathyroidectomy is only recommended in cases of severe hypercalcaemia due to hyperparathyroidism refractory to medical treatment.

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Haemodialysis

Calcium-free haemodialysis is indicated when the presence of severe renal failure prevents the administration of large volumes of IV fluids to hypercalcaemic patients.

Long-term management

Long-term management of hypercalcaemia is aimed at the underlying cause. As mentioned before, parathyroidectomy is the definitive treatment for PHPT. If contraindicated, conservative approach should be adapted with at least yearly monitoring of calcium and creatinine levels and bone density measurement every two to three years (Fenech and Turner, 2013). Similar principles apply to the management of primary parathyroid cancer.

Treatment of cancer should prevent or reduce recurrence and severity of malignancy-related hypercalcaemia. In palliative cases repeated interval doses of bisphosphonates may be needed to decrease the persistently high calcium levels. Generally, treatment of the underlying condition, for example granulomatous disease or thyrotoxicosis helps to normalise calcium levels.

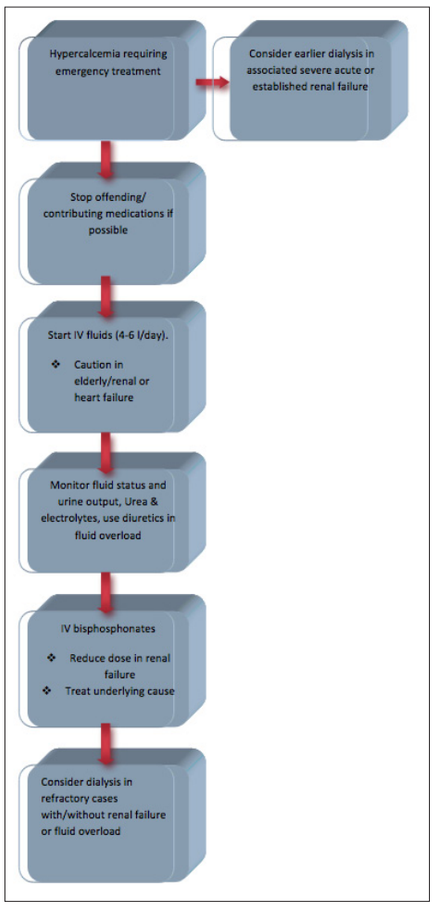

Figure 3: Algorithm for treatment of acute hypercalcaemia (Society for Endocrinology, 2013A).

Hypocalcaemia

IV calcium replacement

Symptomatic patients or those with an adjusted calcium levels below 2 mmol/L (<8 mg/dl) should be given IV calcium replacement urgently (see figure 4). 10-20 ml of 10% calcium gluconate should be infused slowly in 50-100 ml of 0.9% saline (or 5% dextrose) over 10-20 minutes. Calcium gluconate is the preferred formulation for acute calcium replacement and it should be given in hospital. Infusions should be repeated until the patient is symptom-free. The initial infusion should be followed by a slow infusion of 100 ml of 10% calcium gluconate in 1L 0.9% saline (or 5% dextrose). The infusion should be commenced at 50-100 ml/hour and titrated to normalise serum calcium. Calcium levels should be monitored 4-6 hourly. It is advised that oral calcium should be started as soon as possible so that serum calcium levels can be maintained once IV calcium is stopped.

Infusion of calcium compounds may occasionally lead to cardiac arrhythmias and infarction. Therefore, cardiac function should be monitored.

Extra care should be taken in the following situations (Society for Endocrinology, 2013b). Firstly, patients taking digoxin might develop digoxin toxicity as calcium levels increase. Secondly, aggressive calcium replacement in patient with hyperphosphataemia my result in precipitation of calcium phosphate salts and metastatic calcification, typically seen in tumour lysis syndrome. Lastly, correction of acidaemia in renal failure patients with hypocalcaemia may lead to tetany due to increased protein binding of calcium. Hypocalcaemia should always be corrected before addressing acidaemia.

Magnesium replacement

Hypomagnesaemia causes inhibition of PTH secretion and resistance to its action and therefore should always be corrected; otherwise correction of hypocalcaemia may prove difficult. Underlying causes of hypomagnesaemia should be diagnosed and treated (or removed if possible), particularly proton pump-inhibitor drugs.

Oral therapies

Oral calcium replacement therapy should be started as soon as possible to enable discontinuation of calcium infusions. Correction of vitamin D deficiency is important as it will help to stabilise patients on oral replacement. Pharmacokinetic studies in patients with severe vitamin D deficiency indicate that a single oral dose of 300,000 IU normalises serum calcidiol levels within 48-72 hours, without risk of hypercalcaemia, whereas the same dose given intramuscularly can take weeks to achieve this (Romagnoli et al., 2008). However, calcitriol (1,25-(OH)2D3) has a more rapid onset of action and should be started immediately at an initial dose of 0.5 mcg-1 mcg/day.

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Maintenance therapy

Maintenance therapy may not be required in patients who had only transient post-operative hypocalcaemia and were not vitamin D deficient. For patients with intact parathyroid function but previous vitamin D deficiency oral vitamin D supplements and avoidance of other precipitating factors should be sufficient. The prolonged effective half-life and large volume of distribution of vitamin D (Holick et al., 2011) means that 25OHD levels should be checked around 3 months after the start of therapy (National Osteoporosis Society, 2013). Calcitriol and alfacalcidol are only used long-term to supplement vitamin D-replete patients with permanent hypoparathyroidism or end-stage CKD. Decreased PTH action at the renal tubule predisposes to unopposed calciuria so correction of calcium levels to the upper limit of the normal range in these patients may lead to excessive urinary calcium excretion, predisposing them to nephrolithiasis or nephrocalcinosis. Replacement therapy should therefore aim to achieve serum ACa level at, or just below, the lower end of the normal range.

Calcium monitoring should be more frequent in pregnancy and doses should be adjusted more often (Bilezikian et al., 2011). Calcium levels should be kept at the lower end of normal range.

Emerging therapies

Synthetic injectable PTH(1-84) may be useful in the treatment of primary hypoparathyroidism (Mannstadt et al., 2013. PTH(1-84) may improve bone health in hypoparathyroidism by restoring normal bone metabolism (Rubin et al., 2011). However, it is not yet approved for use in hypoparathyroidism due to the high cost and the need for more data.

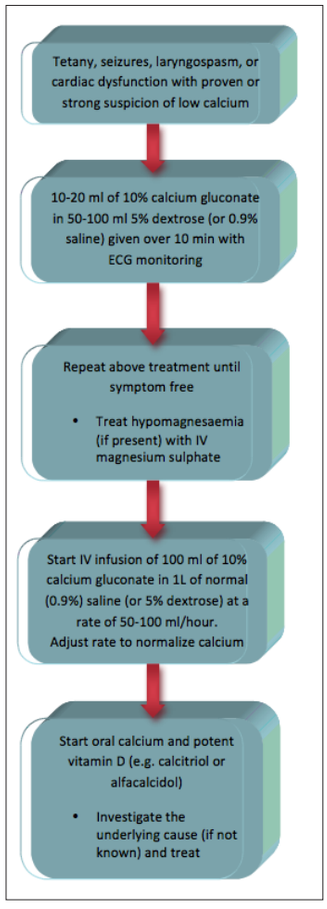

Figure 4: Algorithm for treatment of acute hypocalcaemia (Society for Endocrinology, 2013b).

Conclusions

Disorders of calcium homeostasis are common, especially in the inpatient setting. If left untreated, they are associated with serious cardiac, neurological and renal implications resulting in significant morbidity and mortality, hence they should be managed as a medical emergency, with early involvement of specialists (e.g. endocrinologist, metabolic bone physician, or oncologist). Although there are multiple, overlapping causes of calcium imbalance, much of the acute management is generic, logical and intuitive. However, making a correct diagnosis remains important for the quality of management and long-term outcomes.

Diagnosis of the underlying cause of calcium disorder is needed to guide long-term management, but this should not delay the acute treatment while awaiting results of specific investigations. Once the underlying cause is diagnosed, prompt involvement of the relevant specialist is crucial to efficient and well-directed further management.

DISORDERS OF CALCIUM HOMEOSTASIS

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References

1. De Lusignan S, Gallagher H, Chan T, et al. The QICKD Study Protocol: a Cluster Randomised Trial to Bilezikian, JP, Khan, A, Potts, JT Jr, et al. (2011) Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research. J Bone Miner Res; 26: 2317–37.
2. Body, JJ, Lotholary, A, Romieu, G et al. (1999) A dose finding study of zoledronate in hypercalcemic cancer patients. J Bone Miner Res; 14:1557-61.
3. Brasier, AR, Nussbaum, SR (1988) Hungry bone syndrome: clinical and biochemical predictors of its occurrence after parathyroid surgery. Am J Med; 84(4):654-60
4. Desai, TK, Carlson, RW, Geheb, MA (1988) Prevalence and clinical implications of hypocalcemia in acutely ill patients in a medical intensive care setting. Am J Med; 84(2):209-214.
5. Doorenbos, CJ, Ozyilmaz, A, van Wijnen, M (2003). Severe pseudohypocalcemia after gadolinium-enhanced magnetic resonance angiography. N Engl J Med; 349(8):817-818.
6. Egbuna, OI, Brown, EM (2008) Hypercalcaemic and hypocalcaemic conditions due to calcium-sensing receptor mutations. Best Pract Res Clin Rheumatol; 22: 129-148.
7. Endres, DB (2012) Investigation of hypercalcemia. Clinical Biochemistry; 45/12(954-63): 0009-9120,1873-2933.
8. Favus, MJ, Goltzman, D (2013) Regulation of calcium and magnesium. In Rosen CJ, editor: Primer on the metabolic bone diseases and disorders of mineral metabolism, 8 ed, Washington, DC, American Society for Bone and Mineral Research, p. 173-179.
9. Fenech, ME, Turner, JJO (2013) Hypercalcaemia and primary hyperparathyroidism. Medicine (United Kingdom); 41/10(573-576):1357-3039,1365-4357.
10. Hoffman, E (1958) The Chvostek sign: a clinical study. Am J Surg; 96:33–37.
11. Holick, MF (2007) Vitamin D deficiency. N Engl J Med; 357:266-281.
Holick, MF, Brinkley, NC, Bischoff-Ferrari, HA et al. (2011) Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab; 96:1911-1930.
12. Hurley, K, Baggs, D (2005) Hypocalcemic cardiac failure in the emergency department. J Emerg Med; 28(2):155-159.
13. Jesus, JE, Landry, A (2012) Chvostek's and Trousseau's Signs. N Engl J Med; 367:e15.
14. Juppner, H (2011) Phosphate and FGF-23. Kidney Int; 79:S24–S27.
15. Li, J, Ma, H, Tong, X, Su, C, Zheng, D, Chen, M, Lu, C (2013) Blastoid mantle cell lymphoma involving skin and orbit with hypercalcemia: A case report and literature review. Dermatologica Sinica; 31/2(98-101):1027-8117; 2223-330X.
16. Liamis, G, Milionis, H, Elisaf, M (2009). A review of drug induced hypocalcemia. J Bone Miner Metab; 27; 635-642.
17. Mannstadt, B et al. (2013) Efficacy and safety of recombinant human parathyroid hormone (1–84) in hypoparathyroidism (REPLACE): a double-blind, placebo-controlled, randomised, phase 3 study. Lancet Diabetes & Endocrinology; 1: 275-283.
18. Murphy, E, Williams, G (2009) Hypocalcaemia. Medicine; 37; 465-468.
19. National Osteoporosis Society (2013) Vitamin D and Bone Health: A Practical Clinical Guideline for 20. Patient Management. http://www.nos.org.uk/document.doc?id=1352 Accessed January 20th 2014
Pearce, SHS, Cheetham, TD (2010) Diagnosis and management of vitamin D deficiency. BMJ; 340:142-147.
21. Percival, RC, Yates, AJ, Gray, RE et al. (1984) Role of glucocorticoids in management of malignant hypercalcemia. BMJ; 289:287.
22. Romagnoli, E, Mascia, ML, Ciprianj, C, Fassino, V, Mazzei, F, D'Erasmo, E, Carnevale, V, Scillitani, A, Minisola, S (2008) Short and long-term variations in serum calciotropic hormones after a single very large dose of ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3) in the elderly. J Clin Endocrinol Metab; 93(8):3015-3020.
23. Rosner, MH, Dalkin, AC (2012) Onco-nephrology: the pathophysiology and treatment of malignancy-associated hypercalcemia. Clinical Journal of The American Society of Nephrology: CJASN; 7/10(1722-9):1555-9041, 1555-905X.
24. Rubin, MR, Dempster, DW (2011) PTH(1-84) administration reverses abnormal bone-remodeling dynamics and structure in hypoparathyroidism. J Bone miner Res; 26(11):2727-2736.
25. Saidek, Z, Brazier, M, Kamel, S, Mentaverri, R (2009) Agonists and allosteric modulators of the calcium-sensing receptor and their therapeutic applications. Mol Pharmacol; 76:1131-1144.
26. Schafer, AL, Shoback, D (2013) Hypocalcemia: definition, etiology, pathogenesis, diagnosis, and management. In Rosen CJ, editor: Primer on the metabolic bone diseases and disorders of mineral metabolism, 8 ed, Washington, DC, American Society for Bone and Mineral Research, p. 572-578.
27. Sharma, OP (2000) Hypercalcaemia in granulomatous disorders. A clinical review. Current Opin Pul Med; 6:442-7.
28. Shoback, D (2008) Hypoparathyroidism. N Engl J Med; 359:391-403.
29. Shoback, DM, Bilezikian, JP, Turner, SA et al. (2003) The calcimimetic cinacalcit normalizes serum calcium in subjects with primary hyperparathyroidism. J Clin Endocrinol Metab; 88:5644-9. Singh, A, Ashraf, A (2012) Hypercalcemic crisis induced by calcium carbonate. Clinical Kidney Journal; 5/4(288-291): 2048-8505;2048-8513.
30. Society for Endocrinology (2013a) Acute hypercalcaemia. https://www.endocrinology.org/policy/docs/13-02_EmergencyGuidance-AcuteHypercalcaemia.pdf ; Accessed on 28/02/2014.
31. Society for Endocrinology (2013b) Acute hypocalcaemia. http://www.endocrinology.org/policy/docs/13-02_EmergencyGuidance-AcuteHypocalcaemia_(inAdults).pdf ; Accessed on 20/01/2014.
32. Tanvetyanon, T, Stiff, PJ (2006) Management of the adverse effects associated with intravenous bisphosphonates. Ann Oncol; 17:897-907.
33. Wang, TS, Roman, SA, Sosa, JA (2012) Postoperative calcium supplementation in patients undergoing thyroidectomy, Current Opinion in Oncology; 24/1(22-28).
34. Wei, CH, Harari, A (2012) Parathyroid carcinoma: update and guidelines for management. Current Treatment Options in Oncology. 13/1(11-23):1534-6277.
35. Zivin, J, Gooley, T, Zager, R, Ryan, M (2001) Hypocalcemia: A pervasive metabolic abnormality in the critically ill. Am J Kidney Dis; 37:689-698.

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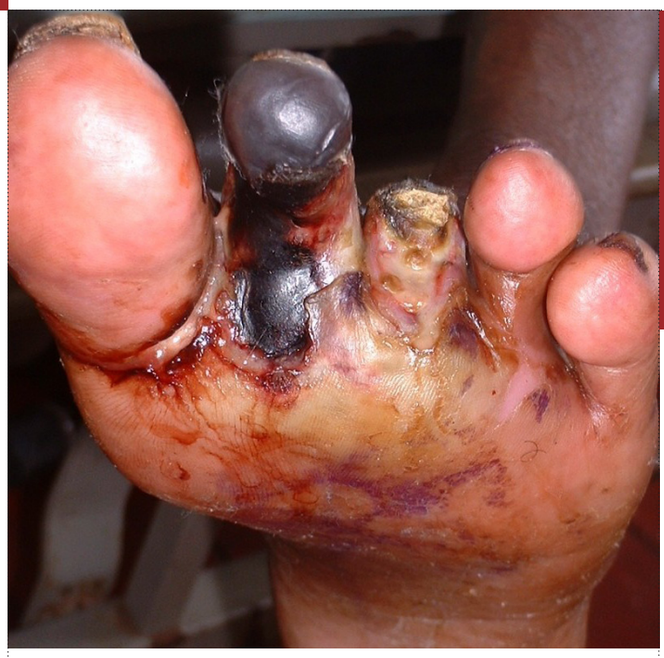
DEALING WITH DIABETES FOOT PROBLEMS IN THE ACUTE SETTING - ASSESSMENT & MANAGEMENT

A Abou-Saleh, M Haq, D Barnes



Dealing With Diabetes Foot Problems In The Acute Setting - Assessment & Management
Patient Management

Abstract

Diabetic foot disease is common and is often poorly managed leading to adverse complications. Every diabetes patient admitted to hospital should have both feet inspected and carefully examined. Any features of inflammation, ulceration or deformity should lead to a prompt referral to a member of the multidisciplinary diabetes foot care team. This will help ensure patients receive the best possible treatment early, leading to a shorter length of stay and a reduction in possible amputation.

Case History

A 65 year old gentleman was referred to the Diabetes department with a swollen left big toe. Despite multiple courses of antibiotics the inflammation had failed to improve over a 3 month period. The patient's glycaemic control was stable on oral therapy. On assessment, the left hallux appeared red, hot, and swollen with evidence of ulceration. Peripheral pulses and sensation were both intact. Osteomyelitis of the hallux was suspected and confirmed on a plain x-ray. The patient was admitted for intravenous antibiotics and proceeded to have the left hallux and underlying infected bone excised under local anaesthetic. Post-operatively the patient made an excellent recovery following completion of a short course of antibiotics.

Discussion

Foot disease is the commonest cause of hospital admission in diabetes patients (1). In many cases this results in amputation which is caused by a "foot attack" – a foot ulcer or infection failing to heal (2,3). These complications can often have a significant impact on a patient's quality of life and potentially can be fatal. Early involvement of the multidisciplinary foot care team is essential, as this has been shown to reduce length of stay, promote healing of ulcers, leading to fewer amputations. The team is typically composed of a diabetes physician, vascular and orthopaedic surgeon, podiatrist, and diabetes specialist nurse. This article helps to provide trainees with a better understanding of the different types of foot problems that may be encountered in the acute setting.

Foot Ulcers

In patients with diabetes, foot ulcers are classified as neuropathic, ischaemic or mixed, depending on the predominant pathology. Neuropathic ulcers are due to peripheral nerve damage resulting from chronic hyperglycaemia whilst ischaemic ulcers are due to impaired peripheral arterial blood supply secondary to atherosclerosis. As it is uncommon to find an ulcer exclusively due to one or the other, mixed ulcers are far more common (see Figure 1).

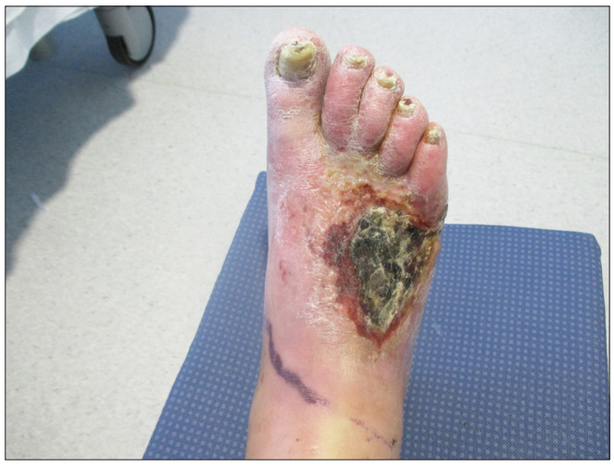


Figure 1: Mixed neuroischaemic ulcer.

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If an ulcer occurs, there is a serious risk of infection which can rapidly progress to gangrene, septicaemia and even death. It is therefore essential that infected foot ulcers are both diagnosed and treated promptly.

