

Expanding boundaries of endocrinology

Alistair Lumb and John Wass

The multisystem nature of endocrinology means that endocrinologists are already involved in the care of patients with a broad range of differing conditions. Recent years have seen clinically important developments in traditional endocrine disciplines; they have also seen endocrinologists expanding their interests into fields such as osteoporosis, obesity, hypertension, and the late endocrine effects of cancer and cancer treatments.

Osteoporosis and calcium metabolism

Osteoporosis is an extremely important clinical problem and the prevalence of osteoporotic fractures in patients over the age of 65 is 1:3 females and 1:12 males. Fractures of the wrist, spine and hip are classical osteoporotic fractures and should warn patients and their medical attendants of possible osteoporosis. Once one fracture has occurred there is an increased risk of further fractures. This emphasises the importance of fracture liaison services currently being set up all over the country in which, after osteoporotic fracture, patients are investigated and treated with anti-osteoporosis drugs in order to try and prevent further fractures. Most osteoporosis, particularly in women, is primary and it is largely a genetic disease. Some 20% of women and 50% of men have secondary causes. Steroids, by suppressing osteoblast activity, increase the risk of osteoporotic fracture. A number of other drugs may also increase the risk of fracture, in particular aromatase inhibitors used in the treatment of carcinoma of the breast and gonadotrophin-releasing hormone analogues which suppress testosterone production and are used to treat carcinoma of the prostate.

Bisphosphonates are the main stay of treatment of osteoporosis but upper gastrointestinal side effects are moderately common. More recently intravenous zoledronate, the longest acting of the bisphosphonates, has been shown to decrease spinal fractures by 70% after three annual infusions of 5 mg.¹ Denosumab, a RANKL inhibitor administrable by six-monthly injections, similarly decreases fracture risk by 70% at the end of three years. This, however, is not yet available in the UK.

Compliance is a problem with the oral bisphosphonates and it is said that up to 40% of patients are not taking these drugs orally at the end of a year. The newer medications, administrable yearly or six-monthly, may overcome the compliance problems.

Alistair Lumb, specialist registrar in endocrinology, Churchill Hospital, Oxford; **John Wass**, professor of endocrinology, Oxford University

This conference took place at the Royal College of Physicians on 27 January 2009 and was organised by Professor John Wass

Side effects of zoledronate are important. A significant minority (around 17%) get an acute phase reaction after the first injection. Osteonecrosis of the jaw is a much reported effect when zoledronate is given for malignant disease but very rarely occurs in patients given this drug for osteoporosis. Future therapies of osteoporosis, apart from denosumab, include inhibitors of sclerostin and cathepsin K inhibitors.

Vitamin D deficiency

Vitamin D deficiency or insufficiency is extremely common and in a survey in Oxford 86% of patients presenting with fractured neck of femur had either insufficiency or deficiency of vitamin D. Vitamin D deficiency is related to bone mineral density (BMD) and further has an adverse effect on muscle strength.

High dose oral cholecalciferol (vitamin D₃) is the optimum way of replacing vitamin D² but there is currently a supply problem and an unlicensed drug has to be imported from Germany.

Hyperparathyroidism

Hyperparathyroidism is the most common cause of hypercalcaemia, accounting for around 90% of cases. It is therefore quite common, particularly in elderly females, and is often asymptomatic. It may, however, have an adverse effect on BMD, increase cardiovascular risk factors and cause hypertension. Parathyroidectomy is usually a straightforward operation and can now be done by minimally invasive techniques, usually when the adenoma has been localised preoperatively.

The question arises as to what to do in the asymptomatic patient. A study following 116 patients with hyperparathyroidism over 15 years demonstrated progression of disease in 37% of patients. Baseline characteristics were not helpful in predicting progression of disease. The current consensus is for operations to be recommended in patients with hypercalcaemia >2.85 mmol/l, hypercalciuria >10 mmol/24hrs, renal impairment, osteoporosis (t-score <2.5) and age less than 50 years.³ Whether patients with lesser biochemical abnormalities benefit from surgery is currently unclear.⁴ Larger studies are needed to assess this aspect and these should include an assessment of cardiovascular and bone changes as well as quality of life in patients dealt with either surgically or non-surgically.