Assessment

It is important to determine whether the patient has known peripheral neuropathy. Such patients often describe numbness in the feet. The presence of intermittent claudication or rest pain may give a clue as to whether the patient has peripheral vascular disease. A previous history of large vessel complications such as heart disease, transient ischaemic attacks (TIA) or a previous stroke will often be present in such patients. A number of common risk factors for ulceration are listed in Table 1

Peripheral neuropathy
Previous ulcer or amputation
Peripheral vascular disease
Long standing history of diabetes
Poor glycaemic control
Retinopathy
Diabetes nephropathy
Altered foot shape
Autonomic neuropathy

Table 1: Risk factors for ulceration.

On clinical examination, neuropathic ulcers are often identified at major pressure points on the sole of the foot, such as the 1st and 5th metatarsal heads. They are typically punched out and surrounded by callus, but may be associated with underlying abscess formation and osteomyelitis. Mixed neuroischaemic ulcers often develop at pressure points of badly fitting shoes and may be associated with localised gangrene. In patients with diabetes who present with a foot-related problem, it is essential to check and document foot pulses. If pulses are present, then significant large vessel ischaemia is unlikely but be aware that pulses can sometimes be difficult to detect if oedema or associated cellulitis are present.

Management

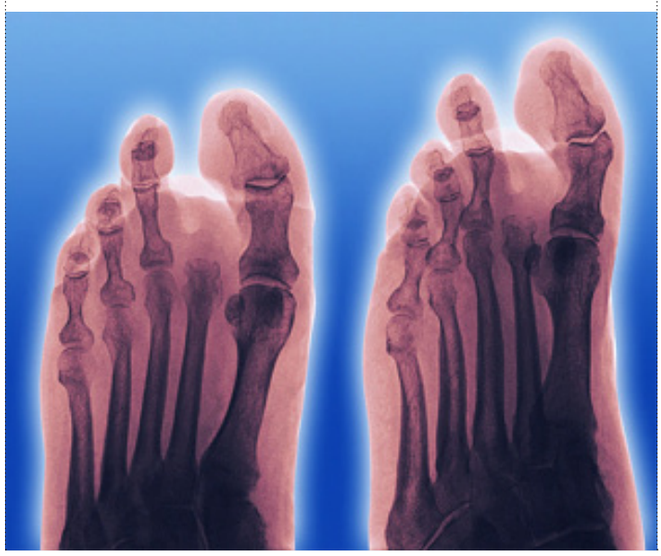
If a patient requires hospital admission to treat their active foot problem, it is important to recommend bed rest and elevation of the affected leg, especially if oedema is present. This helps to promote ulcer healing. Optimising glycaemic control is a crucial aspect of management and all such patients should be referred to the diabetes specialist team. Swabs should be taken for culture and sensitivities prior to initiating antibiotics. When ulcers are deep, have a visible sinus or there is exposed bone, osteomyelitis should be suspected. A plain x-ray of the foot should be requested as this may reveal a foreign body, soft tissue gas, bone destruction or even a fracture.

Superficial infections that do not require admission can often be treated with a course of oral antibiotics with subsequent GP follow-up. Deeper and more complex ulcers require hospital admission and treatment with intravenous antibiotics. The choice of antibiotics will depend on local antibiotic policies, allergies, presence of MRSA, and likelihood of osteomyelitis. It is good practice to seek microbiology advice at this stage. A common choice is triple therapy with intravenous flucloxacillin, benzylpenicillin and metronidazole.

Surgical input is important in order to help determine whether local debridement or an amputation may be indicated. An urgent vascular assessment is needed if there is any evidence of ischaemia as this can rapidly progress. If significant peripheral vascular disease is present, then magnetic resonance angiography (MRA) or computerised tomography (CT) angiography will often be necessary. Revascularisation with bypass grafting, reconstruction or angioplasty can help to improve blood supply and will promote the healing of ulcers. This may negate the need for distal amputation. If vascular intervention proves unsuccessful or not possible, then amputation may be required. In many cases, this will involve a below knee amputation.

Osteomyelitis

Another important complication of diabetic foot disease is osteomyelitis, where infection becomes established in the bones of the foot, usually via an open ulcer.



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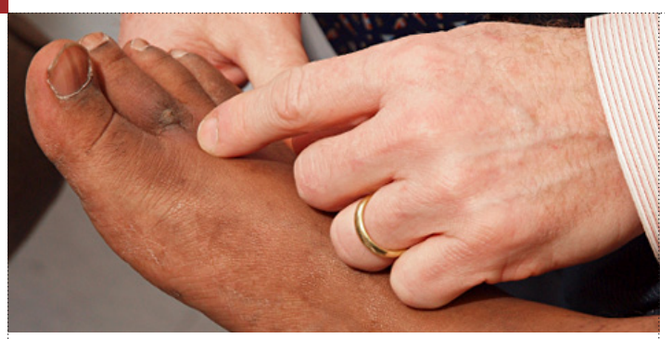

Assessment & Management

Confirmation of osteomyelitis can be difficult. It should be suspected clinically in the context of a diabetic foot ulcer if the ulcer probes down to bone or heals poorly (see Figure 2, photograph taken from case history). A swollen and 'sausage- shaped toe' is often consistent with underlying osteomyelitis. A plain radiograph may be help to confirm the diagnosis with typical features being loss of bone density or cortical outline. Initial x-rays, however, may be normal, so when suspected, treatment should not be delayed. An MRI may demonstrate early changes in such cases. Osteomyelitis is typically treated with an initial course of intravenous antibiotics in combination with either oral sodium fusidate or rifampicin which both have good bone penetration. This would then be followed by an extended course of oral antibiotics for up to 12 weeks. In refractory cases, surgical amputation may be necessary.

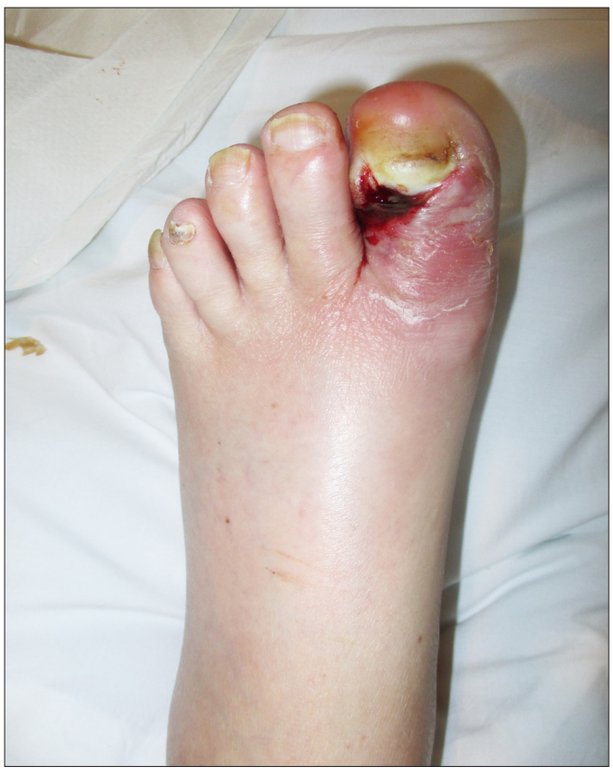

Figure 2: Osteomyelitis affecting left 1st hallux.

Charcot Foot

Charcot foot is a destructive arthropathy characterised by bone and joint destruction. It is an uncommon complication of diabetes occurring in patients with existing peripheral neuropathy and if undiagnosed can have disastrous consequences leading to ulceration and amputation.

Assessment & Management

In the 'acute phase', the condition typically presents with a hot swollen foot. Pain can sometimes be present but in most cases there is none. It can often be mistaken for other conditions such as cellulitis, deep vein thrombosis or an acute flare up of gout. If suspected, the foot should be imaged. Be aware that an initial x-ray may only demonstrate subtle changes such as a small fracture or dislocated joint. An MRI will often help to confirm the diagnosis. Initial treatment should focus on 'offloading' the affected foot. The patient should elevate the affected foot and remain on bed rest initially. The ideal option is then to use a total contact cast. Alternatively, an air cast boot could be used. These measures should help to stabilise the joint and should be continued for several weeks until there is clinical improvement.

A chronic Charcot foot typically has a "rocker bottom" appearance due to collapse of the midfoot. Signs of active inflammation will not be present. Management includes long-term use of specially designed footwear to reduce the risk of ulceration.

Multiple Choice Questions

1. What is the most common type of foot ulcer in diabetic patients?

a) Ischaemic
b) Venous
c) Mixed neuroischaemic
d) Neuropathic

2. If a patient with a diabetic foot ulcer has a normal foot x-ray despite clinical evidence of osteomyelitis, what investigation would you do next?

a) Bone biopsy
b) MRI scan of the affected foot
c) Technetium-labelled white cell scan
d) PET scan

3. What is the best first line treatment for acute Charcot arthropathy of the foot?

a) Steroids
b) Offloading measures
c) Surgery
d) Intravenous antibiotics

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4. Which members should make up the multidisciplinary team necessary for the management of diabetic foot disease?

a) Vascular surgeons
b) Podiatrists
c) Diabetologists
d) All of the above

Answers

1. Answer: c)
Mixed neuroischaemic – while purely neuropathic or ischaemic ulcers do occur, they are far less common. Most ulcers have a mixed neuroischaemic origin. Venous ulceration is a common problem in both diabetic and non-diabetic patients and typically affects the gaiter area of the leg.

2. Answer: b)
MRI scan - Even if the foot x-ray is normal, osteomyelitis can still be present. MRI scans of the foot carry a greater sensitivity and specificity for detecting osteomyelitis. Although, a bone biopsy can help to confirm osteomyelitis, this is only considered when the diagnosis is inconclusive.

3. Answer: b)
Offloading. Offloading is first line treatment with bed rest and use of total contact casting or air cast boots. This helps to prevent further damage to the affected bones. Steroids have no place in the treatment of Charcot arthropathy. Neither does the administration of intravenous antibiotics as infection is not a feature.

4. Answer: d)
All of the above - all of these specialties are vital to the functioning of the multidisciplinary team.

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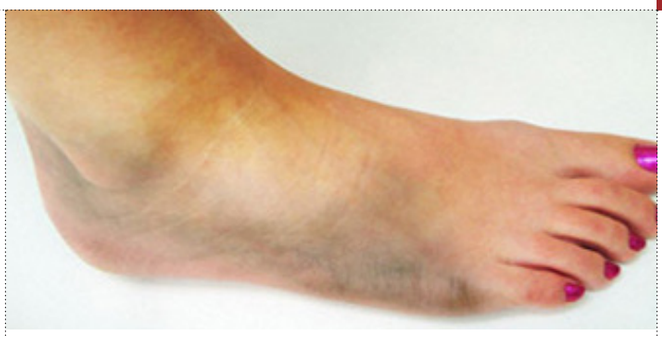

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References

1) Ramsey SD, Newton K, Blough D, McCulloch DK, Sandhu N, Reiber GE, Wagner EH. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. Diabetes Care 1999; 22:382-87.
2) National Institute for Clinical Excellence. Diabetic Foot Problems: inpatient management of diabetic foot problems. Clinical guideline 119. London: NICE, 2013. Available from http://www.nice.org.uk/nicemedia/live/13416/53556/53556.pdf.
3) Edmonds ME Foster AVM, Managing the Diabetic Foot, 3rd Edition. Wiley Blackwell 2014.

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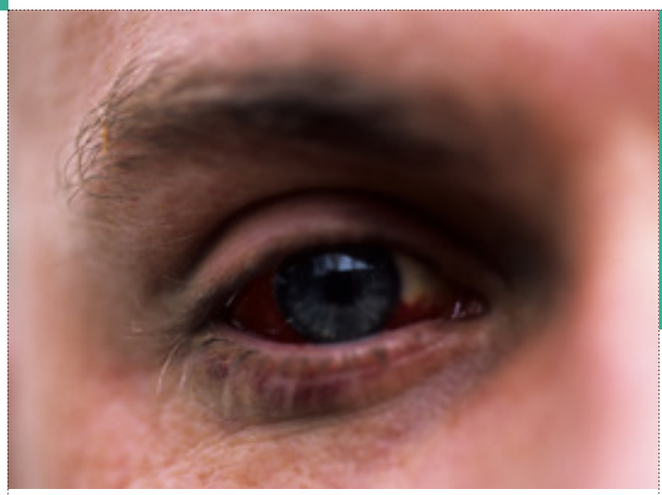
DIABETIC RETINOPATHY & EYE SCREENING

K Shotliff, M Shotliff, N Aldin



Abstract

Diabetic retinopathy remains one of the commonest causes of blindness in the working population of the western world, the impact of which can be reduced by early detection and treatment. Currently 2% of people with diabetes in the UK are registered blind with up to 98% of those with type 1 diabetes for 30 years and 60-85% of those with type 2 diabetes for 15 years having evidence of retinopathy.

The clinical features of diabetic retinopathy and the referral criteria to Ophthalmology are discussed in this article along with potential treatment options.

Introduction

Diabetes is a major challenge for health care providers around the world. It is a chronic condition, associated with significant morbidity and mortality, and is increasing in frequency worldwide. The UK prevalence of diabetes has increased from 1.4 million people in 1996 to 2.9 million currently and is expected to reach 4 million by 20251,2. Currently almost 1 in 20 of the UK population has diabetes, and that is closer to 1 in 12 people worldwide. The NHS spends approximately £173 million per week on diabetes care, much on the chronic complications of diabetes (1). These complications develop due to chronic hyperglycaemia, alongside other factors, causing damage to the small and large blood vessels within the body.

The microvascular complications of diabetes affect the eye (diabetic retinopathy), the kidney (nephropathy) and nerves (neuropathy). Macrovascular complications affect the heart (ischaemic heart disease), the brain (cerebrovascular disease) and the lower limbs (peripheral vascular disease). This article focuses on diabetic retinopathy, and discusses how to identify, prevent and treat the condition.

Diabetic Retinopathy & Eye Screening
Teaching & Training

Diabetic Retinopathy – Facts & Figures

- *2% of people with diabetes in the UK are registered blind, which equates to a 10-20 fold increase in their risk of blindness compared to a 'non-diabetic'.*
- *Diabetes UK and The Health and Social Care Information Centre suggest that each year there are 4,200 people in England at risk of blindness due to diabetic retinopathy resulting in 1,280 new cases of blindness each year.*
- *It is said to be the most common cause of blindness in the working population of the Western world, with 8.7% of overall UK blind and partially sighted registrations being due to complications of diabetes.*
- *Diabetic maculopathy is the most common cause of central vision loss in the working population in the developed world, with sight threatening eye disease affecting 9.4% of Europeans with diabetes, 14.7% of African-Caribbeans and 15.2% of Africans.*
- *In patients with Type 1 diabetes <2% have any lesions of retinopathy at diagnosis, rising to 8% after 5 years and 87-98% 30 years later. 30% of these will have proliferative retinopathy (3,4).*
- *In patient with Type 2 diabetes 20-37% will have retinopathy at the time of diagnosis, rising to 85% of those on insulin therapy 15 years later or 60% if controlled on diet and oral agents (5,6).*

Diabetic Retinopathy – Risk Factors For Development/Progression

- *Duration of diabetes*
- *Type of diabetes (proliferative disease in type 1 and maculopathy in type 2)*
- *Poor diabetic / glycaemic control*
- *Hypertension*
- *Diabetic nephropathy*
- *Recent cataract surgery*
- *Pregnancy*
- *Alcohol*
- *Smoking (variable results but appears worse in young people with exudates and older women with proliferative disease)*
- *Ethnic origin*

DIABETIC RETINOPATHY & EYE SCREENING

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Detection Of Retinopathy - Screening

In the early stages, retinopathy tends to develop and progress in the absence of symptoms so can be unrecognised and untreated, potentially leading to blindness. Treatment can modify this progression and save sight, making screening / early detection in an asymptomatic population essential.

A national screening programme for the detection of diabetic retinopathy was therefore advised by the National Service Framework for Diabetes (NSF 2001) suggesting all people over 12 years of age with diabetes should be offered annual eye screening. The English National Screening Programme for Diabetic Retinopathy (ENSPDR) has 87 screening programmes covering England (7).

A full examination should include checking visual acuity as well as photography of the retina or a slit lamp examination if this is not possible.

Visual Acuity (VA): Using a standard Snellen Chart, if VA is <6/9 recheck with a pinhole, to correct for refractive errors. If not able to correct to ≥6/9, or if deteriorating by >2 lines on a Snellen chart in the last year an Ophthalmology review may be needed as some maculopathy cannot be seen easily with a hand held ophthalmoscope. Cataracts are however a more likely cause. If vision deteriorates with a pin hole, assume maculopathy is there until proven otherwise! Remember high blood glucose readings can cause myopia (difficulty in distance vision) and low blood glucose can cause hypermetropia (difficulty in reading) although this is not always universal.

Retinal Photography: Digital retinal photography using mydriasis (drops to dilate the pupil) with 2 images per eye is the preferred method of screening in England and Wales (one 45° image centred on the macula and one on the optic disc), while in Scotland a single 45° image centred on the macula is used.

The images are then graded (as shown in Table 1 and Figure 1) by a quality assured grader. The screening programme is managed locally but is monitored and externally assessed / quality assured by the ENSPDR.

Diabetic retinopathy - how it develops:

- *A healthy retina, necessary for good vision, is fed by many tiny blood vessels. The large blood vessels seen in a retinal photograph have a network of smaller blood vessels and capillaries between them and diabetic changes occur in these small vessels.*
- *Hyperglycaemia results in thickening of the basement membrane in the capillaries, selective destruction of the pericytes managing this capillary network and loss of endothelial cell adhesion and so loss of integrity of these small vessels.*
- *This causes a change in blood vessel permeability and the leakage of water, blood, protein and lipid into the surrounding retinal tissue. In addition proliferation of endothelial cells causes microaneurysms in the capillary wall which can become visible, and occlusion of other capillaries causing ischaemia.*
- *The end result is a reduction in oxygen supply to the retina.*
- *The retina attempts to correct this hypoxia, with the help of locally produced growth factors, by producing new, more fragile vessels, which can leak and cause scar tissue to form which can then affect vision*
- *Sight is often not impaired in the early stages of the process, and may not be until very late in the progression of this condition.*

Diabetic Retinopathy – The Stages

As diabetic retinopathy develops, lesions relating to the underlying pathological process become evident on fundoscopy or in retinal photographs. This forms the basis for classification of retinopathy as outlined in table 1 and figure 1:

Stage of Retinopathy	Feature	Pathological process	Appearance
Normal fundi / retina (Grade R0 – no retinopathy)	None	None seen, but thickening of capillary basement membrane and loss of capillary pericytes may be occurring at this stage	Normal fundus
Background (Grade - R1)	Capillary microaneurysms 'Dot haemorrhages'	Out pouchings / disruption to the wall of the capillaries	Minute red dots, usually found far from visible blood vessels
	Haemorrhages 'Blot haemorrhages'	Intra-retinal haemorrhages	Small red dots, with indistinct margins
	Hard exudates	Leakage of lipids	Shiny yellow lesions – edges clearly defined
Pre-proliferative (Grade - R2)	Soft exudates 'cotton wool spots'	Infarcts in the nerve fibre layer	Pale or white, fuzzy edged lesions
	'IRMAs'	Intra-retinal microvascular abnormalities due to retinal ischaemia are tortuous dilated capillaries	Tortuous, dilated collection of capillaries which branch abnormally, occur in the tissue away from visible / larger blood vessels
	Venous beading	Alternating dilatation and constriction of veins –due to local growth factor production and associated with extensive retinal ischaemia	Sacular bulges and contractions in the walls of vessels like a string of beads or sausages
Proliferative (Grade - R3)	NVD New vessels on the optic disc or within one disc diameter of the disc NVE New vessels elsewhere	New blood vessels grow out from existing blood vessels due to local growth factors released from ischaemic areas of the retina	A collection of abnormal looking blood vessels which appear to be growing like fronds of seaweed into an area they should not be
No - Maculopathy Grade M0	None	None seen, but thickening of capillary basement membrane and loss of capillary pericytes may be occurring at this stage	Normal fundus
Maculopathy Grade M1	Any of the above R1 to R3 features	Any of the above in the region of the macula, or within one disc diameter of the macula	Any of the above (OCT – optical coherence tomography scanning of the retina, is also used which can also show and quantify the degree of oedema in the retinal layers as shown in figures 2 and 3)

Table 1 : Stages of Diabetic Retinopathy, Associated Features and Appearances on Fundoscopy.