Medical therapy with cinacalcet is an expensive treatment for patients in whom there is symptomatic hypercalcaemia and in whom surgery is unsuitable or the parathyroid adenoma cannot be found surgically.⁵

Obesity and polycystic ovary syndrome

It is widely recognised that obesity is an increasing problem in developed societies. There is an understanding that genotype is important in an individual's susceptibility to weight gain, with 40–70% of variability explicable by genetic factors. One striking example is congenital leptin deficiency in which treatment with leptin normalises previously very abnormal eating behaviour leading to significant weight loss, 90% of which is fat. Mutations of the MC4R gene receptor have been linked to obesity in a wider population. It is clear that there is a need for further developments in the field of obesity research as well as access to multidisciplinary care of obesity. At present, bariatric surgery seems to be effective at reducing weight in large numbers of patients.

Polycystic ovary syndrome occurs in around 1:10 of the female population of reproductive age. The Rotterdam criteria used to define it necessitate two out of three of polycystic ovarian morphology, oligo/amenorrhoea and hyperandrogenism. Insulin resistance is also a very common feature.⁶ It is clear that this is, at least in part, a genetically determined disease and a number of candidate genes have been assessed. The fat mass and obesity associated (FTO) gene has been shown to be one important genetic factor.

Endocrine hypertension

Phaeochromocytoma accounts for 0.1% of patients with hypertension but can, if undiagnosed, be fatal so a high index of suspicion is important. Primary hyperaldosteronism probably accounts for 10% of patients with hypertension, although different series report proportions varying from 2.3% to 23%. Its incidence has increased due to greater use of the aldosterone-renin ratio in diagnosis. More patients than previously are diagnosed with bilateral adrenal hyperplasia as opposed to a mineralocorticoid secreting adenoma.

Phaeochromocytoma was traditionally thought of as 'the 10% tumour', with 10% bilateral, 10% malignant, 10% extra-adrenal and 10% familial. This is no longer true as genetic causes are now found in up to 25% of cases. New genetic associations with phaeochromocytoma have been described, in particular the succinate dehydrogenase complex subunits C and D which are associated with familial head and neck paraganglioma. Other genetic causes which are well acknowledged are multiple endocrine neoplasia type 2, von Hippel-Lindau syndrome and neurofibromatosis. Patients with phaeochromocytoma should have genetic tests particularly if they present aged 50 or less.

Importantly, primary hyperaldosteronism is not always associated with hypokalaemia and 70% of patients with the condition are estimated to have a normal potassium level.⁸ The index of suspicion for diagnosis is increased by a family history of stroke, a young patient and refractory hypertension requiring triple therapy. The most important screening test is the aldosterone-renin ratio and it should be remembered that beta blockers increase this and that angiotensin-converting enzyme inhibitors and diuretics decrease it. In the presence of an increased aldosterone-renin ratio, confirmation of aldosterone

excess is most easily obtained by salt loading, usually intravenously. This, if positive, does not show suppression of aldosterone. In patients below the age of 40 with a radiologically detectable adenoma, operation can be recommended. Because of the increasing prevalence of adrenal incidentaloma in patients over the age of 40, adrenal venous sampling is required to lateralise hypersecretion prior to surgery in this age group. In patients with bilateral secretion of aldosterone the mineralocorticoid antagonist spironolactone may be used. This also acts at the progesterone and androgenic receptors and has a fairly high incidence of side effects. A more specific mineralocorticoid antagonist, epleronone, may be used, although high doses may be required.

Subclinical thyroid disease

Subclinical hypothyroidism, which occurs in around 4.3% of the population, is defined by normal levels of thyroid hormone in

Conference programme

Hypercalcaemia and hyperparathyroidism – is mild disease worth treating?

Dr Neil Gittoes, Queen Elizabeth Hospital, Birmingham

Osteoporosis – effective new treatments become available

Professor Juliet Compston, University of Cambridge School of Clinical Medicine

Vitamin D deficiency – diagnostic difficulties and safe treatment

Dr Kassim Javaid, University of Oxford

Prolactinomas – new developments

Professor John Wass, Oxford Centre for Diabetes, Endocrinology and Metabolism

Late endocrine effects of cancer treatment – under recognised and under resourced

Professor Richard Ross, Sheffield University

SIR MICHAEL PERRIN LECTURE

Graves' disease revisited

Professor Wilmar Wiersinga, University of Amsterdam

Sub-clinical thyroid disease – when should we intervene?

Professor Jayne Franklyn, University of Birmingham

Obesity, molecular insights and new treatments

Dr Sadaf Farooqi, University of Cambridge

Polycystic ovary syndrome – does the syndrome need redefining?

Dr Tom Barber, Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism

Endocrine hypertension – prevalence and diagnostic strategies

Professor Paul Stewart, University of Birmingham

association with an elevated thyroid-stimulating hormone (TSH). Subclinical hyperthyroidism occurs in around 3.2% and refers to a TSH below normal in the presence of normal thyroid hormone levels. Around 20% of patients on thyroxine have a suppressed TSH.

Subclinical hyperthyroidism is most commonly caused by a nodular goitre. An initially sub-normal TSH should be repeated as this is frequently a transient finding. Treatment of subclinical hyperthyroidism is recommended in patients with TSH persistently < 0.1 mIU/L, in spite of a paucity of intervention trials, because of potential adverse effects on cardiac function and bone density. Treatment should be considered particularly in patients already at risk from these problems, including all those over 60.

In patients with subclinical hypothyroidism, there are potential effects on cognitive function and wellbeing, lipid profile and adverse cardiovascular events. The consensus is that this condition should not routinely be treated if the TSH is less than 10 mU/l. If it is greater than 10 mU/l treatment should be considered. In patients wishing to become pregnant any TSH abnormality should be treated because of the adverse consequences of low maternal thyroxine levels in the initial stages of pregnancy on neurological development of the foetus.

Prolactinomas

Prolactinoma is the most common of the pituitary hypersecretory syndromes occurring in around 40:100,000 of the population. Microadenomas (less than 1 cm) are most common but macroadenomas also occur. It is important to differentiate true prolactinoma (which respond well to dopamine agonist therapy) from hyperprolactinaemia caused by a non-functioning pituitary tumour. The latter results from compression of the pituitary stalk interrupting dopaminergic suppression of prolactin secretion. One useful method of differentiation is that disconnection hyperprolactinaemia rarely, if ever, exceeds 2000 mU/L. Drugs are another important cause of hyperprolactinaemia. Most microadenomas respond to dopamine agonists but about 6% are resistant. Cabergoline is the treatment of choice over bromocriptine because of its increased efficacy and lower incidence of side effects. Safety concerns have recently been raised following evidence of cardiac valve fibrosis in patients with Parkinson's disease treated with much higher doses of cabergoline. This has not been observed in at least six out of seven studies published so far looking at patients treated with the lower doses of cabergoline used for endocrine disease. A higher proportion of patients with macro prolactinoma are resistant to treatment (8–10%). Cerebrospinal fluid rhinorrhea occurs in about 9% of patients successfully treated for macroprolactinoma. There is an association both with those patients who are male and those that are partially resistant to treatment.¹⁰

Cabergoline causes a decrease in cell size of the lactotroph adenoma cells and studies have suggested that treatment can be stopped in patients whose tumours have decreased in size

considerably at the end of five years. Hyperprolactinaemia recurs in a proportion of patients, and treatment needs to be restarted if this occurs. The menopause may also be a time when dopamine agonists can be stopped in patients with prolactinoma, presumably because of the loss of oestrogen stimulation of lactotrophs.

Endocrine effects of cancer and cancer treatment

One in 900 children is affected by cancer. Of these, 20–30% will have ovarian or testicular dysfunction. Late endocrine effects of childhood cancer include hypopituitarism, the development of thyroid nodules and even cancer, and fertility problems. There are also other problems associated with late effects of cancer treatment including cardiomyopathy after anthracyclines and skin cancer after radiotherapy.

In adults there are potential consequences of brain irradiation for brain tumours and postnasal space tumours as well as gonadal effects in patients having systemic chemotherapy. All of these need monitoring and replacement therapy. Quality of life can be adversely affected in patients with untreated gonadal failure or growth hormone deficiency.