DIABETIC RETINOPATHY & EYE SCREENING

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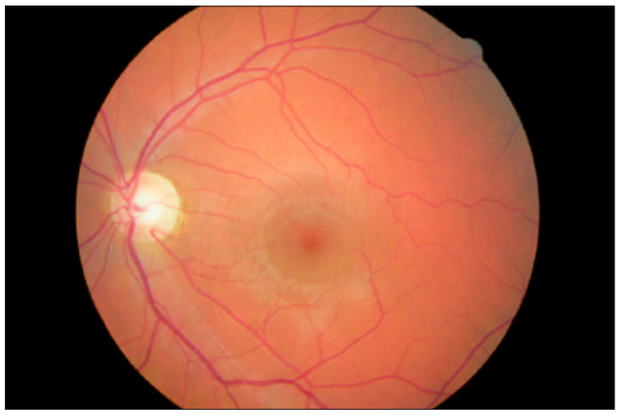
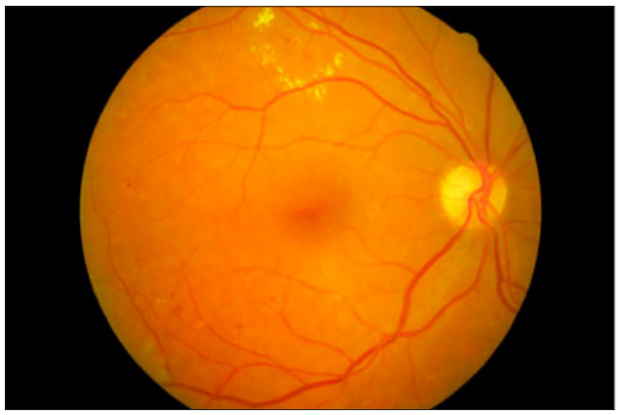
Diabetic Retinopathy & Eye Screening
Teaching & Training

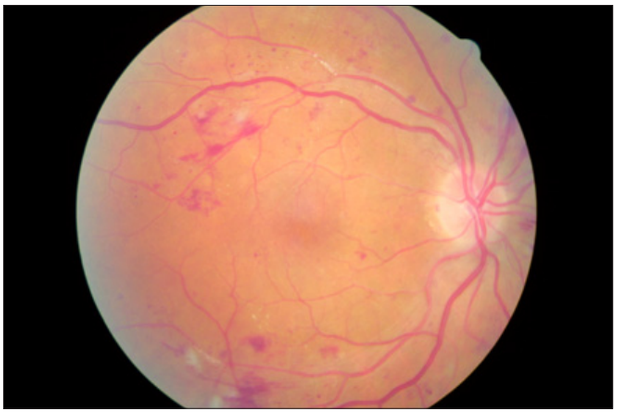
Figure 1:



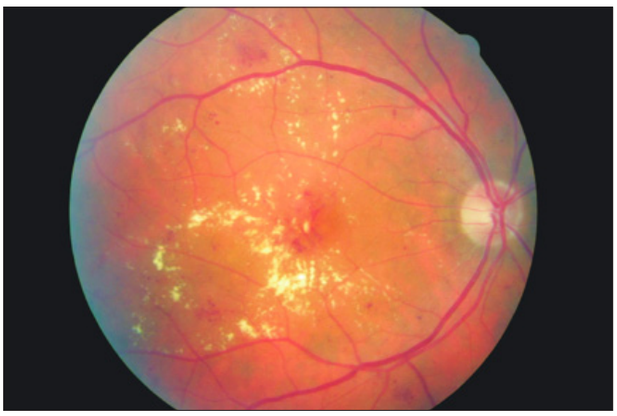
Normal retina with no diabetic retinopathy - NSC grade R0M0 .



Background diabetic retinopathy with microaneurysms, haemorrhages and exudates - NSC grade R1.



Pre-proliferative diabetic retinopathy with CWS, IRMA and multiple blot haemorrhages – NSC grade R2.



Diabetic maculopathy with haemorrhages and circinate exudates – NSC grade M1.

DIABETIC RETINOPATHY & EYE SCREENING

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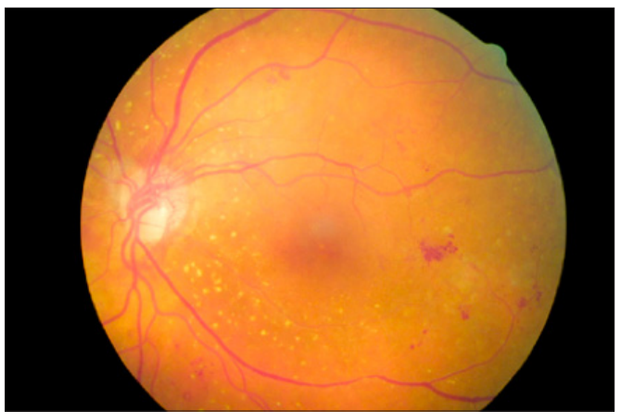
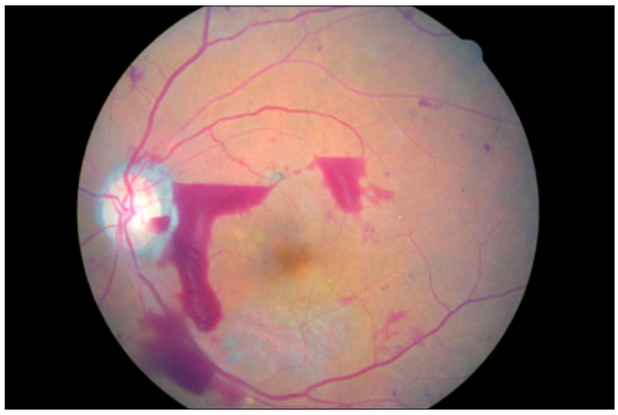
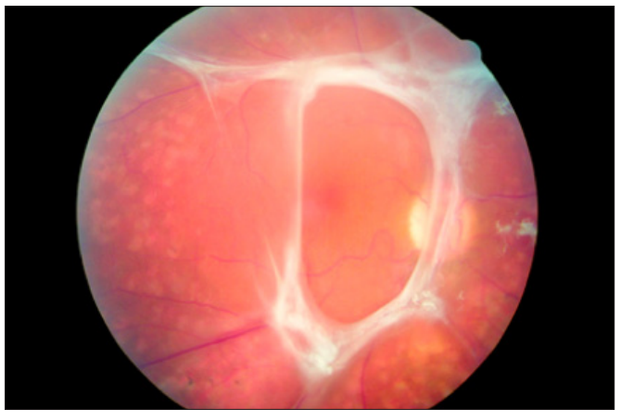


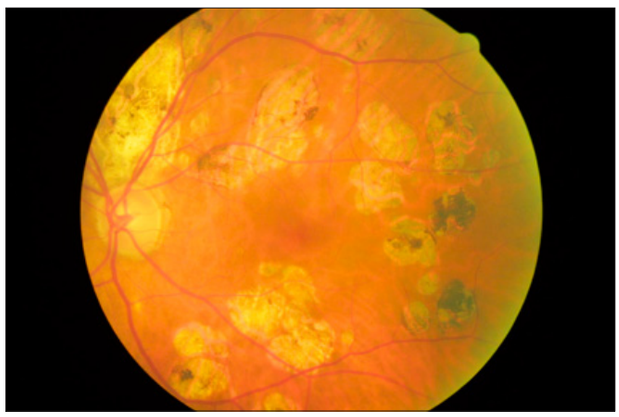
Proliferative diabetic retinopathy with new vessels at the optic disc (NVD) – NSC grade R3.



Proliferative diabetic retinopathy with pre-retinal and vitreous haemorrhages – NSC grade R3.



Proliferative diabetic retinopathy with fibrous proliferation – NSC grade R3.



Evidence of previous laser therapy – NSC grade P.

When to refer to an Ophthalmogist:

Certain symptoms and screening findings warrant referral to an Ophthalmologist -often these referrals are made directly by the retinal screening service. The urgency with which the patient needs to be referred and reviewed varies according to the presenting problem:

Immediate Referral
- Sudden loss of vision
- Retinal detachment
- New vessel formation (untreated carries a 40% risk of blindness in <2 years)
- Central retinal vein occlusion
- Haemorrhage with the eye / Vitreous haemorrhage
- Advanced retinopathy with fibrous tissue / rubeosis iridis / neovascular glaucoma

Early referral (within 6 weeks)
- Pre-proliferative changes
- Maculopathy (M1)
- Visual Acuity Fall of > 2 lines on a Snellen chart (in last year with annual screening)

Routine Referral
- Cataracts
- Non-proliferative retinopathy not threatening the macula/fovea

DIABETIC RETINOPATHY & EYE SCREENING

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Management of Diabetic Retinopathy

Based on our knowledge of risk factors, the key points are:

Medical management:

- *Optimisation of glycaemic control-strong evidence from large trials in both type 1 and type 2 patients (3,6)*
- *Blood pressure control (8) – aim <140/180 using ACE inhibitors as 1st line therapy*
- *Lipid control – aggressive control, particularly in maculopathy (9)*
- *Antiplatelet therapy – some evidence for Aspirin therapy*
- *Smoking cessation – advise and support*

Surgical therapy consists of:

- *Intra-vitreal injection of anti-VEGF (anti-Vascular Endothelial Growth Factor) agents*
- *Laser therapy*
- *Vitrectomy*

Laser Treatment (photocoagulation)

This treatment is given to selected patients and the primary aim is to reduce further visual loss. This is predominantly achieved through a reduction in new vessel formation and maculopathy.

It is usually administered over 3 – 4 sessions in an out-patient setting but can be uncomfortable and some patients require a general anaesthetic for adequate treatment. It can involve 1500-7000 burns of 100-500 microns in diameter each taking up to 0.1 second to apply for pan retinal treatment or for a macula grid 100-200 burns of 100-200 micron diameter separated by 200-400 micron gaps, avoiding the fovea. Common side effects include temporary blurring of vision and photophobia but more severe complications, including accidental burns to the fovea are rare. If deterioration in vision is noted after therapy, the patient should be reviewed by a specialist and advised not to drive.

Laser treatment of the macula is successful in reducing macular oedema in a proportion of cases with one third of eyes treated in the Diabetic Retinopathy Clinical Research Network Trial (DRCR.net) for diabetic maculopathy gaining ≥2 lines on a Snellen Chart at 2 years post therapy but almost 1 in 5 were worse having lost ≥2 lines.

Anti-VEGF (anti-Vascular Endothelial Growth Factor) agents:

The introduction of these agents has greatly improved the treatment offered to people with diabetic retinopathy, in particular those with maculopathy. Agents such as Lucentis / Ranibizumab are administered by injection directly into the eye (intravitreal) at 1-2 monthly intervals initially with the RESOLVE trial suggested a 10.3 letter improvement in visual acuity from Ranibizumab compared to 1.4 letter with a sham injection at 12 months, while the READ-2 study suggested better visual outcomes from Ranibizumab (improved by 7.24 letter) compared to laser therapy alone (reduced by 0.43 letters) or both therapies together (improved by 3.8 letters) at six months. The RESTORE trial suggested 16% of those treated with laser had a visual acuity improving by ≥10 letters at 12 months compared to 37% treated with Ranizumab and 43% treated with a combination of both.

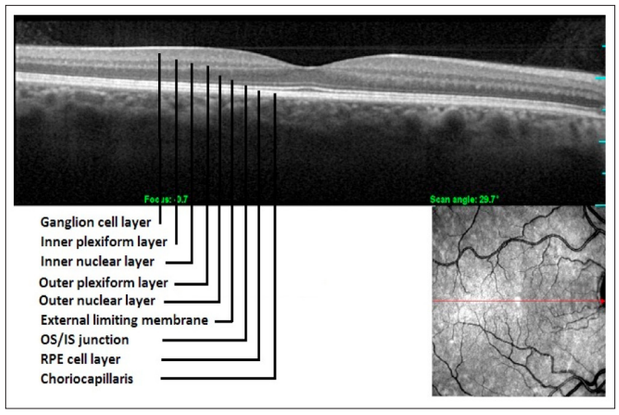

Figure 2: Labelled optical coherence tomography (OCT) scan of the macula.

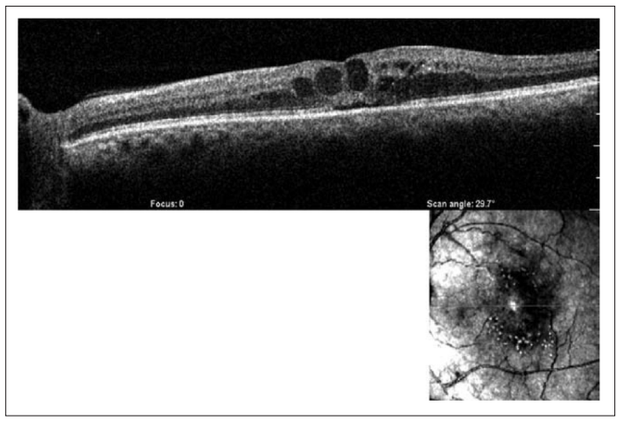

Figure 3: Optical coherence tomography (OCT) scan of a patient with cystic diabetic macular oedema.

DIABETIC RETINOPATHY & EYE SCREENING

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Conclusion

Diabetic retinopathy remains one of the commonest causes of blindness, a significant proportion of which is preventable if patients are entered into a structured and quality assured population based retinal screening program. Careful management of blood glucose, blood pressure and lipids as well as standardized grading of the digital retinal photographs obtained allowing early access of suitable patients to an Ophthalmologist will hopefully prevent sight threatening disease developing in a significant proprtion.

What Patients Need to Know:

- *Diabetic retinopathy is a leading cause of blindness.*
- *A lack of symptoms does not indicate a lack of retinopathy.*
- *A robust and free screening service is in place within the UK and patients should attend annually.*
- *Serious abnormalities picked up at screening are referred on to an Ophthalmologist for further input.*
- *If new abnormal blood vessels are detected early, they can be treated effectively.*
- *Laser treatment is given to reduce further visual loss but not to restore vision.*
- *Patients should be encouraged to attend regular diabetes follow-up (either in primary or secondary care) and take their prescribed medications regularly.*
- *Optimal control of blood sugar, blood pressure and cholesterol can help minimise retinopathy and may reduce its progression to more sight threatening forms.*
- *In pregnancy, retinopathy may progress rapidly and women should have their eyes screened as soon as pregnancy is confirmed and again in each trimester.*

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References

1. www.diabetes.org.uk.
2. Chapter 113, Diabetic Eye Disease, Oxford Handbook of Endocrinology and Diabetes, 2nd Edition, Editors H.E. Turner and J.A.H. Wass, Oxford Medical Publications, ISBN 978-0-19-856739-4.
3. DCCT Research Group. The effect of intensive treatment of diabetes on the development and treatment and progression of long-term complications in insulin dependent diabetes mellitus. New England Journal of Medicine 1993;329:977-1034.
4. Klein R, Klein BEK, Moss SE, Cruickshanks KJ. The Wisconson Epidemiologic Study of diabetic retinopathy: XVII. The 14 year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. Ophthalmology 1998;105:1801-15.
5. Klein R, Klein BEK, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of diabetic retinopathy: X. Four year incidence and progression of diabetic retinopathy when age at diagnosis is 30 years or more. Archives of Ophthalmology 1989;107:244-9.
6. The United Kingdom Prospective Diabetes Study Group: Intensive blood glucose control with sulphonylureas or insulin compared to conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS report number 38). Lancet 1998;352:837-53.
7. National Screening Committee / NSC and Public Health England NHS diabetic eye screening programme: www.diabeticeyescreening.nhs.uk.
8. UK Prospective Diabetes Study Group. Tight Blood Pressure control and risk of macrovascular and microvascular compolications in type 2 diabetes (UKPDS report number 38). BMJ 1998;317:703-712.
9. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. The Lancet, Volume 366, Issue 9500, Pages 1849 - 1861.

Useful Resources / Further Reading

- www.nice.org.uk (Diabetic retinopathy: Early Management and Screening).
- www.diabetic-retinopathy.screening.nhs.uk/overview-of-screening-models.html (Preservation of sight in diabetes: a risk reduction program).
- www.doh.gov.uk/NSF/diabetes.
- www.retinalscreening.nhs.uk.
- www.eyescreening.org.uk.

Royal National Institute of the Blind
105 Judd Street, London, WC1H 9NE.
www.rnib.org.uk

Diabetes UK
Macleod House, 10 Parkway, London, NW1 7AA.
www.diabetes.org.uk

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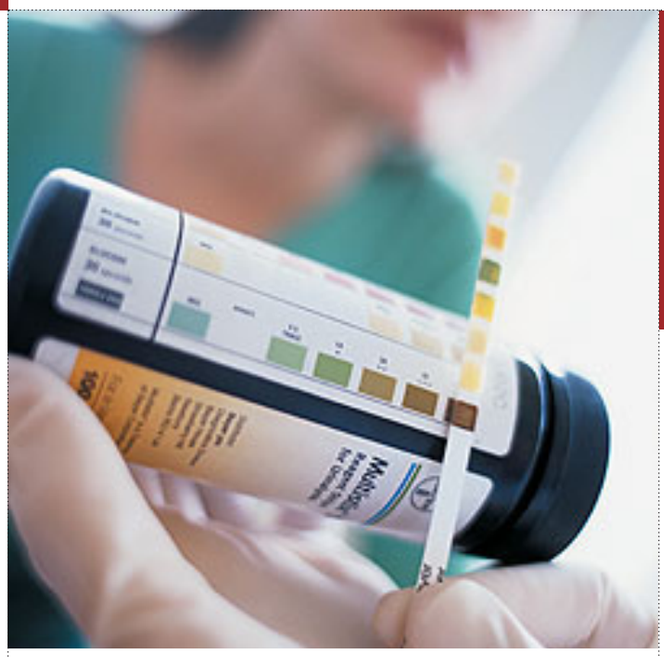
THE MANAGEMENT OF DIABETIC KETOACIDOSIS

IW Seetho, KJ Hardy



Abstract

Diabetic Ketoacidosis (DKA) is a potentially life threatening condition characterised by hyperglycaemia, ketonaemia and metabolic acidosis, as a result of relative or absolute insulin deficiency. As the prevalence of diabetes continues to rise, it is important to be able to understand why each treatment is given and to be able to manage patients who present with this condition effectively. In this article, we discuss the pathophysiological aspects of DKA, followed by an overview of aspects of management from presentation leading to recovery.

Case Presentation

A 24 year old man was admitted to A&E resuscitation with a one day history of abdominal pain and vomiting. There was no past medical history of note and he was normally well, although he had developed polydipsia, polyuria and 9kg weight loss in the preceding month. He was not on any regular medication and there was no family history of note. On examination, GCS was 15, he was thin and he appeared dehydrated; HR was 110, BP 90/70, RR>30, temperature 35.8°C, oxygen saturations 98%.

The Management of Diabetic Ketoacidosis
Patient Management

His chest was clear and abdomen was generally tender with no evidence of rebound tenderness and normal bowel sounds. Venous blood gases revealed metabolic acidosis pH 6.8, bicarbonate was 4.5mmol/l; blood ketones were >3mmol/l and blood glucose was 35mmol/l with an anion gap of > 16. A diagnosis of diabetic ketoacidosis (DKA) and new type 1 diabetes was made and the patient was admitted to the High Dependency Unit for treatment using the hospital Adult Diabetic Ketoacidosis (DKA) guideline. On recovery, he was commenced on a subcutaneous insulin regimen with support and education from the diabetes team.

Introduction

Diabetic Ketoacidosis (DKA) is a potentially life threatening condition characterised by hyperglycaemia, ketonaemia and metabolic acidosis, as a result of relative or absolute insulin deficiency. DKA has a mortality of about 5% in adults (1), typically as a result of electrolyte abnormalities, cardiac arrest, cerebral oedema or an underlying illness.

Pathophysiology of DKA

Insulin inhibits hepatic gluconeogenesis, glycogenolysis and ketogensis and facilitates glucose uptake by muscle. In insulin deficiency there is a lack of peripheral glucose uptake by muscle and increased hepatic gluconeogenesis and glycogenolysis leading to increased blood glucose. Simultaneously, insulin deficiency leads to release of amino acids and free fatty acids into the circulation and the free fatty acids are metabolised in the liver mitochondria to ketone bodies, such as 3 beta-hydroxybutyrate and acetoacetate (ketogensis).

THE MANAGEMENT OF DIABETIC KETOACIDOSIS

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As blood glucose concentrations rise and the renal threshold to reabsorb glucose is exceeded, urinary losses of glucose increase and an osmotic diuresis ensues that leads to further loss of water and electrolytes. Additionally, electrolyte depletion occurs due to binding with ketone bodies to make them water-soluble for urinary excretion. A combination of osmotic diuresis and insufficient fluid replacement due to vomiting or decreased consciousness eventually reduces renal plasma flow and glomerular filtration rate compromising renal excretion of glucose and ketones and leading to rising blood ketones and acidosis as bicarbonate buffering capacity is depleted (2,3).

Typically, DKA is associated with release of counter-regulatory hormones such as glucagon, cortisol, catecholamines and growth hormone (4). There is also evidence that inflammatory and hypercoagulable states, and increased oxidative stress occur with hyperglycaemia in DKA, with elevated inflammatory cytokines, reactive oxygen species and C reactive protein (4).

Precipitants of DKA include infections, new onset type 1 diabetes, poor compliance or omission of insulin, stroke, alcohol abuse, pancreatitis, myocardial infarction, trauma and drugs (4). Patients with type 2 diabetes may be susceptible to DKA under stressful conditions such as trauma, surgery or infections with deficient insulin levels - DKA cannot be considered pathognomonic of type 1 diabetes (5).

Factors associated with poor adherence to insulin treatment include fear of hypoglycaemia or weight gain, dislike of authority or the presence of other chronic disease (4).

DKA is a metabolic state that is characterised by acidosis, ketonaemia and hyperglycaemia.
DKA can present in both type 1 and type 2 diabetes.
Do not rely on blood glucose meter readings alone as modest rises in blood glucose may accompany significant ketoacidosis.
Careful monitoring of clinical parameters such as blood glucose, venous bicarbonate, urea & electrolytes is important.
When monitoring response to treatment, blood ketones measurements are useful.
Get help early. Early involvement of the Diabetes Team is pivotal for on-going management, patient education and subsequent follow-up.

Table 1: Key Points.

Diagnosis

A swift history and examination, followed by prompt treatment is important. It must be emphasised that the commencement of treatment should not be delayed merely on the pretext of waiting for laboratory test results. Patients typically present with osmotic symptoms of diabetes such as polydipsia, polyuria and weight loss, together with vomiting, dehydration, weakness and sometimes altered consciousness. Some patients may report blood ketones from their home meters or ketonuria from urine dipstick. Others may have a history of long-term poor control of their diabetes or recurrent DKA admissions.

Careful clinical assessment for a precipitating cause should be made. Patients may be normothermic or hypothermic, and an absence of fever does not exclude an infective process because acidosis causes vasodilatation with heat loss (6,7). An increased respiratory rate (Kussmaul respirations) secondary to acidosis is typically present. Abdominal pain with nausea and vomiting may be a consequence of DKA or associated with some underlying abdominal pathology that has caused the DKA; surgical assessment may be necessary.

Rarely, typically after more prolonged fasting, patients may present with so-called ''euglycaemic diabetic ketoacidosis,'' where blood sugar is normal or mildly elevated (8).

Differential diagnoses include: starvation ketosis and alcoholic ketoacidosis, as well as ingestion of drugs such as salicylates, methanol or ethylene glycol (4).

Management

Initial assessment is based on the principles of airway, breathing and circulation. An assessment of the severity of DKA determines the need for critical care (Table 2). Laboratory investigations include blood ketones, capillary and venous blood glucose, urea and electrolytes, venous blood gas and urinalysis. Other investigations may include a chest x-ray and sepsis screen. Further tests are guided by clinical judgement.

Hypokalaemia (K<3.5mmol/l) present at admission
Young (aged 18-25 years) and elderly patients
Pregnant women (obstetric input is also important)
Cardiac or Renal failure or other serious comorbidities
GCS<12
Hypotension (systolic BP<90mmHg) or HR>100 or <60 per minute
blood ketones>6mmol/l or bicarbonate<5mmol/l or blood pH<7.1
Low oxygen saturations; hypoxia
Patients who are not responding as expected or are clinically deteriorating despite treatment
(adapted from Joint British Diabetes Societies guidelines second edition[10])

Table 2: Situations when a higher level care should be considered.

THE MANAGEMENT OF DIABETIC KETOACIDOSIS

IW Seetho, KJ Hardy

The Management of Diabetic Ketoacidosis
Patient Management

A raised white cell count is common and does not necessarily indicate infection. Serum amylase may be raised in DKA in the absence of pancreatitis or abdominal pathology – subtyping will typically show a salivary origin. Careful monitoring of potassium levels is necessary in DKA, especially in those treated with drugs that block the renin angiotensin system.

DKA management is best guided by a local DKA protocol and is best monitored on form designed for this purpose. Regular monitoring in the form of early warning charts, fluid balance charts and protocol charts should be used. Initial treatment is one of fluid replacement to correct for dehydration and electrolyte anomalies and insulin treatment.

Fluid therapy is necessary to correct circulating volume and is based on clinical parameters such as blood pressure and heart rate. Initial fluid replacement includes 0.9% normal saline, adjusted according to the severity of dehydration. Usually 3-5 litres of fluid is required over 24 hours, but careful consideration should be given to fluid replacement in the young, the elderly and those with cardiac or renal impairment to prevent over-replacement. Excessive fluid replacement in the young may be associated with cerebral oedema which presents as a deterioration in consciousness.

Potassium replacement should not be started until potassium levels are known. Potassium levels may be raised at admission but may fall rapidly after commencing insulin infusion as total potassium stores are typically low and intravenous fluids restore renal elimination of potassium while insulin binds cell membrane receptors stimulating sodium-potassium ATPase activity that shifts potassium intracellularly (9).

Potassium levels therefore should be monitored regularly. Potassium replacement is guided by local protocol, but generally if serum potassium is >5.5mmol/l, then no potassium replacement is necessary whereas for levels between 3.5-5.5mmol/l, potassium replacement is needed (40mmol per litre of normal saline).

Insulin treatment increases glucose uptake and inhibits hepatic glycogenolysis, gluconeogenesis, ketogenesis and peripheral lipolysis resulting in falling blood glucose, ketone and lipid levels. Rapid correction of hyperglycaemia is not advised and patients are commenced on an intravenous insulin infusion (Actrapid or Humulin S 50 units in 50 ml of normal saline). A fixed rate intravenous insulin infusion based on body weight is recommended as this takes into consideration differences in patient demographics (10). The infusion rate is typically 0.1units/kg/hr. If a patient normally taking a subcutaneous long acting insulin analogue - such as Glargine (Lantus), Detemir (Levemir) or insulin degludec (Tresiba), then this should be continued at the usual subcutaneous dose at the usual time.

Hourly monitoring of capillary blood glucose measurements guide insulin infusion treatment. Venous blood may have to be sent to the laboratory for glucose measurements if capillary glucose readings exceed the quality assurance limits of the bedside glucose meters (for example, when readings>20mmol/l or 'Hi'). When blood glucose levels fall below 14mmol/l, intravenous 10% dextrose should be commenced (at 125ml/hr) in addition to the normal saline infusion and the insulin infusion (10). The insulin infusion rates should be guided by local protocols.

Hourly blood ketones measurements are useful in monitoring response to treatment, but urinary ketone measurements are less helpful because ketonuria may be present after DKA has resolved. The routine use of intravenous bicarbonate is not recommended to correct acidosis (11,12).

Thromboprophylaxis with low molecular weight heparin is typically indicated. A nasogastric tube may be necessary for persistent vomiting and central venous pressure monitoring and a urinary catheter for measuring urine output are sometimes necessary.

For all patients, early involvement of the diabetes specialist team is recommended to guide treatment and to provide appropriate education and support during recovery.

THE MANAGEMENT OF DIABETIC KETOACIDOSIS

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Subsequent management

Patients should be transferred to subcutaneous insulin therapy when they are well and ready to eat. Current national guidance suggests blood ketones should be <0.6mmol/l and venous pH >7.3. Intravenous insulin should be continued until 30-60 minutes after the first short-/rapid-acting subcutaneous insulin injection.

Prevention of DKA

All patients should receive education to try to prevent recurrence of DKA, including "sick-day rules", home blood/urine ketone testing, injection technique, blood glucose monitoring, nutrition and insulin dose adjustment. Support groups such as Diabetes UK may be a useful source of further information and support.

Conclusion

As the prevalence of diabetes continues to rise, DKA may present in all areas of medicine and therefore knowledge of the fundamentals of management of this acute medical complication is essential. The management of DKA should be guided by early input from the diabetes specialist team, with the appropriate use of local protocols and guidelines.

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References

1. Steenkamp DW, Alexanian SM, McDonnell ME. Adult Hyperglycemic Crisis: A Review and Perspective. Curr. Diabetes Rep. Feb 2013;13(1):130-137.
2. Nyenwe EA, Kitabchi AE. Evidence-based management of hyperglycemic emergencies in diabetes mellitus. Diabetes Res. Clin. Pract. Dec 2011;94(3):340-351.
3. Van Ness-Otunnu R, Hack JB. HYPERGLYCEMIC CRISIS. J. Emerg. Med. Nov 2013;45(5):797-805.
4. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic Crises in Adult Patients with Diabetes. Diabetes Care. Jul 2009;32(7):1335-1343.
5. Barski L, Nevzorov R, Harman-Boehm I, et al. Comparison of Diabetic Ketoacidosis in Patients With Type-1 and Type-2 Diabetes Mellitus. Am. J. Med. Sci. Apr 2013;345(4):326-330.
6. Gale EAM, Tattersall RB. Hypothermia - Complication of Diabetic Ketoacidosis. Br. Med. J.1978;2(6149):1387-1389.
7. Nambu T, Mori K, Shinoto Y, et al. Diabetic ketoacidosis accompanied by hypothermia: A case report. Diabetes Res. Clin. Pract. Jun 2012;96(3):326-330.
8. Munro JF, Campbell IW, McCuish AC, Duncan LJP. Euglycemic Diabetic Ketoacidosis. Br. Med. J. 1973;2(5866):578-580.
9. Nyirenda MJ, Tang JI, Padfield PL, Seckl JR. Hyperkalaemia. Br. Med. J. Oct 2009;339.
10. The Management of Diabetic Ketoacidosis in Adults- Second Edition. In: Group JBDSIC, ed2013.
11. Trachtenbarg DE. Diabetic ketoacidosis. Am. Fam. Physician. May 2005;71(9):1705-1714.
12. Hardern RD, Quinn ND. Emergency management of diabetic ketoacidosis in adults. Emerg. Med. J. May 2003;20(3):210-213.

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HYPERTHYROIDISM: FAILURE OF MEDICAL TREATMENT

DLJ Morris, AM El-Sharkawy, DM Green, N Nandwani, K Lingam

Abstract

Background

Medical management of hyperthyroidism involves thionamides with adjunctive administration of beta-blockers. However, medically resistant hyperthyroidism has been reported, requiring further treatment with radioiodine ablation or thyroidectomy; management options for which the patient should be euthyroid.

Case Presentation

A 42 year old male presented with weight loss, fine resting tremor, proximal muscle weakness, abdominal pain and vomiting. He was found to have primary hyperthyroidism and primary hypercalcaemia. Treatment with carbimazole, propylthiouracil, Lugol's iodine and prednisolone were unsuccessful in achieving euthyroidism. Thionamide treatment precipitated deranged liver function tests. The patient refused radioiodine ablation and underwent a successful total thyroidectomy whilst hyperthyroid.

Conclusion

This case highlights the challenge posed by failure of medical treatment in hyperthyroidism, as further management options require patient euthyroidism. We demonstrate that a total thyroidectomy can be performed in a hyperthyroid patient if necessary.

Hyperthyroidism:
Failure of medical treatment
Patient Management

Case Presentation

A 42 year old male presented to a medical assessment unit with weight loss, fine resting tremor, proximal muscle weakness, abdominal pain and vomiting. He had no significant past medical history and took no regular medications. Blood tests were performed, revealing free T4 (fT4) >100 pmol/L (normal range 12 to 22), free T3 (fT3) >40 pmol/L (3.1 to 6.8), thyroid stimulating hormone (TSH) <0.05 miu/L (0.3-5.5), albumin adjusted calcium 2.77 mmol/L (2.2-2.6), parathyroid hormone 12 ng/L (15-65), phosphate 0.91 mmol/L (0.8-1.4) and vitamin D 48 ng/ml (32-100) indicating primary hyperthyroidism and primary hypercalcaemia.

Thyroid antibody screening revealed thyroid stimulating hormone receptor antibodies (TRAbs) and anti-thyroid peroxidise (Anti-TPO) antibodies. A chest radiograph was unremarkable. Hypercalcaemia was a consequence of hyperthyroidism.

The patient was given fluid rehydration and commenced upon carbimazole 40mg once per day and propranolol 40mg three times per day. Blood tests were repeated after a week of treatment. Albumin adjusted calcium had risen to 2.94 mmol/L. Thyroid function tests (TFTs) again showed primary hyperthyroidism (fT4 85 pmol/L, fT3 19.8 pmol/L, TSH<0.05 miu/L). Liver function tests showed a rise in alanine transaminase (ALT) to 262 iu/L (0-40). This had previously been normal.

In view of the increased ALT, it was decided to stop carbimazole and commence propylthiouracil 200mg 3 times daily. Propranolol was continued. Despite a further week of these interventions the patients ALT continued to rise (400 iu/L) and calcium remained high (albumin adjusted 2.93 mmol/L). TFTs continued to show a primary hyperthyroidism (fT4 63.5 pmol/L, fT3 13.4 pmol/L, TSH<0.05 miu/L). Concerned about our patient's rising ALT, propylthiouracil treatment was stopped and the other available treatment options, radioactive iodine treatment and total thyroidectomy, were offered. The patient declined radioactive iodine treatment, due to a concern over the radioactivity involved and post-treatment isolation.

HYPERTHYROIDISM: FAILURE OF MEDICAL TREATMENT

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An endocrine surgeon agreed to perform a total thyroidectomy if euthyroidism could be achieved to reduce risk of precipitating an intraoperative thyroid crisis. Our patient was commenced on Lugol's iodine 0.1ml 3 times daily. However, five days later, the patients TFTs again showed primary hyperthyroidism (fT4 48.3 pmol/L, fT3 10.2 pmol/L, TSH<0.05 miu/L) and so the Lugol's iodine dose was increased to 0.3ml 3 times daily and 30mg of prednisolone was given. Despite a further five days of treatment TFTs continued to show primary hyperthyroidism (fT4 37.4 pmol/L, fT3 8.0 pmol/L, TSH<0.05 miu/L). In the interim the patient progressively developed peripheral oedema and dyspnoea.

A chest radiograph revealed pulmonary oedema. It was decided to abandon medical management due to concerns regarding impending cardiac failure. Following discussions between the patient and surgical, endocrine and anaesthetic teams it was decided to proceed with total thyroidectomy whilst the patient was still hyperthyroid. The procedure was a success with no complications. Postoperative recovery was unremarkable and propranolol was stopped.

Lifelong levothyroxine was commenced. TFTs, calcium and ALT performed two weeks postoperatively were normal (fT4 17.3 pmol/L, fT3 5.0 pmol/L, TSH 0.5 miu/L, albumin adjusted calcium 2.46, ALT 45). Histopathological appearances of the thyroid gland tissue were consistent with partially treated Graves' disease (Image 1).

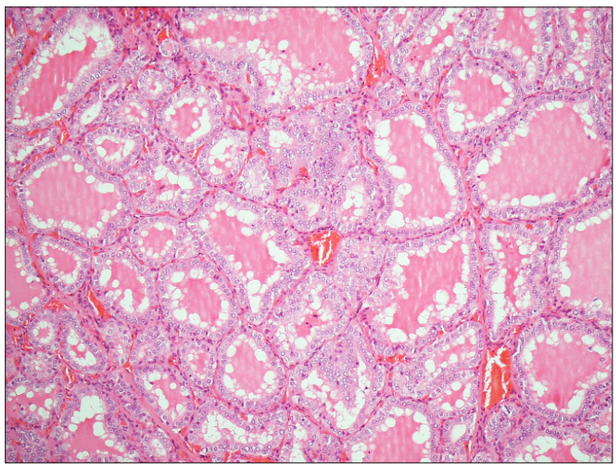


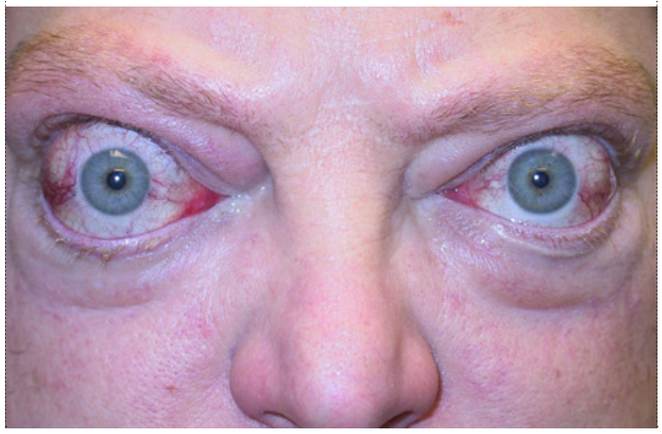
Image 1: Histopathological appearances of thyroid gland tissue in this case. Findings were consistent with partially treated Graves' disease due to hyperplastic areas with simple, non-branching papillary projections into the central follicle lumina.

Discussion

Failure of medical treatment in hyperthyroidism presents a challenging dilemma. Conventional management of hyperthyroidism involves thionamides with adjunctive administration of beta-blockers. Management of hyperthyroidism with thionamides achieves euthyroidism in 60% of cases (1). Given failure of medical management, patients are offered radioactive iodine ablation or thyroidectomy. However, in an actively hyperthyroid patient these interventions can precipitate a thyroid crisis. A thyroid crisis is a rare presentation of hyperthyroidism, affecting 1-2% of those with overt hyperthyroidism (2). It may be precipitated by stress, infection, surgery or radioiodine therapy and is characterised by delirium, severe tachycardia, fever, vomiting, diarrhoea, and dehydration (3). It has a mortality of 10-20%. Consequently, it is essential that patients are euthyroid prior to these treatments. Iodides and corticosteroid are given for several days prior to these procedures to induce temporary euthyroidism. However, our patient remained hyperthyroid despite high doses of two thionamides, an iodide and glucocorticoid. He also developed a significant increase in ALT which made continued treatment with thionamides an unviable option.

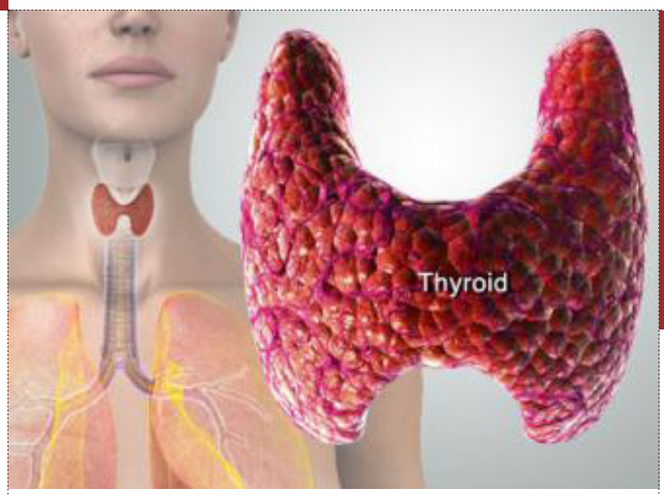
Refractory cases have often shown resistance to high dose thionamides and beta-blockers, with resistance to iodides and radioactive iodine rarely reported (4-11). Mechanisms suggested for this resistance include drug malabsorption, rapid drug metabolism, anti-drug antibodies and impairment of intrathyroidal drug accumulation or action (12). Poor patient compliance should also be considered. In our case the patient was an inpatient within our institution and was observed taking his medications as prescribed.