Multidisciplinary teams are therefore necessary in this area to monitor and care for late endocrine and other effects of cancer treatment but to date, except in some parts of the UK, these have not been set up systematically.

Summary

There have been huge advances in endocrine care as a consequence of improved biochemistry and diagnostic techniques as well as improved imaging. Specialist transethmoidal endoscopic surgery has improved results in pituitary tumour patients and minimally invasive parathyroid surgery has had the same consequence in patients with parathyroid disease. Multidisciplinary teams have improved outcomes in a number of areas and, as described above, endocrinologists are dealing with more in the way of endocrine disease to expand boundaries. Much work remains to be done particularly concerning the care of children and adults with late endocrine effects of cancer treatment and obesity.¹¹

References

- 1 Black DM, Delmas PD, Eastell R *et al*. HORIZON Pivotal Fracture Trial. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356:1809–22.
- 2 Romagnoli E, Mascia ML, Cipriani C *et al*. Short and long-term variations in serum calcitropic hormones after a single very large dose of ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3) in the elderly. *J Clin Endocrinol Metab* 2008;93:3015–20.
- 3 Bilezikian JP, Potts JT Jr, Fuleihan Gel-H *et al*. Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. *J Bone Miner Res* 2002;17(Suppl 2):N2–11.
- 4 Mihai R, Wass JAH, Sadler GP. Asymptomatic hyperparathyroidism: need for multicentre studies. *Clin Endocrinol (Oxf)* 2008;68:155–64.
- 5 Peacock M, Bilezikian JP, Klassen PS *et al*. Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2005;90:135–41.

- 6 Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. *Hum Reprod* 2004;19:41–7.
- 7 Barber TM, Bennett AJ, Groves CJ *et al.* Association of variants in the fat mass and obesity associated (FTO) gene with polycystic ovary syndrome. *Diabetologia* 2008;51:1153–8.
- 8 Funder JW, Carey RM, Fardella C *et al.* Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2008;93:3266–81.
- 9 Surks MI, Ortiz E, Daniels GH *et al.* Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 2004;291:228–38.
- 10 Suliman SG, Gurlek A, Byrne JV *et al.* Nonsurgical cerebrospinal fluid rhinorrhea in invasive macroprolactinoma: incidence, radiological, and clinicopathological features. *J Clin Endocrinol Metab* 2007;92:3829–35.
- 11 Monson J. Advances in endocrinology. *Clin Med* 2009;9:358–65.

**Address for correspondence: Dr A Lumb, Department of Medicine, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU.
Email: alilumb@hotmail.com**

WORKING PARTY REPORTS

Oral feeding difficulties and dilemmas

A guide to practical care, particularly towards the end of life

Endorsed by the Association of British Neurologists, the British Association for Parenteral and Enteral Nutrition, the British Dietetic Association, the British Geriatrics Society, the Royal College of Nursing, and the Royal College of Speech and Language Therapists

Feeding is basic to life but it can also be an artificial medical procedure in the power of health professionals. Sometimes it causes dilemmas and strong differences of opinion between patients, relatives and professionals. This report is the result.

It acknowledges the confusion and uncertainty that sometimes surround decision-making and practice, including the difficulties of carrying out some of the technical interventions involved.

The report provides evidence-based guidance on the mechanisms and techniques of oral and artificial nutrition in health and disease. It sets out the ethical and legal concerns that provide the framework for decision-making. Case studies then illustrate dilemmas and solutions, for example on deciding whether to withhold or provide artificial nutrition.

This report is essential reading for all those involved in caring for people who have nutritional and oral feeding difficulties, including gastroenterologists, ward nurses, geriatricians, dietitians, speech therapists, neurologists, care home and community nurses, as well as carers, families and the patients themselves.

For a detailed contents list please visit
<http://bookshop.rcplondon.ac.uk/details.aspx?e=295>

Published January 2010 ISBN 978-1-86016-371-5
Price: £20.00 UK, £22.00 overseas (prices include postage and packing)
10% discount on all RCP publications to fellows and members
► Please quote the reference Clinical Medicine when making your order



**Royal College
of Physicians**
Setting higher medical standards