In this context of failure of medical management a difficult dilemma presents. The hyperthyroid patient requires treatment, but the available treatment options require euthyroidism. In our case, after prolonged consultation between the patient and surgical, endocrine and anaesthetic teams it was decided it was in the patients best interests to proceed with total thyroidectomy whilst the patient was still hyperthyroid. The urgency of surgery was necessitated by concerns regarding impending cardiac failure. It should be noted that in the absence of such concerns we would have persevered with Lugol's iodine treatment for longer, in the hope that prolonged treatment would render the patient euthyroid and safer for surgery. Lithium treatment could have also been attempted.



HYPERTHYROIDISM: FAILURE OF MEDICAL TREATMENT

DLJ Morris, AM El-Sharkawy, DM Green, N Nandwani, K Lingam



Meticulous anaesthetic and surgical preparation was key to operative success. The anaesthetic team ensured that the patient was transferred to a high dependency area postoperatively for continued monitoring. A hyperthyroid thyroid gland is typically highly vascular and so it was felt the patient was at increased risk of postoperative bleeding. The thyroid gland in this case was highly vascular (Image 2).

Furthermore, hyperthyroidism increases risk of airway obstruction from vocal cord oedema. Surgical handling of the thyroid gland intraoperatively increases thyroid hormone release. In a hyperthyroid patient this can trigger thyroid crisis or precipitate tachycardia or arrhythmias, therefore patients require close monitoring. A short-acting beta-blocker such as esmolol may have been required to treat such cardiac rhythm disturbances. With appropriate preoperative, perioperative and postoperative management an experienced endocrine surgeon was able to successfully perform a successful total thyroidectomy without complications. This procedure cured our patients hyperthyroidism and hypercalcaemia.

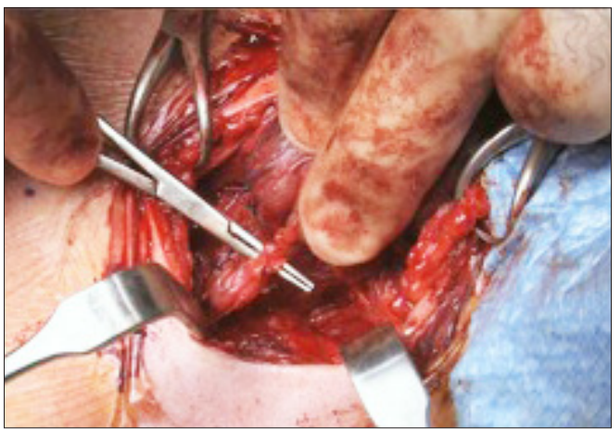


Image 2: Intraoperative image. Isolating the inferior thyroid artery supplying a vascular thyroid gland.

Hyperthyroidism: Failure of medical treatment
Patient Management

This case highlights the challenge posed by failure of medical treatment in hyperthyroidism, as further management options require patient euthyroidism. We demonstrate that a total thyroidectomy can be performed in a hyperthyroid patient if necessary.

MCQs

1. For which of the following hyperthyroidism treatments should a patient be euthyroid prior to commencement?

1. Corticosteroids
2. Thionamides
3. Beta-blockers
4. Total thyroidectomy
5. Iodides

2. Which of the following risks are associated with performing a total thyroidectomy in a hyperthyroid patient?

1. Addisonian crisis
2. Thyroid crisis
3. Hypothyroid coma
4. Hypoglycaemic coma
5. Hypertensive crisis

Answers

Question 1

1. No - Given prior to radioactive iodine ablation or total thyroidectomy to induce temporary euthyroidism.
2. No - Given as first line treatment for hyperthyroidism.
3. No - Given as first line symptomatic relief in hyperthyroidism.
4. Yes - Total thyroidectomy in a hyperthyroid patient can precipitate a thyroid crisis.
5. No - Given prior to radioactive iodine ablation or total thyroidectomy to induce temporary euthyroidism.

HYPERTHYROIDISM: FAILURE OF MEDICAL TREATMENT

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Question 2

1. No - Associated with Addison's disease.
2. Yes - Associated with hyperthyroidism and can be precipitated by stress, infection, surgery or radioiodine therapy.
3. No - Associated with hypothyroidism.
4. No - Associated with hypoglycaemia.
5. No - Associated with phaeochromocytoma.

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References

1. Harper MB, Mayeaux EJ Jr. Thyroid disease. In: Taylor RB. Family medicine: principles and practice. 6th ed. New York: Springer, 2003:1042–52.
2. Karger S, Fuhrer D. Thyroid storm--thyrotoxic crisis: an update. Dtsch Med Wochenschr. 2008 Mar;133(10):479-84.
3. Reid J R, Wheeler S F. Hyperthyroidism: Diagnosis and Treatment. Am Fam Physician. 2005 Aug 15;72(4):623-630.
4. Pandey CK, Raza M, Dhiraaj S, Agarwal A, and Singh PK. Rapid preparation of severe uncontrolled thyrotoxicosis due to Grave's disease with Iopanoic acid—a case report. Canadian Journal of Anesthesia, vol. 51, no. 1, pp. 38–40, 2004.
5. Jude EB, Dale J, Kumar S, and Dodson PM. Treatment of thyrotoxicosis resistant to carbimazole with corticosteroids. Postgraduate Medical Journal, vol. 72, no. 850, pp. 489–491, 1996.
6. Bogazzi F, Aghini-Lombardi F, Cosci C et al. Iopanoic acid rapidly controls Type I amiodarone-induced thyrotoxicosis prior to thyroidectomy. Journal of Endocrinological Investigation, vol. 25, no. 2, pp. 176–180, 2002.
7. Sebastián-Ochoa A, Quesada-Charneco M, Fernández-García D, Reyes-García R, Rozas-Moreno P, and Escobar-Jiménez F. Dramatic response to cholestyramine in a patient with Graves' disease resistant to conventional therapy. Thyroid, vol. 18, no. 10, pp. 1115–1117, 2008.
8. Li H, Okuda J, Akamizu T, Mori T. A hyperthyroid patient with Graves' disease who was strongly resistant to methimazole: investigation on possible mechanisms of the resistance. Endocrine Journal, vol. 42, no. 5, pp. 697–704, 1995.
9. Hoogenberg K, Beentjes JAM, Piers DA. Lithium as an adjunct to radioactive iodine in treatment-resistant Graves thyrotoxicosis. Annals of Internal Medicine, vol. 129, no. 8, p. 670, 1998.
10. Corvilain B, Schinohoritis P. Carbimazole—Resistant thyrotoxicosis. Postgraduate Medical Journal, vol. 73, no. 864, p. 686, 1997.
11. Lowenstein JM. Extremely resistant hyperthyroidism. Calif Med. 1964 Oct;101:288-90.
12. Saleem T, Sheikh A, Masood Q. Resistant Thyrotoxicosis in a Patient with Graves Disease: A Case Report. Journal of Thyroid Research. Volume 2011 (2011), Article ID 649084.

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HYPONATREAMIA: AN APPROACH TO INVESTIGATION & MANAGEMENT

B Mukhopadhyay, S Duffy

Hyponatreamia: An Approach To Investigation & Management
Patient Management

Abstract

Hyponatraemia is the most common electrolyte abnormality in clinical practice.(1) It is defined as serum sodium of less than 135mmol/L.(2) Its presentation varies between patients and will often relate to both the severity of hyponatraemia as well as the rate of fall.(3) The causes of hyponatraemia are numerous, and a systematic diagnostic workup is necessary in most cases. This article will review the case of a 65 year old lady who presented with complications of severe hyponatraemia, and discuss a structured method of investigating and managing similar patients in the hospital setting.

Case History

A 65 year old south Asian female, with a past medical history of schizophrenia, stroke, osteoporosis and hypertension, presented to Accident & Emergency (A&E) following two successive generalised tonic-clonic seizures witnessed by her son. She had increased agitation and restlessness over the preceding one week. She had residual left sided weakness from a previous right occipital stroke, but had no history of seizures. She was normally mobile with walking aids, but housebound. Her admission medications included Aripiprazole, Aspirin, Telmisartan, Amlodipine, Enalapril, Atorvastatin, Calcium and Vitamin D supplements, Alendronic acid and Lactulose; The Aripiprazole had been commenced 4 weeks prior to admission.

She was found collapsed and unconscious by her son on her bedroom floor with no clear evidence of head injury, and moments later she had her first generalized seizure. On arrival to A&E her Glasgow Coma Score (GCS) was 6/15 (E1V2M3), she was able to make incomprehensible groans and flex limbs to painful stimulus. There was left hemiparesis, presumed secondary to previous stroke. She was tachycardic (HR 120 and regular) and normotensive BP 120/65 mm Hg. She had cold peripheries, increased respiratory effort but no added respiratory sounds. She had a soft, non tender abdomen.

On admission, her biochemistry showed a serum sodium of 105mmol/L (normal range 133 - 146), potassium 3.0 mmol/l (normal range 3.5 – 5.3), urea 3.7 mmol/l (normal range 2.5 – 7.8) and creatinine 58 µmol/l (normal range 60 – 110). Plasma glucose was 5.0 mmol/l, CRP < 6 mg/L, and normal liver function tests. Her lipids were normal. Her serum lactate was 0.53 mmol/l (normal range 0.6 – 2.4). A CT brain was requested in A&E which showed no evidence of a new ischaemic event or any mass effect.

What would be the next key step in managing this patient?

Differential Diagnosis

Identifying the underlying cause of hyponatraemia is a challenge for any junior doctor. The first step in diagnosis is to confirm that the hyponatraemia is true, and serum osmolality should be checked. If serum osmolality is normal or raised, pseudohyponatraemia should be suspected, although this is less common nowadays with use of ion selective electrodes. Pseudohyponatraemia may be caused by severe hyperglycaemia or hyperlipidaemia.(4) For example, serum sodium reduces by 1.6 mmol/l for every 5.6 mmol/l rise in blood glucose (5).

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The flow diagram below shows a reliable and methodical approach to diagnosis of hyponatraemia:

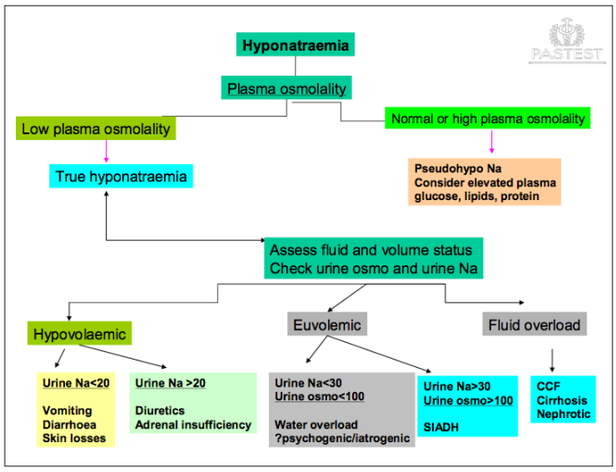

Figure 1

Once true hyponatraemia is confirmed, the next step is assessment of fluid status. This step will distinguish patients as either hypovolaemic, euvolaemic or hypervolaemic. The common causes are outlined above (figure 1). One should then proceed to measure serum and urine osmolality and urinary sodium levels.

In euvolaemic patients, SIADH (Syndrome of Inappropriate Anti Diuretic Hormone excess) is by far the commonest cause.(6) Other causes such as chronic water retention and psychogenic polydipsia are less common. The aetiology of SIADH is complex and encompasses a range of multi-system disorders. The mainstay of treatment includes fluid restriction and management of the underlying cause. If it is due to medications, one should try to withdraw or replace the responsible drug.

Diagnostic criteria for SIADH include (6):

- *Hyponatraemia.*
- *Plasma hypoosmolality proportional to hyponatraemia.*
- *Inappropriately elevated urine osmolality (>100mOsmol/kg).*
- *Persistent increased urinary sodium (>30mmol/l).*
- *Euvolaemia.*
- *Normal thyroid and adrenal function.*

Case History - Clinical Outcome

The patient was transferred to intensive care and intubated for protection of her airway. It was felt that her low sodium level required urgent management. Over the next 48 hours her serum sodium gradually improved with careful normal saline infusion in ITU. On day 3 her serum sodium was 125 mmol/L. The patient was extubated that day and sent to a general medical ward on Day 4 post admission. By this time she was alert and orientated, GCS 15 and her vital signs remained satisfactory. Further investigations revealed plasma osmolality of 252 mOsm/Kg (normal range 275 – 295), compared with a paired urine osmolality of 452 mOsm/kg, and urinary sodium of 51mmol/l, normal thyroid function (FT4 21pmol/L,TSH 1.6mU/L). Her short synacthen test showed an appropriate rise in cortisol level (494nmol/L to 736nmol/).

Given the inappropriately high urine osmolalility in an euvolaemic hyponatraemic patient in association with normal thyroid function and adrenal function shown in subsequent biochemistry, a diagnosis of Syndrome of Inappropriate ADH secretion (SIADH) was established, presumed secondary to the antipsychotic Aripiprazole.

Discussion

Drug induced Hyponatraemia and SIADH

Some of the more common medications that cause hyponatraemia include diuretics, particularly thiazide diuretics, and psychotropic medications as well as antidepressants like selective serotonin re-uptake inhibitors.(7) While diuretics can cause sodium depletion, and mild hypovolemia, particularly when other fluid loss (like diarrhoea) is present, most other medications involved cause SIADH, resulting in euvolaemic hyponatraemia. In most cases, stopping the responsible drug is sufficient to correct the electrolyte imbalance.

Aripiprazole is a newer atypical antipsychotic drug, and causes fewer cases of SIADH compared to other such agents; however SIADH secondary to this drug has been clearly described.(8) Psychotropic agents, such as phenothiazines and SSRI's, have been commonly implicated in causing SIADH and drug induced hyponatraemia. However, nearly 7% of patients with schizophrenia develop primary polydipsia which may account for the rise in incidence in this particular population (7).

Given the patient's past medical history and long term use of antipsychotic treatment for schizophrenia, it was strongly suspected that her underlying SIADH may be due to her psychotropic medications which were changed recently. After her plasma sodium had risen to an acceptable level, a different antipsychotic medication (trifluoperazine) was re-introduced by the psychiatry team. In combination with fluid restriction, the patient's serum sodium had risen to 126mmol/L by day 6 of admission. The Na levels fluctuated between 125-130 mmol/l prior to her discharge. Her mental status had returned to her baseline level and she was discharged with appropriate support and medical advice including mild fluid restriction of 1.5 litres per day.

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Complications of severe Hyponatraemia

Current NICE guidelines recommend that a level of <115mmol/L is considered severe hyponatraemia and warrants admission to hospital for urgent treatment.(9) Similarly, any patient with signs or symptoms indicative of hyponatraemia and/or a clear reversible cause such as infection or hypovolaemia may require hospital management. As mentioned before, the risk of complications due to hyponatraemia is related to both the severity of relative sodium depletion and the rate of fall.(3) Therefore, a chronic, progressive hyponatraemia may remain asymptomatic until severe whilst a sudden, even mild, drop in plasma sodium may be sufficient to expose signs and symptoms. Acute severe hyponatraemia (i.e. less than 125 mmol/L) is usually associated with neurological symptoms, such as seizures, and should be treated urgently because of the high risk of cerebral oedema and hyponatraemic encephalopathy (10).

Management of Hyponatraemia

Correcting hyponatraemia is best done by treating the underlying pathology (11,12). Recently clinical practice guidelines have been developed by a cross specialty European group (15). The guidelines emphasise management based on severity of symptoms of hyponatraemia. When a diagnosis is not apparent, or when severe complications arise as a consequence of hyponatraemia as in our case, initial management may involve direct replacement of sodium. This must be done carefully and depends greatly on the suspected clinical diagnosis.

The guideline recommends cautious use of 3% (hypertonic) saline in management of severe hyponatraemia, as in our case, regardless of acute or chronic hyponatraemia. Current NICE guidelines published in 2011 recommend that the rate of sodium repletion should not exceed 0.5mmol/L/hr.(9) This equates to a maximum correction of 12mmol/L in the first 24 hours, especially if the duration of hyponatraemia is unknown.

The European guideline recommends maximum correction of 10 mmol/L in the first 24 hours. If hyponatremia is corrected too rapidly the rapid osmotic shift can cause osmotic demyelination, otherwise known as central pontine myelinolysis. (13) However, when a patient is severely symptomatic, the rate of sodium correction may rise to 1-2mmol/L/hr under expert advice.(12) This will require closer observation and regular biochemical and neurological assessments.

The mainstay of treatment for stable patients with hyponatraemia who are euvolaemic is fluid restriction. Intake should be restricted to 500-1000ml of fluids per day according to current guidelines.(12) In these cases, several days of restriction may be required before a rise in sodium levels becomes apparent.

The use of pharmacological agents such as demeclocycline is spared for patients who do not respond to initial measures. This may be because patients struggle to adhere to fluid restriction. Democlocycline acts by inducing mild negative free water balance.(7) It should be avoided in patients with hepatic or renal failure, and new European guidelines do not recommend its use.

Other agents that are less commonly used in the treatment of hypervolaemic and euvolaemic hyponatraemia include selective vasopressin receptor antagonists, such as Tolvaptan and Conivaptan. They act on V2 receptors to potentiate the action of vasopressin on the renal collecting ducts(14). However these drugs need specialist endocrine input and a systematic review have failed to show any mortality benefit, with the additional risk of rapid correction of sodium levels (16); the European guidelines do not recommended use of these agents. Instead the guidelines have suggested increasing solute intake, although our experience with this approach is currently limited.

Multiple choice self-test questions

1. The following statements are correct about diagnosis and investigation of hyponatraemia:

A. Hyponatraemia is clinically relevant only if serum sodium is less than 125 mmol/l.
B. Low sodium is a common electrolyte abnormality in hospitalised patients.
C. Hyponatraemia can cause confusion and stupor.
D. Renal function and short synacthen test are the most important diagnostic tests in an elderly patient with hyponatraemia.
E. Urinary sodium is reduced in hyponatraemia secondary to SIADH.

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2. A 70 year old gentleman presents with falls and admission biochemistry confirms Na 126 mmol/l, the rest of electrolytes and renal functions and full blood count are normal. His medications include Fluoxetine and a diagnosis of SIADH is suspected. Which of the following are appropriate in his management?

A. He may be discharged with advice to stop fluoxetine.
B. Overnight intravenous normal saline should be given until a senior medical review in the morning.
C. Postural blood pressure measurements should be taken immediately after admission.
D. Serum and urine osmolality should be checked at the time of admission prior to fluid restriction.
E. A Chest XRay is only indicated if he complains of chest pain or breathlessness.

Correct Answers

1. B, C.

The symptoms of hyponatraemia may be mild confusion and may be apparent in some patients with a mild rapid drop in serum sodium levels from normal, even at levels of 130 – 132 mmol/L. Following clinical examination to assess fluid status, the most important diagnostic tests include serum and urine osmolality to establish the cause of hyponatraemia. A synacthen test is necessary in a small proportion of patients who present with hypovolaemic hyponatraemia without an apparent cause. Urine sodium is typically > 30 mmol/L in SIADH.

2. C, D

An elderly patient with low sodium and falls needs admitted for further evaluation, a Chest XRay must be undertaken as part of diagnostic workup if SIADH is confirmed as chest pathology is one of the commonest causes of SIADH. If SIADH is suspected, fluid restriction is the mainstay of treatment. Postural blood pressure is the single most important bedside test for assessment of fluid status. Serum and urine osmolality should be checked at the first available opportunity in all patients with hyponatraemia.

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References

1. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatraemia. American Journal of Medicine. 2006 July;110 (7 Suppl 1):S30-35.
2. Reynolds RM, Padfield PL, Seckl JR. Disorders of sodium balance. BMJ. 2006 Mar 25;332(7543):702-5.
3. Thompson CJ. Hyponatraemia: new associations and new treatments. European Journal of Endocrinology. 2010 Jun;162 Suppl 1:S1-3.
4. Lien Y, Shapiro J. Hyponatremia: clinical diagnosis and management. American Journal of Medicine. 2007;120(8):653-658.
5. Katz MA et al. Hyperglycaemia-induced hyponatraemia – calculation of expected serum sodium depletion. New England Journal of Medicine. 1973 Oct 18;289(16):843-4.
6. Ellison DH, Berl T. Clinical practice. The syndrome of inappropriate antidiuresis. N Engl J Med. 2007 May 17;356(20):2064-72.
7. Chan TY. Drug-induced syndrome of inappropriate antidiuretic hormone secretion. Causes, diagnosis and management. Drugs Aging. 1997;11:27–44.
8. Bachu K, Godkar D, Gasparyan A, Sircar P, Yakoby M, Niranjan S. Aripiprazole-induced syndrome of inappropriate antidiuretic hormone secretion (SIADH). Am J Ther. 2006 Jul-Aug;13(4):370-2.
9. Guidelines for management of hyponatraemia. National Institute for health and care excellence. January 2011.
10. Asadollahi, K., Beeching, N. and Gill, G. (2006) Hyponatraemia as a risk factor for hospital mortality. QJM 99(12), 877-8.
11. Sterns R, Nigwekar SU, Hix JK. The Treatment of Hyponatraemia. Seminars in Nephrology. 2007; 29:282-299.
12. Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH. Hyponatremia treatment guidelines 2007: expert panel recommendations. Am J Med. 2007 Nov;120(11 Suppl 1):S1-21.
13. Sterns RH, Riggs JE, Schochet SS Jr. Osmotic demyelination syndrome following correction of hyponatremia. New England Journal of Medicine. 1986; 314:1535–42.
14. Schrier R, Gross P, Gheorghiade M, Berl T, Verbalis J, et al. Study of Ascending Levels of Tolvaptan in Hyponatremia (SALT-1 and -2 trials) N Engl J Med 2006 Nov 16;355(20):2099.
15. Spasovski G, Vanholder R, Allolio B, et al. Clinical Practice Guidelines on diagnosis and treatment of hyyponatraemia. European Journal of Endocrinology 2014; 170: G1 – G47.
16. Rozen-Zvi B, Yahav D, Gheorghiade M, et al. Vasopressin receptor antagonists for the treatment of hyponatraemia: systematic review and meta-analysis. American Journal of Kidney Diseases 2010; 56: 325 – 337.

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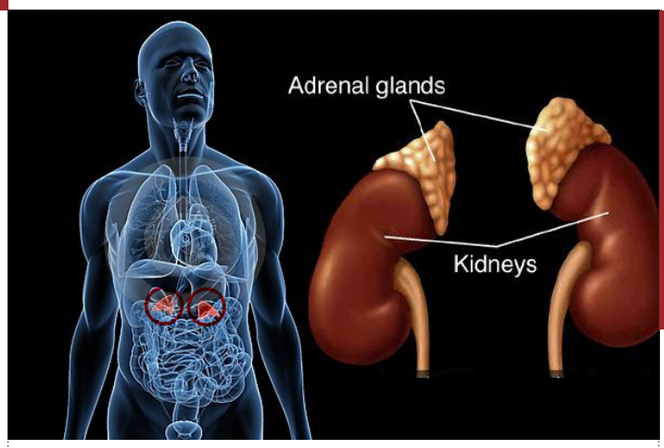
ADRENAL PHYSIOLOGY & PRIMARY ADRENAL INSUFFICIENCY

MA Karamat, MS Ahmed



Adrenal Physiology & Primary Adrenal Insufficiency
Patient Management

Learning Objectives

Learning normal adrenal physiology.

Clinical features of primary adrenal insufficiency.

Management approach to primary adrenal insufficiency.

Recognition and management of acute adrenal crisis.

Abstract

The adrenal gland is composed of adrenal cortex (which is divided into 3 zones in the adult gland) and the adrenal medulla. The cortex produces aldosterone, sex hormones and cortisol, which are all synthesized from cholesterol. Adrenal medulla produces the catecholamines. Cortisol is an endogenous steroid, which is essential for life. Aldosterone promotes sodium retention and potassium elimination by the kidney. Catecholamines stimulate the "fight or fight" reaction.

Adrenal insufficiency is a life-threatening disorder, which is characterized by deficient production or action of glucocorticoids and/or mineralocorticoids and adrenal androgens. Adrenal insufficiency may result from disorders affecting the adrenal cortex (primary), or the anterior lobe of pituitary gland /hypothalamus (secondary).The clinical diagnosis of adrenal insufficiency can be confirmed by demonstrating inappropriately low cortisol secretion.

Treatment of adrenal insufficiency should be initiated as soon as the diagnosis is confirmed, or even sooner if the patient presents in an adrenal crisis. Education to the patient and caregivers is essential part of the management. Acute adrenal crisis is an emergency, which requires prompt intervention, can manifest as a hypovolemic shock. Management is by supportive measures and intravenous glucocorticoid replacement.

Adrenal Gland Physiology

Eustachius first described the adrenal gland in 1563 and its importance was later recognized by the work of Thomas Addison in 1855 and Brown-Sequard in 1856.

The adrenal glands are small, yellowish organs that rest on the upper poles of the kidneys in the Gerota fascia. Each adrenal gland is composed of two distinct parts (figure 1), the adrenal cortex and the adrenal medulla. The cortex is divided into 3 zones. From exterior to interior, these are the zona glomerulosa, the zona fasciculata, and the zona reticularis. The adrenal cortex secretes 3 types of hormones: 1.mineralocorticoids (the most important of which is aldosterone), secreted by the zona glomerulosa; 2. glucocorticoids (predominantly cortisol), secreted by the zona fasciculata and, to a lesser extent, the zona reticularis; and 3. adrenal androgen (mainly dehydroepiandrosterone [DHEA]), which is predominantly secreted by the zona reticularis, with small quantities released from the zona fasciculata. All adrenocortical hormones are steroid compounds derived from cholesterol (Figure 2).

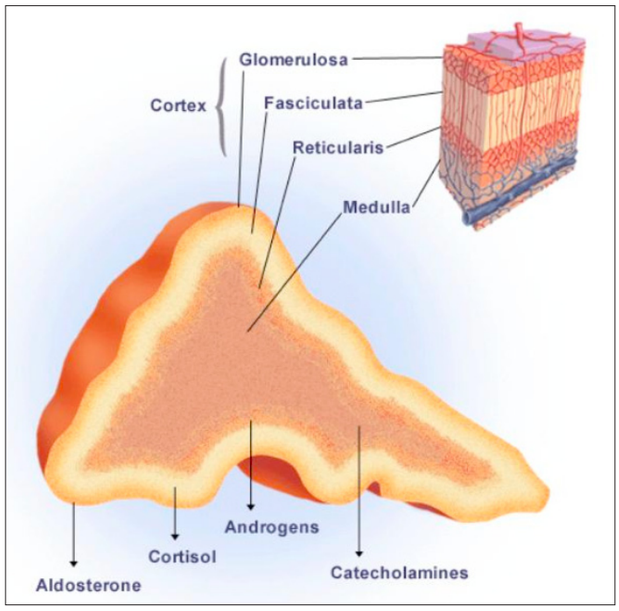


Figure 1: The adrenal gland. Adapted from Mercury toxicity endocrinology.

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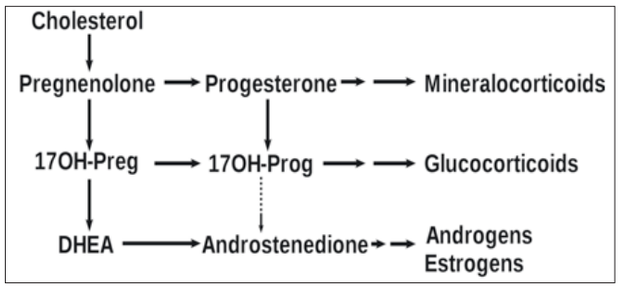

Figure 2: Adrenocortical hormones are steroid compounds derived from cholesterol.

Cortisol binds to proteins in the blood, mainly cortisol-binding globulin or transcortin. More than 90% of cortisol is transported in the blood in this bound form. Aldosterone accounts for 90% of mineralocorticoid activity, with some activity contributed by deoxycorticosterone, corticosterone, and cortisol. Approximately 95% of glucocorticoid activity comes from cortisol, with corticosterone, a glucocorticoid less potent than cortisol, making up the rest. Cortisol release is almost entirely controlled by the secretion of adrenocorticotropic hormone (ACTH) by the anterior pituitary gland, which is controlled by corticotrophin-releasing hormone (CRH) secreted by the hypothalamus.

In normal situations, CRH, ACTH, and cortisol secretory rates demonstrate a circadian rhythm, with a zenith in the early morning and a nadir in the evening (Figure 3).Various stresses also stimulate increased ACTH and, thus, cortisol secretion. Cortisol in turn acts back on the hypothalamus and pituitary (to suppress CRH and ACTH production) in a negative feedback cycle.

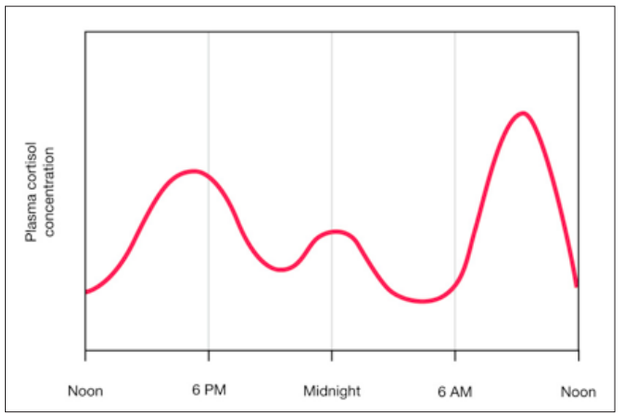

Figure 3: The normal circadian rhythm of cortisol secretion.

Cortisol has many effects on the body:

- *Stimulates gluconeogenesis in the liver by stimulating the involved enzymes and mobilizing necessary substrates, specifically amino acids from muscle and free fatty acids from adipose tissue. It simultaneously decreases glucose use by extra hepatic cells in the body. The overall result is an increase in serum glucose.*

- *Decreases protein stores in the body, except in the liver, by inhibiting protein synthesis and stimulating catabolism of muscle protein.*

- *Has clinically significant anti-inflammatory effects.*

Aldosterone promotes sodium reabsorption and potassium excretion by the renal tubular epithelial cells of the collecting and distal tubules. As sodium is reabsorbed, water follows passively, leading to an increase in the extracellular fluid volume with little change in the plasma sodium concentration. Many factors affect aldosterone secretion, the most important of which involve the renin-angiotensin system and changes in the plasma potassium concentration.

The adrenal cortex continually secretes several male sex hormones, including DHEA, DHEA sulfate (DHEAS), androstenedione, and 11-hydroxyandrostenedione, with small quantities of the female sex hormones progesterone and oestrogen.

The adrenal medulla is a different entity. Adrenaline (80%) and noradrenaline (20%), with minimal amounts of dopamine, are secreted into the bloodstream due to direct stimulation by acetylcholine release from sympathetic nerves. These hormones are responsible for an increase in cardiac output and vascular resistance and for all the physiologic characteristics of the stress response.

Case Study

20-year-old medical student is referred with symptoms of fatigue, increased pigmentation and weight loss.

Unable to complete the rotation (Capillary blood glucose 2.2 mmol/l)

FT4 5.5 pmol/l (9.0-19.0)
TSH 18.7 mIU/l (0.4-4.9)
Na 123 mmol/l (133-146)
K 5.8 mmol/l (3.5-5.3)

- **What is the diagnosis?**
- **How would you measure whether she is on adequate replacement?**
- **Why has she developed increased pigmentation?**
- **Is this primary or secondary adrenal failure?**

ADRENAL PHYSIOLOGY & PRIMARY ADRENAL INSUFFICIENCY

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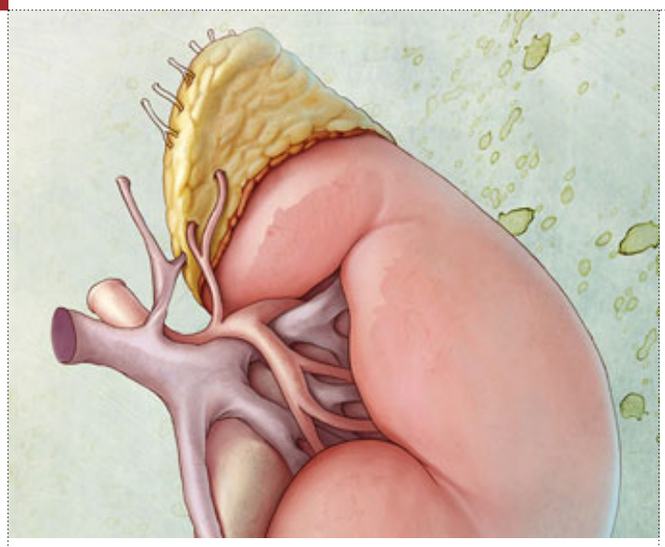

The primary adrenocortical insufficiency (Addison's disease) was first described in the mid-19th century. Adrenal tuberculosis was the most common cause of primary adrenocortical insufficiency for more than a century. However, autoimmune adrenocortical insufficiency is the predominant cause in the last twenty years. The prevalence of Addison's disease in Western countries was calculated at 35–60 per million ,but a review by Laureti et al demonstrated 2- to 3-fold higher numbers than those previously reported in other studies. (1)

Diagnosis is established by demonstrating sub optimal response to the short synacthen test (SST) which is performed by administering 250 mcg of tetracosactin via intravenous or intramuscular route and checking cortisol levels at 0 and 30 minutes. A normal response is suggested by a basal cortisol of 170 nmol/L rising to 550 nmol/L at 30 minutes.

ACTH can be useful in differentiating between primary and pituitary adrenal insufficiency. Other investigations include checking adrenal auto antibodies and looking for associated auto immune conditions. Renin is useful to monitor response to mineralocorticoid therapy. Prior to SST, if the patient is on steroids like hydrocortisone it's important to ensure that none is taken the night prior to the test and on the morning of the test. The final dose of hydrocortisone should be at midday, on the day prior to the test. HRT or any oestrogen should be discontinued for 6 weeks before the test.

Long-term management is to replace glucocorticoids usually in the form of oral hydrocortisone (15-20mgs) in divided doses and mineralocorticoids in the form of fludrocortisone. It is important to note that different glucocorticoids also have different mineralocorticoid activities, e.g. dexamethasone is devoid of any mineralocorticoid activity and prednisolone has less than hydrocortisone. Thus, a patient with primary adrenocortical insufficiency on dexamethasone would require a higher fludrocortisone dose than such a patient treated with hydrocortisone.

Undiagnosed and untreated primary adrenocortical insufficiency can lead to serious consequences. Asking patients after treating an acute adrenal crisis revealed that onset of symptoms occurred in every second patient, at least one year before hospitalization. (2)

50% of affected individuals report obvious symptoms of adrenocortical insufficiency at least 6 months prior to establishing the diagnosis. (3)

The symptoms of adrenal insufficiency are not specific, suggesting gastrointestinal disease (abdominal pains, lack of appetite, nausea and vomiting, body mass loss), muscular pain or depression .The arterial blood pressure decreases in most cases, but they can also present with orthostatic hypotension only. The lack of specific symptoms can delay establishing the diagnosis, which increases the risk of the potentially lethal complication, that is, adrenal crisis (4, 5).

An imminent adrenal crisis is a period of intensified symptoms of adrenocortical insufficiency in the form of nausea and vomiting, substantial hypotension, and severe debilitation precluding daily activities. If treatment with hydrocortisone is not started immediately, these symptoms will intensify and turn into a crisis. Adrenal crisis usually presents as persistent shock despite adequate volume repletion, and abnormal laboratory results (hypoglycemia, hyponatremia).

Management comprises intravenous glucocorticoid replacement: Hydrocortisone 100 mg I.V every 6 hours for 24 hours, then hydrocortisone 50 mg every 6 hours, when stable followed by maintenance oral therapy (10 mg 3 times/day). In addition general and supportive measures include correcting volume depletion, treating hypoglycemia with IV saline and glucose and treating infection and other precipitating causes.

The most common causes are mainly infection and fever (45%), but significant other causes include surgery and pregnancy. Patients with comorbidities are especially prone to crisis.

In the patients with established primary adrenocortical insufficiency, a major factor in the precipitation of adrenal crisis is lack of adequate education of the patient and their care givers in terms of what actions to take in the event of an imminent adrenal crisis.

During the last few years, several actions, by the EU-funded "Euradrenal" project (6). The UK Addison's advisory panel7 and the UK society for endocrinology 8were undertaken to improve doctors' and patients' knowledge of diagnosis and treatment of adrenocortical insufficiency and adrenal crisis. A review by Grossman et al (9) highlights and offers suggestions to address the challenges endocrinologists encounter in treating patients with adrenal insufficiency.

One challenge is that none of the conventional glucocorticoid treatments can perfectly match the physiological cortisol rhythm. Hydrocortisone is the most commonly used glucocorticoid for adrenal insufficiency therapy. It has high oral bioavailability, but has a short half-life between 60 and 120 min.

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However, even when hydrocortisone is administered multiple times per day the serum cortisol profile is far from matching the normal physiological cortisol circadian rhythm. (10)

New, oral, timed-released hydrocortisone preparations, match the physiological release of cortisol better than conventional preparations. Some are now available in European countries while others are currently under development. (11, 12)

In both primary and secondary adrenocortical insufficiency, DHEA secretion is clearly decreased and often even absent in both men and women with hypoadrenalism. DHEA deficiency with reduced vitality and libido is clinically more evident in women, due to the usually preserved gonadal androgen production in men. (13)

Apart from its mild androgenic effects, DHEA may also act as a neuro -steroid with possible effects on mood, cognition and well-being. However studies with DHEA replacement in patients with adrenocortical insufficiency, showed conflicting results with regard to sexual function and Quality Of Life (QOL), and in general any effects seen are usually relatively minor. (14) Based on the evidence currently available, DHEA replacement is not undertaken routinely in clinical practice in patients with adrenocortical insufficiency.

It is essential that all patients with adrenocortical insufficiency should receive a 'steroid emergency card', which provides information as to the necessity for treatment, the current replacement regimen and any relevant contact information for the responsible clinician. The card should be recognized by other healthcare personnel such as paramedics and emergency responders. It is important to ensure patients and their care givers are made aware of steroid sick day rules. As an example if the patient becomes ill with flu they need to double the dose of their hydrocortisone.

All patients should also be provided with an emergency kit and be trained in the appropriate use of all components usually in the form of an ampoule of 100 mg hydrocortisone for intramuscular injection. Injection devices and an instruction leaflet on self-administration should be provided for emergency situations (e.g. diarrhoea and vomiting) and situations in which the increased oral hydrocortisone dose fails to sufficiently improve the patient's symptoms. The patient or their regular caregiver or partner should be instructed in its use.

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References

1. S. Laureti, L. Vecchi, F. Santeusanio, and A. Falorni, "Is the prevalence of Addison's disease underestimated?" Journal of Clinical Endocrinology and Metabolism, vol. 84, no. 5, article 1762, 1999.
2. P. M. Zelissen, Addison Patients in the Netherlands: Medical Report of the Survey, Dutch Addison Society, The Hague, The Netherlands, 1994.
3. B. Bleicken, S. Hahner, M. Ventz, and M. Quinkler, "Delayed diagnosis of adrenal insufficiency is common: a cross-sectional study in 216 patients," The American Journal of the Medical Sciences, vol. 339, no. 6, pp. 525–531, 2010.
4. P. M. Stewart and N. P. Krone, The Adrenal Cortex, Williams Textbook of Endocrinology, Elsevier, London, UK, 12th edition, 2011.
5. S. Hahner, M. Loeffler, B. Bleicken et al., "Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies," The European Journal of Endocrinology, vol. 162, no. 3, pp. 597–602, 2010.
6. http://ec.europa.eu/research/health/medical-research/rare-diseases/projects/euradrenal_en.html.
7. https://www.addisons.org.uk/comms/publications/gpdiagnosingaddisons.pdf and http://www.addisons.org.uk/info/manual/crisismanagement.pdf.
8. http://www.endocrinology.org/policy/docs/11-03_adrenal%20insufficiency.pdf.
9. a grossman,therapy of endocrine disease: perspectives on the management of adrenal insufficiency: clinical insights from across europe, eur j endocrinol. dec 2013; 169(6): r165–r175.
10. Debono M, Ross RJ, Newell-Price J. Inadequacies of glucocorticoid replacement and improvements by physiological circadian therapy. European Journal of Endocrinology. 2009;160:719–729.
11. Johannsson G, Filipsson H, Bergthorsdottir R, Lennernäs H, Skrtic S. Long-acting hydrocortisone for glucocorticoid replacement therapy. Hormone Research. 2007; 68:182–188.
12. Debono M, Ghobadi C, Rostami-Hodjegan A, Huatan H, Campbell MJ, Newell-Price J, Darzy K, Merke DP, Arlt W, Ross RJ. Modified-release hydrocortisone to provide circadian cortisol profiles. Journal of Clinical Endocrinology and Metabolism. 2009; 94:1548–1554.
13. Miller KK, Sesmilo G, Schiller A, Schoenfeld D, Burton S, Klibanski A. Androgen deficiency in women with hypopituitarism. Journal of Clinical Endocrinology and Metabolism. 2001; 86:561–567.
14. Alkatib AA, Cosma M, Elamin MB, Erickson D, Swiglo BA, Erwin PJ, Montori VM. A systematic review and meta-analysis of randomized placebo-controlled trials in DHEA treatment effects on quality of life in women with adrenal insufficiency. Journal of Clinical Endocrinology and Metabolism. 2009; 94:3676–3681.

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NEWLY DIAGNOSED TYPE 2 DIABETES: A GUIDE FOR THE FOUNDATION DOCTOR

TA Chowdhury, A Moolla

Newly Diagnosed Type 2 Diabetes: A Guide For The Foundation Doctor
Patient Management

Abstract

We focus on a 53 year-old man admitted to hospital with an acute coronary syndrome whose random capillary blood glucose is found to be 18 mmol/L. We discuss the diagnostic tests required to diagnose diabetes, and describe the acute management of hyperglycaemia and well as subsequent in hospital and community based management required for such patients with a new diagnosis of type 2 diabetes.

Case History

A 53 year-old South Asian male accountant is admitted with chest pain, and found to have a non-ST elevation myocardial infarction (NSTEMI). He is treated according to an Acute Coronary Syndrome (ACS) protocol, and listed for an in-patient coronary angiogram. On admission, his random capillary blood glucose is found to be 18 mmol/L.

What aspects of the history would be useful in this case?

Some assessment of his symptoms and risk factors for diabetes should be undertaken, in view of the high capillary glucose reading. Important aspects of the history will include any assessment of symptoms of diabetes, such as tiredness, polyuria, polydipsia, weight loss, skin infections or oral/genital candidiasis. Symptoms of complications such as eye problems or peripheral neuropathy should be also sought. Family history of diabetes and diabetes related complications is important, and presence of other risk factors, such as poor diet, low levels of physical activity, medications (steroids, beta-blockers, thiazides, atypical anti-psychotics) should be assessed.

What are the important features of the clinical examination?

The presence of diabetes risk factors and related complications (eyes, feet, kidneys) should be sought. Weight and body mass index should be measured, and skin signs of diabetes should be examined (for example acanthosis nigricans). Eyes should be examined for signs of diabetic retinopathy, and feet for ulceration, peripheral pulses and neuropathy (fine touch and vibration sensation).

What investigations should be undertaken?

The latest World Health Organisation (WHO) diagnostic criteria for diabetes are shown in box 1 (1). In the context of ACS, however, diagnostic criteria for diabetes are controversial, and a firm consensus has not been reached (2). National Institute for Health and Clinical Excellence (NICE) guidelines on management of hyperglycaemia in ACS suggest that hyperglycaemia (blood glucose >11.0 mmol/L) without known diabetes should be followed up with a haemoglobin A1c (HbA1c) measurement before discharge, and a fasting glucose four days after the onset of ACS (3).

	Diabetes	Impaired Fasting Glucose	Impaired Glucose Tolerance
Random plasma glucose	11.1 mmol/L + Symptoms (Polyuria, Polydipsia, Weight Loss, Tiredness)	-	-
Fasting plasma glucose	>7.0 mmol/L	6.1-6.9 mmol/L	-
Two-hour plasma glucose following 75 g glucose	≥ 11.1 mmol/L	-	7.8 – 11.0 mmol/L
Glycated Haemoglobin	≥ 48 mmol/mol (6.5%)	-	Pre-diabetes: 42-47 mmol/mol (6.0-6.4%)

Box 1: World Health Organisation diagnostic criteria for diabetes (1)

If patient is asymptomatic, abnormal test should be repeated to confirm diagnosis.

Urinalysis should be performed to look for proteinuria and ketonuria. Presence of heavy ketonuria should alert the clinician to a possible diagnosis of type 1 diabetes, as ketonuria would not be expected in type 2 diabetes, although "+" ketones may be present in a patient who has starved for a number of hours.

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How should this patient be managed acutely?

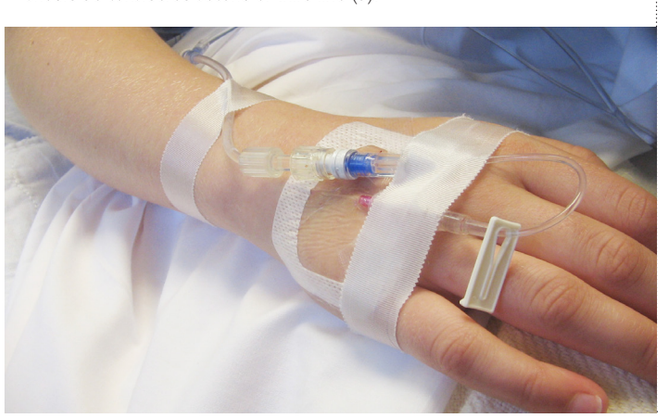
Whilst achieving tight glycaemic control during ACS or acute myocardial infarction (AMI) has not been shown to improve outcomes (4), NICE guidelines suggest treating hyperglycaemia acutely with dose adjusted intravenous insulin aiming to achieve capillary blood glucoses under 11.0 mmol/L, and to avoid hypoglycaemia (3). Intensive insulin therapy to lower glucose levels further is not recommended.

How should this patient be counselled and subsequently managed?

The patient requires a careful explanation of the diagnosis of diabetes. In the context of acute illness, hyperglycaemia can be related to stress, but persistently elevated glucoses, osmotic symptoms, and an elevated HbA1c make the diagnosis of type 2 diabetes highly likely.

Counselling for newly diagnosed diabetes should include; what the diagnosis means (in layman's terms), the lifelong nature of the condition and management, the need for lifestyle change and regular clinical reviews to observe for complications. Whilst in hospital, or very shortly after discharge, it would be desirable to ensure the patient is seen by a dietitian, and diabetes nurse specialist. The patient should be referred for structured education in the community, as this has been shown to improve outcomes in patients with newly diagnosed diabetes.

In-hospital management of this patient's diabetes will depend on his level of hyperglycaemia. If high doses of intravenous insulin (more than 4 units per hour) are required to maintain euglycaemia then subcutaneous insulin therapy is likely to be required prior to discharge. If modest doses are maintaining euglycaemia, then cessation of the intravenous insulin and careful monitoring of glucose levels may be sufficient. If medication is required, NICE guidelines on the management of hyperglycaemia in type 2 diabetes suggest metformin should be first line therapy, providing renal function is stable (estimated glomerular filtration rate (eGFR) above 30 mls/min) and there is no evidence of acute heart failure (5). Metformin should be started slowly – 500mg once daily after the main meal, and titrated slowly to avoid gastrointestinal side effects. Sulfonylurea therapy may be added if metformin is insufficient. According to NICE guidelines, the place of newer drugs (di-peptidyl-peptidase-4 inhibitors, glucagon-like peptide-1 analogues, sodium glucose transport-2 inhibitors) should be considered second or third line (5).



Remember that very tight glucose control in hospital may not be desirable as the patient may later develop hypoglycaemia post discharge due to the wearing off of the stress response and as they become more physically active at home. In-hospital pre-meal blood glucose readings of 5 - 10mmol/L are acceptable.

Smoking cessation will be extremely important, along with careful management for secondary prevention, as people with diabetes and AMI are at high risk of re-infarction, and have poorer mortality and morbidity following AMI. The place of self monitoring of capillary blood glucoses is controversial in patients not treated with insulin, and routine self testing should be discouraged.

Discussion

Whilst the diagnosis of type 2 diabetes may be found incidentally by a routine blood test, diabetes can also present with complications (eg cardiovascular disease) or with an acute decompensation. Symptoms include polyuria, polydipsia, thirst, weight loss, tiredness and blurred vision. Occasionally, the patient may present with dermatological problems such as recurrent skin abcesses, oral or genital candidiasis, granuloma annulare, necrobiosis lipoidica diabeticorum or acanthosis nigricans.

An extreme decompensation which may occur in patients with type 2 diabetes is hyperosmolar hyperglycaemic state (HHS), which is characterised by severe dehydration, marked hyperglycaemia (>30 mmol/L) without significant ketonaemia (serum ketones <3 mmol/L) or acidosis (pH>7.3, bicarbonate >15 mmol/L). Remember that modest ketonuria may be seen in this condition, due to starvation ketosis. Calculated serum osmolality (2xNa+ + urea + glucose) is usually 320 mosmol/kg or more. Treatment of HHS requires careful specialist input for fluid management and very low dose insulin therapy to avoid rapid drops in glucose levels which can lead to major shifts in osmolality and sodium (6).

Once a person is diagnosed with type 2 diabetes, they need to be offered structured diabetes care, ideally within a multi-disciplinary team setting (5). This includes attendance at a culturally appropriate structured education programme in order to understand self management of diabetes, with particular focus on lifestyle change and dietary management, as well as access to diabetes nurse specialists, chiropodists and ophthalmologists where required. In addition, all patients need to have nine diabetes key care processes undertaken each year, as outlined by NICE (Box 2) to help ensure good diabetes care. In the UK, most patients with uncomplicated diabetes will have their care managed in primary care. Patients may be referred to specialist diabetes care if they develop significant renal or foot problems, difficulty achieving euglycaemia, if they are pregnant, if they have type 1 diabetes, or if they are an in-patient.

NEWLY DIAGNOSED TYPE 2 DIABETES: A GUIDE FOR THE FOUNDATION DOCTOR

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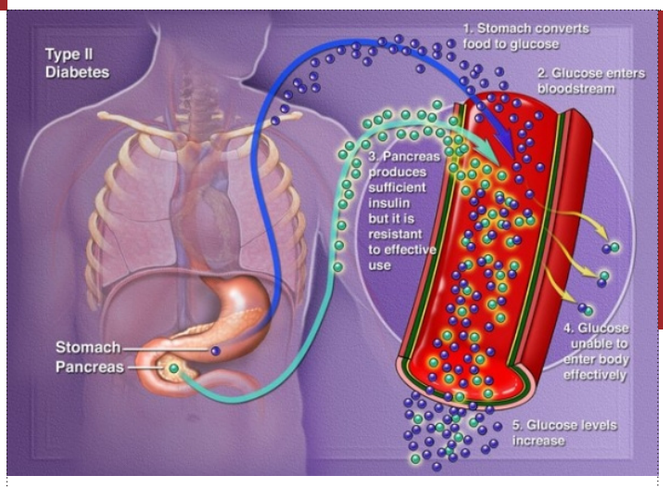

- **Assessment of glucose control - HbA1c**
- **Blood pressure measurement**
- **Cholesterol level measurement**
- **Digital retinal screening**
- **Check of feet for neuropathy, pluses, deformity, callus, ulcers and nail care**
- **Kidney function testing (urine albumin : creatinine ratio)**
- **Kidney function testing (estimated GFR)**
- **Weight check**
- **Smoking status check.**

Box 2: Nine regular care processes for all patients with diabetes.

Chronic complications of diabetes can be devastating, and costly to the patient and society (figure 1). Diabetes significantly increases risk of premature mortality by 2 - 2.5 fold. In the UK, diabetes is the commonest cause of end stage renal failure, blindness in people of working age and of non-traumatic limb amputation (7). The total cost for treating diabetes in the UK in 2010 was £13.8 billion, which accounted for around 9% of the entire NHS budget. Therefore, treatment to prevent complications is of great importance, and indeed is highly cost effective.

Newly Diagnosed Type 2 Diabetes: A Guide For The Foundation Doctor
Patient Management

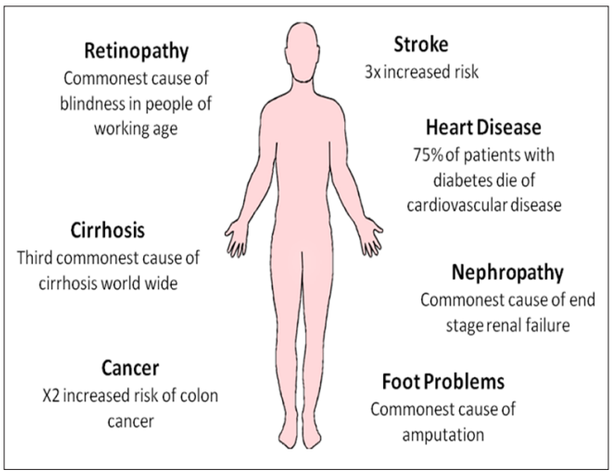

Figure 1: Chronic complications of diabetes.

The aim of diabetes management is ensure the person with diabetes is asymptomatic and well, is regularly screened for early development of complications, and has careful treatment of risk factors to reduce risk of complications. As well as regular patient education to promote healthy diet, physical activity and weight loss, other risk factors must be managed aggressively (5). All patients with diabetes over the age of 40 years should be on a statin irrespective of serum cholesterol levels, aiming for a serum cholesterol under 4.0 mmol/L. Optimal blood pressure for someone with diabetes is under 140/80 mmHg, although a target of less than 130/80 mmHg should be achieved in patients with renal, retinal or cardiovascular complications. ACE-inhibitors are the first line anti-hypertensives of choice, although frequently combination therapy is required.

NEWLY DIAGNOSED TYPE 2 DIABETES: A GUIDE FOR THE FOUNDATION DOCTOR

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Management of glucose control in patients with type 2 diabetes has undergone re-evaluation following the publications of a number of large trials of tight versus less tight glucose control (8). Most studies show that tight glycaemic control is an important risk factor for prevention of microvascular disease, but its impact on development of macrovascular disease is less significant, and extremely tight glucose control may lead to adverse cardiovascular outcomes, possibly due to hypoglycaemia. Therefore, glycaemic targets should be individualised to the person. Some factors that might suggest a tight glucose target (e.g. HbA1c around 53 mmol/mol or 7.0%) would include younger age, shorter duration of diabetes (less than 10 years), and fewer co-morbidities. Certainly in the over 75 year age group, there is no substantial evidence that tight glycaemic control improves outcomes, and indeed may increase harm due to risk of hypoglycaemia.

Conclusions

In many hospitals in the UK, around 1 in 5 beds may be occupied by a patient with diabetes. People with diabetes have poorer outcomes and longer lengths of stay compared to non-diabetic patients. Junior doctors need to be aware of how to diagnose diabetes in patients acutely admitted to hospital, how to institute initial management, and how to refer appropriately to specialist teams. We would encourage all junior doctors to be aware of diabetes, and to take interest in the management of their diabetic patients, in order to improve their short term and long term health outcomes.

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References

1. World Health Organisation 2011. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Abbreviated report of a WHO consultation. WHO Geneva. http://www.who.int/diabetes/publications/report-hba1c_2011.pdf Accessed 19.03.14.
2. Gholap N, Davies MJ, Mostafa SA, Squire I, Khunti K. A simple strategy for screening for glucose intolerance using glycated haemoglobin in individuals admitted with acute coronary syndrome. Diabet Med 2012;29:838-43.
3. National Institute for Health and Clinical Excellence CG130, Oct 2011. Hyperglycaemia in acute coronary syndromes. http://www.nice.org.uk/nicemedia/live/13589/56817/56817.pdf Accessed 19.03.14.
4. Malmberg K, Ryden L, Wedel H et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur Heart J 2005;26:650-61.
5. The management of type 2 diabetes. National Insititute for Health and Care Excellence. CG87, May 2009. http://www.nice.org.uk/nicemedia/live/12165/44322/44322.pdf. Accessed 19.03.14.
6. The management of the hyperosmolar hyperglycaemic state (HHS) in adults with diabetes. Joint British Diabetes Societies, Inpatient Care Group, August 2012 http://www.diabetologists-abcd.org.uk/JBDS/JBDS_IP_HHS_Adults.pdf Accessed 19.03.14.
7. Diabetes UK, Improving services & standards, State of the Nation 2012; http://www.diabetes.org.uk/Documents/Reports/State-of-the-Nation-2012.pdf Accessed 19.03.14.
8. Inzucchi SE, Bergenstahl RM, Buse JB et al. Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach. Position Statement of the American Diabetes Association (ADA)) and the European Association for the Study of Diabetes (EASD). Diab Care 2012;35:1364-79.

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HYPOGLYCAEMIA

UM Graham, JR Lindsay

Hypoglycaemia
Patient Management

Abstract

Diabetes mellitus is highly prevalent in hospitalised patients affecting around 15% of inpatients in England and Wales (1). Hypoglycaemia is a feared complication of diabetes and affected around a fifth of inpatients with diabetes surveyed during the recent National Inpatient Diabetes Audit (1). Hypoglycaemia episodes are likely to be encountered and managed by doctors in training, particularly during out-of-hours care when specialist support may be limited. Foundation doctors need to be aware of the management of hypoglycaemia in the acute setting and how to prevent further episodes. This case outlines the presentation and emergency management of hypoglycaemia in a patient with type 1 diabetes and discusses the salient points which should be included in their initial assessment and management.

Case description

A 32 year old man with type 1 diabetes was admitted through the emergency department following a hypoglycaemic event. This occurred at 2am when his wife noted him sweating profusely in bed and was unable to wake him. His capillary blood glucose (CBG) was 1.9mmol/l. He was treated with intramuscular glucagon administered by his wife and intravenous glucose administered by the paramedic crew. His CBG on arrival to the emergency department was 10.6mmol/l.

The patient had been well with no recent illness. His diet had not changed on the day of his admission and neither had his dose of insulin. He had attended the gym at 7pm for a high intensity cycling class during which he consumed a high glucose drink. He took his usual dose of insulin at bedtime and capillary glucose at that time was 13.3mmol/l. He did not take a bed-time snack.

The patient was diagnosed with type 1 diabetes at age 18 years and was taking insulin aspart (Novorapid®) 22 units with meals and detemir (Levemir®) 34 units at bedtime. He monitored CBGs at breakfast and before bed. He described occasional symptoms in keeping with hypoglycaemia during the day which he treated with eating a chocolate bar without checking his CBG. This occurred up to 4 times per week. He had no previous hypoglycaemic events during sleep.

He had no other medical problems and was not on any other regular medication. He worked as a manager in a department store. On examination the only significant findings were some areas of lipohypertrophy and bruising in his lower abdomen. Initial investigations, which included full blood picture, electrolyes and renal function were normal. Haemoglobin A1c (HbA1c) was 72mmol/mol (target 53mmol/mol).

The patient was advised to avoid the areas of lipohypertrophy on insulin administration. During his admission CBG was monitored regularly and control remained erratic. He had frequent hypoglycaemic events and insulin was adjusted accordingly. He was reviewed by a consultant diabetologist, diabetic specialist nurse and dietician and advised on the use of insulin during exercise. He was referred to attend an outpatient structured education course.

At outpatient review 6 months after this admission the patient was monitoring at least 4 times daily and was adjusting insulin according to the carbohydrate content of foods. He continued to exercise regularly and hypoglycaemic events were much less frequent. HbA1c in clinic was 58mmol/mol.

Discussion

In patients with diabetes mellitus, hypoglycaemia is regarded as a blood glucose concentration of less than 4.0mmol/l (2). Severe hypoglycaemia is commonly defined as an episode of hypoglycaemia requiring third party assistance (3). This patient presented with severe hypoglycaemia needing intramuscular and intravenous treatment due to impaired consciousness. This is a potentially life threatening presentation, if appropriate treatment is not administered.

Symptoms of hypoglycaemia

The level of blood glucose at which patients develop symptoms of hypoglycaemia varies between patients and relates to their overall level of glycaemic control. For example a patient with poorly controlled diabetes may develop symptoms at a blood glucose reading of 6.0mmol/l whilst one with tight control may be asymptomatic with readings between 3.0-4.0mmol/l. The symptoms of hypoglycaemia manifest initially as autonomic symptoms due to increased sympathetic nervous system activity. This is followed by neuroglycopenic symptoms from cerebral glucose deprivation. The Edinburgh Hypoglycemia Scale is a validated subjective self-rating questionnaire relating to the 11 most common symptoms of hypoglycaemia which are outlined in Table 14.

HYPOGLYCAEMIA

UM Graham, JR Lindsay

Autonomic	Neuroglycopenic	General malaise
Sweating	Confusion	Headache
Palpitations	Drowsiness	Nausea
Shaking	Odd behaviour	
Hunger	Speech difficulty	
	Incoordination	

Table 1: Symptoms of hypoglycaemia.

Acute management of hypoglycaemia

The Joint British Diabetes Societies recently published guidelines on the hospital management of hypoglycaemia in patients with diabetes (5). Management options vary depending on whether the patient is conscious and able to cooperate with treatment (Figure 1).

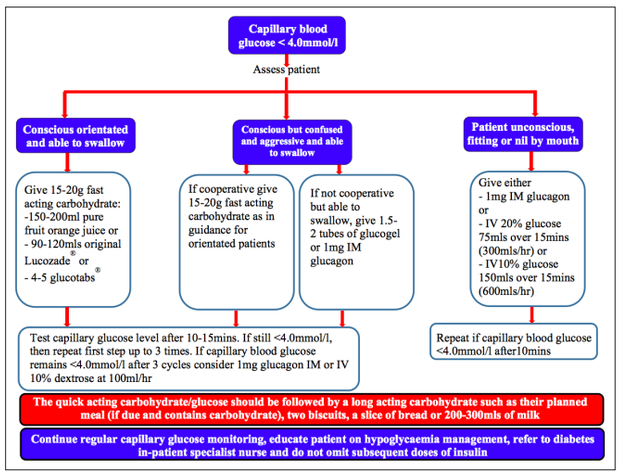


Figure 1: Management of hypoglycaemia

(Adapted from Joint British Diabetes Societies. The hospital management of hypoglycaemia in patients with diabetes mellitus (5))

Fruit juice and the quick acting carbohydrates are recommended in the initial management of hypoglycaemia in the conscious patient as they have a very high glycaemic index. Glycaemic index is a measure of how rapidly a carbohydrate is absorbed and raises plasma glucose concentration following consumption of food6. Our patient had inappropriately been using chocolate to treat hypoglycaemic events prior to admission. Chocolate has a relatively low glycaemic index as the fat content of chocolate delays gastric emptying, slowing down the digestion and absorption of the carbohydrate it contains. It is therefore not a recommended treatment for hypoglycaemia.

Glucagon can be given intramuscularly at a dose of 1mg as a parenteral treatment for patients who are unable to cooperate or safely swallow oral carbohydrate. This has the advantage of not requiring intravenous access and be given by a relative at home, as in this case. Glucagon works by mobilising glycogen from the liver which can take up to 15 minutes to take effect. However there are some situations in which glucagon will be less effective. This includes patients taking sulphonylurea therapy in whom severe hypoglycaemia tends to be prolonged and often requires an intravenous glucose infusion. In addition, malnourished patients, such as individuals with alcohol dependence, have depleted glycogen stores and therefore respond less well to glucagon.

As described in Figure 1, following treatment of hypoglycaemia, the patient should be given a long acting carbohydrate to prevent recurrent hypoglycaemia. However, if the patient is nil by mouth, then an infusion of 10% dextrose at 100ml/hr may be required as an alternative.

What was the cause of hypoglycaemia in this case?

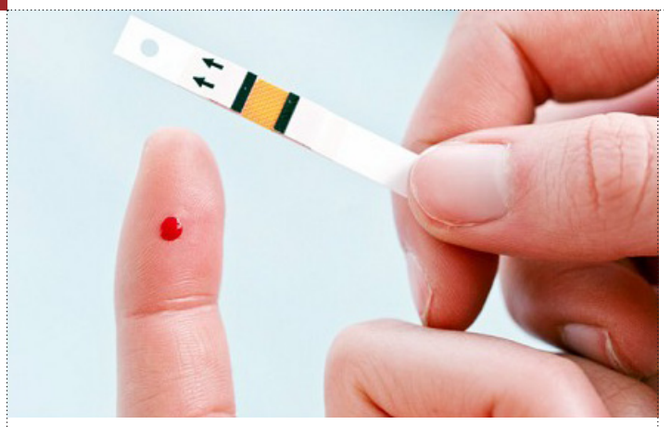
Hypoglycaemic events occur following an imbalance between insulin administered, glucose intake and utilisation. Hypoglycaemia is a relatively frequent occurrence in hospitalised patients with type 1 diabetes. In the 2012 National Inpatient Diabetes Audit, 45.3% of inpatients with type 1 diabetes had a hypoglycaemic event during their inpatient stay (1). A wide range of factors including variations in diet, insulin dosing and other physiological changes may contribute (Table 2). It is therefore important to carry out a detailed history when a patient presents with a severe hypoglycaemic event in attempt to determine the underlying cause.

Insulin related factors
Insulin dose too high
Injecting insulin after forgetting about a previous dose
Inappropriate use of "stat" doses of insulin
Variable absorption of insulin due to lipohypertrophy
Dietary factors:
Eating less than usual
Incorrect estimation of carbohydrate content of a meal
Eating later than usual
Changes in insulin requirments:
Illness or injury
More exercise than usual
Unplanned exercise
Changes in other hormones
Cortisol deficiency
Growth hormone deficiency
Hypothyroidism

Table 2: Factors contributing to hypoglycaemia in patients with type 1 diabetes.

HYPOGLYCAEMIA

UM Graham, JR Lindsay



In this case the most significant change in behaviour was the fact that the patient attended an intense exercise class the evening before his hypoglycaemic event. The class was several hours before the fall in blood glucose. Depending on the type and duration, exercise has a variety of effects on blood glucose. Following moderately intense aerobic exercise, blood glucose may increase initially, due to an increase in counter regulatory hormones including adrenaline.

However, following moderate exercise, blood glucose may fall during the hours of midnight to 6am leading to significant hypoglycaemia, as demonstrated in continuous glucose monitoring studies (7). During intensive exercise muscles are depleted of glycogen stores. For several hours after exercise, the muscles will take up glucose to replenish these stores resulting in a gradual fall in blood glucose. When there has been insufficient glucose intake or excessive insulin to account for this fall in blood glucose, hypoglycaemia will result. To avoid this happening in the future the patient was advised to reduce his dose of insulin before exercise and to take a snack before bedtime after an evening exercise session.

This patient had areas of lipohypertrophy on examination of his injection sites. This is a hard swelling of fatty tissue and is caused by repeated subcutaneous injection of insulin into the same site (8). It results in unpredictable and often delayed absorption of insulin which may lead to hypoglycaemia. To avoid this complication patients are advised to rotate injection sites, use 4 or 5mm sized insulin needles and change needles with each injection. It is therefore important to examine common injection sites such as the abdomen and legs in patients presenting with hypoglycaemia. Although patients are advised to avoid injecting into their arms, this area should also be inspected.

Other issues contributing to hypoglycaemia in this case relate to limited use of CBG monitoring and knowledge about insulin adjustment to facilitate effective self-management. It is therefore important to involve the multidisciplinary diabetes team in the care of these patients to assist in their ongoing education and follow up with ready access to structured education programmes.

Driving and hypoglycaemia

The Driver and Vehicle Licencing Agency (DVLA) set out strict guidelines for driving safety in patients with diabetes treated with insulin or tablets, which carry a risk of causing hypoglycaemia (sulphonylureas or glinides) (9). Hypoglycaemia whilst driving has major consequences for road safety and as a result the guidance is focussed on reducing the risk of such events. For our patient who is insulin treated and has a group 1 licence (car or motorcycle), licencing is dependent on the following conditions:

1. He must have awareness of hypoglycaemia.

2. He must not have had more than one episode of hypoglycaemia requiring the assistance of another person in the preceding twelve months (severe hypoglycaemia).

3. There must be appropriate blood glucose monitoring, which is defined as no more than 2 hours before the start of the first journey and every 2 hours while driving.

4. The patient must not be regarded as a likely source of danger to the public whilst driving.

5. The visual standards for acuity and visual field must be met.

Patients are advised not to drive if their CBG is less than 4.0 mmol/l and to take a snack if their blood glucose is less than 5.0mmol/l. If blood glucose levels are below 4.0mmol/L, the patient should treat their hypoglycaemic episode, then wait 45 minutes after the blood glucose has returned to normal before driving. For our patient who does not regularly monitor before driving it is very important to advise him of his obligation to do so to satisfy the conditions of his licensing. In addition it is important to advise him that a subsequent hypoglycaemic event requiring the assistance of a third party within the year will result in suspension of his licence.

Test yourself

1. A 57yr old male inpatient with a known history of chronic alcohol abuse and secondary diabetes due to chronic pancreatitis was found to be drowsy by the nursing staff and was barely responding to voice. Capillary blood glucose was checked and found to be 2.1mmol/l. What is the best treatment?

1. 20mls of 50% dextrose intravenously.
2. 2 tubes of glucogel squeezed into the patient's mouth.
3. 1mg of glucagon intramuscularly.
4. 150mls of 10% dextrose over 15 minutes.
5. 150mls of pure orange juice.

HYPOGLYCAEMIA

UM Graham, JR Lindsay

2. The Driver and Vehicle Licencing Agency states that before a patient with diabetes who is treated with insulin starts a car journey the following criterion must be satisfied:

1. The patient must not have had a hypoglycaemic event in the preceding 2 hours.
2. Capillary blood glucose must be > 4.0mmol/l within 30 minutes prior to starting the journey and a snack must be taken if < 5.0mmol/l.
3. Capillary blood glucose must be > 5.0mmol/l two hours before starting the journey.
4. Capillary blood glucose must be > 4.0mmol/l and a snack consumed immediately before starting the journey.
5. The patient has never had a hypoglycaemic event requiring the assistance of a third party.

Answers

1. 150mol of 10% glucose over 10 minutes.

In this scenario the patient is drowsy and unresponsive. Glucogel is only appropriate in the uncooperative patient who can swallow. In this case the patient is unlikely to be able to safely swallow thus ruling out oral treatments such as orange juice and glucogel. Previously 50% glucose was used regularly to treat hypoglycaemic events. However this preparation has been associated with extravasation injuries when given through a peripheral line and is also associated with significant hyperglycaemia following treatment of the hypoglycaemic event. Glucagon is an appropriate treatment for the hypoglycaemic unresponsive patient however has been found to be less effective in patients who are chronically malnourished such as alcoholics. This is because it works by mobilising glycogen from the liver and malnourished patients such as alcoholics have depleted glycogen stores. Therefore intravenous 10% glucose is the most appropriate treatment in this case.

2. Capillary blood glucose must be > 5.0mmol/l two hours before starting the journey.

For insulin treated patients driving a car the conditions (in relation to hypoglycaemia) which must be satisfied are:

1.An awareness of hypoglycaemia.

2. No more than one episode of hypoglycaemia requiring the assistance of another person in the preceding twelve months (severe hypoglycaemia).

3. Appropriate blood glucose monitoring, which is defined as no more than 2 hours before the start of the first journey and every 2 hours while driving. Patients are advised not to drive if their CBG is less than 4.0 mmol/l and to take a snack if their blood glucose is less than 5.0mmol/l. If blood glucose levels are below 4.0mmol/L, the patient should treat their hypoglycaemic episode, then wait 45 minutes after the blood glucose has returned to normal before driving.

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References

1. National Diabetes Inpatient Audit 2012. www.diabetes.org.uk/Documents/Reports/NaDIA-annual-report-2012-0613.
2. Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, Service FJ . Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2009; 94:709-728.
3. DCCT Research Group. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. Am J Med 199; 90: 450-459.
4. Deary IJ, Hepburn DA, MacLeod KM, Frier BM. Partitioning the symptoms of hypoglycaemia using multi-sample confirmatory factor analysis. Diabetologia 1993; 36 : 771 –777.
5. Joint British Diabetes Societies. The hospital management of hypoglycaemia in patients with diabetes mellitus. http://www.diabetes.org.uk/About_us/What-we-say/Improving-diabetes-healthcare/The-hospital-management-of-Hypoglycaemia-in-adults-with-Diabetes-Mellitus.
6. Foster-Powell K, Holt SHA, Brand-Miller JC. International table of glycemic index and glycemic load values. Am J Clin Nutr 2002; 76: 5-56.
7. Maran A, Pavan P, Bonsembiante B, Brugin E, Ermolao A, Avogaro A, Zaccaria M. Continuous Glucose Monitoring Reveals Delayed Nocturnal Hypoglycemia After Intermittent High-Intensity Exercise in Nontrained Patients with Type 1 Diabetes. Diabetes Technology & Therapeutics 2010; 12: 763-768.
8. Chowdhury TA, Escudier V. Poor glycaemic control caused by insulin induced lipohypertrophy. BMJ 2003; 327: 383.
9.Driver and Vehicle Licencing Agency. DVLA's current medical guidelines for professionals.https://www.gov.uk/current-medical-guidelines-dvla-guidance-for-professionals-conditions-d-to-f#diabetes---insulin-treated.

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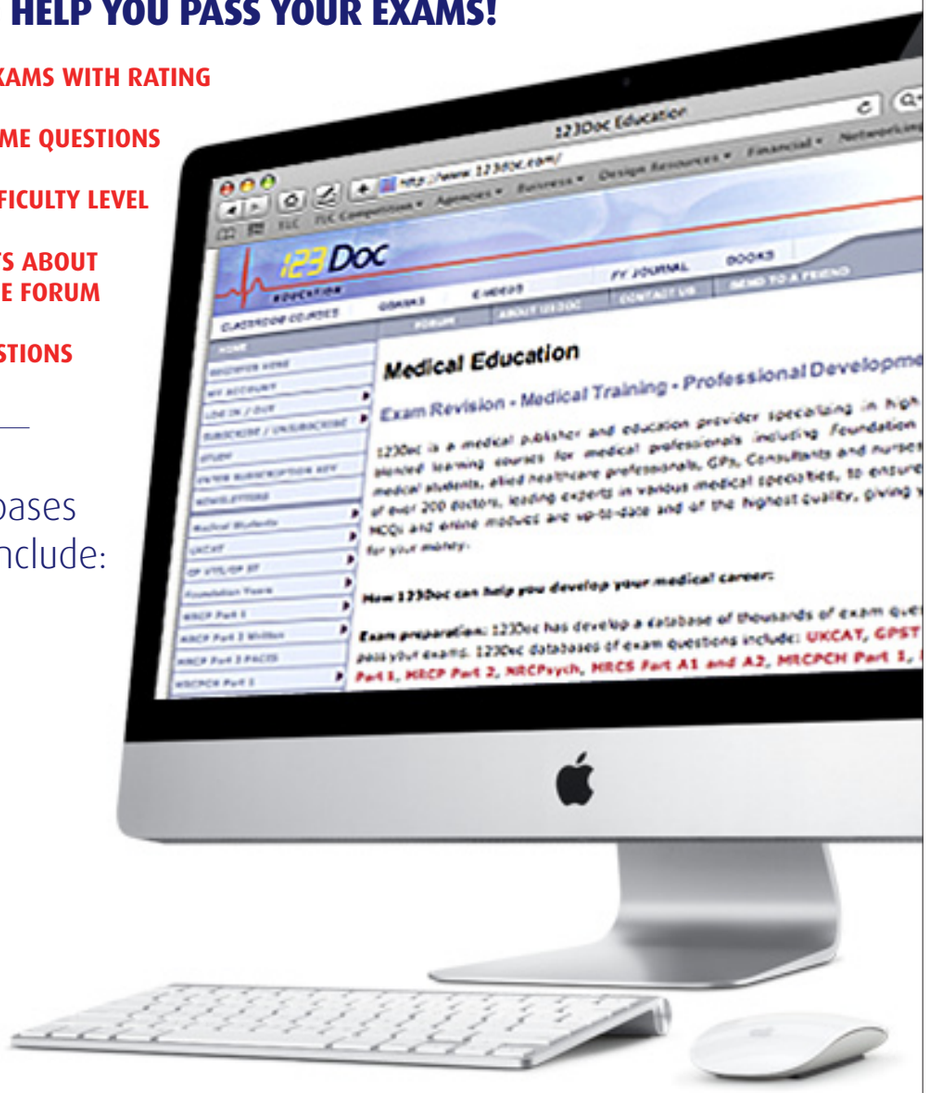

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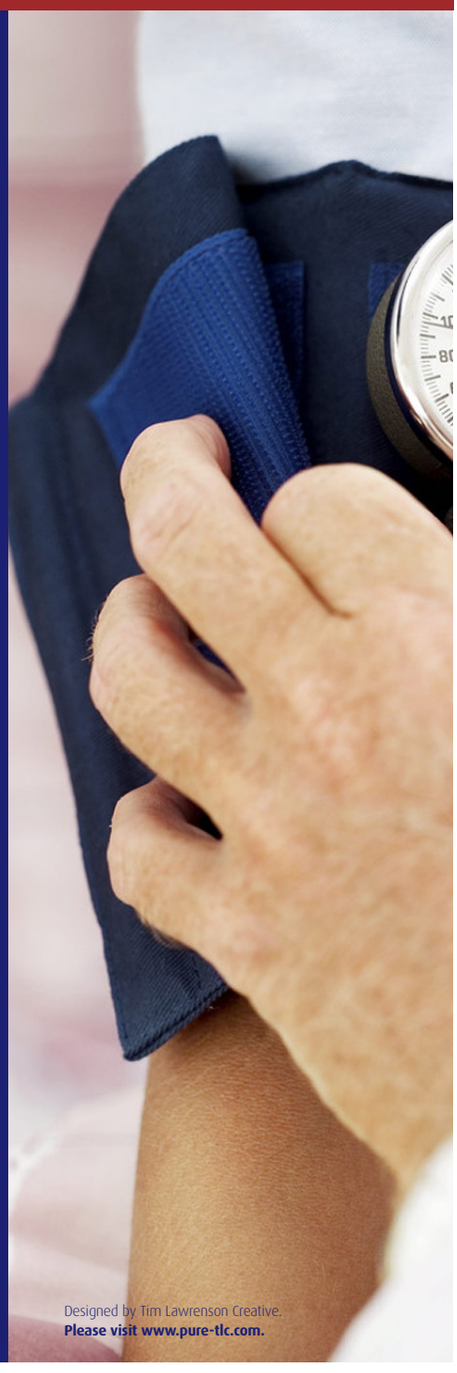

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