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Diabetes & endocrinology: something for everyone

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ABSTRACT This symposium addressed new developments and controversies in diabetes and endocrinology. The practical management of hyperparathyroidism, thyroid nodules, hyperprolactinaemia and diabetes and thyroid disorders in pregnancy were all discussed. In addition to these traditional areas of endocrinology, there was a focus on the role of endocrinology in 'non-endocrine' specialties, namely critical care and cardiovascular disease. We learned that manipulation of the thyroid axis or local glucocorticoids can potentially be used to treat high cholesterol, atrial fibrillation or coronary stent stenosis, and that glucose lowering with insulin reduces mortality in the critically ill.

KEYWORDS Critical illness, gestational diabetes, glucocorticoids, hyperparathyroidism, hyperprolactinaemia, pregnancy, thyroid hormone receptors, thyroid nodules

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EDUCATION

HORMONES AND THE HEART

The opening two lectures of this symposium highlighted how two common hormones, thyroxine and glucocorticoids, can have both beneficial and detrimental effects. Recent insights into the role of these hormones at the molecular level offer the exciting potential for new therapies that selectively target these differential effects.

Professor Brian Walker, University of Edinburgh, outlined epidemiological studies showing that glucocorticoids are associated with increased risk of cardiovascular disease.[1,2] Importantly for clinical practice, this effect is seen at as little as 30 mg of hydrocortisone per day,[3] supporting the rationale to limit hydrocortisone replacement in patients with adrenal insufficiency to 20 mg daily. In addition to the known adverse metabolic effects of glucocorticoids, they have potential antiproliferative, anti-inflammatory and antimigratory benefits. Is it possible to target these beneficial effects selectively? This might be achieved using localised glucocorticoid administration, e.g. glucocorticoid-eluting stents to reduce restenosis;[4] or by selective inhibition of 11-beta-hydroxysteroid dehydrogenase 1 (11-β-HSD1), which is responsible for cortisol production from cortisone, in key tissues.[5]

Professor Graham Williams, Imperial College London, described how thyroid hormones exert their effects by targeting two separate nuclear receptors – thyroid hormone receptors (TR)-α and -β. The beneficial effects (primarily on basal metabolic rate and lipid metabolism in the liver) as well as the feedback regulation at the pituitary are mediated by TR-β, whereas the deleterious effects (e.g. on bone, causing osteoporosis, and on the heart, increasing the risk of dysrhythmia) are mediated by TR-α.[6] In the past year a number of TR-β agonists have been developed that have beneficial lipid effects and are entering clinical trials.[7]

Dr John Petrie, University of Dundee, discussed the role of glycaemic control on macrovascular outcomes in Type 2 diabetes. A recent paper reporting the ten-year post-trial monitoring from the UK Prospective Diabetes Study (UKPDS)[8] shows that the intensive treatment arm had a 15% risk reduction for macrovascular disease. Intriguingly, this effect is seen despite both treatment arms having similar HbA1c in the post-trial period, suggesting a metabolic memory whereby early intensive treatment has long-term benefit. Is there a differential effect of different oral treatments on cardiovascular outcome? Clearly there has been controversy over the thiazolidinediones, particularly rosiglitazone, and despite no new evidence a recent American Diabetes Association/European Association for the Study of Diabetes consensus group stated that rosiglitazone should not be used.[9] Metformin seems to have a greater effect on macrovascular risk reduction than sulphonylureas,[8,10] although this direct comparison has not yet been made in the UKPDS. However, given the fact that the 'number needed to treat' to prevent one cardiovascular event is two- to four-fold higher for glucose lowering than blood pressure or cholesterol lowering,[11] perhaps the primary focus should be on addressing these concerns rather than worrying about what agent should be used to lower glucose.

ENDOCRINOLOGY AND THE SURGEON

In the second session, Mr Barney Harrison, Royal Hallamshire Hospital, urged us to consider a surgical cure for patients with mild hypercalcaemia as, at least in his hands, the procedure carries very low morbidity. Hyperparathyroidism, however, is associated with long-term morbidity, some of which (e.g. hypertension) is not reversible after parathyroidectomy. Pre-operative localisation is not essential, and an inability to localise should not deter surgery. However, where there is concordance between competent ultrasound and a

99mTc-methoxy isobutyl isonitrile (MIBI) scan, a minimally invasive approach (2-cm incision rather than laparoscopic) and single gland removal could be advocated.

SYDNEY WATSON SMITH LECTURE

The Sydney Watson Smith Lecture addressed the endocrinology of the critically ill. Professor Greet Van den Berghe, Director of Intensive Care Sciences, University of Gasthuisberg, Belgium, explained how the critically ill lose lean mass but maintain adipose tissue. She described how in the acute phase of illness there is pituitary hypersecretion and end organ resistance, yet in prolonged critical illness the hypothalamic and pituitary drive is suppressed, leading to low concentrations of growth hormone, testosterone, thyroid hormones and adrenocorticotrophic hormone. By infusing thyrotropin-releasing hormone, gonadotrophin-releasing hormone and growth hormone-related peptide-2, it is possible to restore secretion and, intriguingly, induce an anabolic response[12] and potentially restore lean mass. We heard how critically ill patients are hyperglycaemic, and how normalising blood glucose in the intensive care unit reduces mortality.[13] In discussion it was felt that the failure to replicate these findings in a recent study[14] might be explained by differences in practice between intensive care units, such as the use of parenteral feeding or the skill of the nurses managing the insulin infusion.

PREGNANCY ASPECTS OF ENDOCRINOLOGY

Session 3 focused on the endocrinology of pregnancy. Dr Robbie Lyndsey, University of Glasgow, outlined the results of the Hyperglycaemia and Pregnancy Outcomes (HAPO) study, showing a continuous relationship between the incidence of macrosomia (babies born heavier than the 90th centile adjusted for gestational age) and maternal glucose, with no threshold effect.[15] So where should we draw the line that defines gestational diabetes? The Scottish Intercollegiate Guidelines (two-hour glucose post oral glucose tolerance test >9 mmol/L) would label approximately 4% of pregnant women as having gestational diabetes, whereas the World Health Organization cut-off of >7.8 mmol/L would define ≥10% of pregnant women as having this condition, potentially overloading our clinical services. Should we treat these women with gestational diabetes with insulin or oral hypoglycaemic agents? A recent study, which is changing clinical practice, shows no difference in outcome in those women with gestational diabetes treated with metformin compared with those treated with insulin, although 40% of the metformin arm had to be converted to insulin.[16]

Dr Anthony Toft, Royal Infirmary of Edinburgh, told us that in a study of 17,000 women, 2.3% had a thyroid-stimulating hormone of >6.0 mmol/L (98th centile) at 17 weeks of pregnancy,[17] and this was associated with increased fetal deaths. Despite this, the introduction of a generalised screening approach has not been felt to be cost-effective. Instead, a targeted approach to those with pre-existing autoimmune disease, current or previous thyroid disease or a family history of thyroid disease is advocated. While maternal hypothyroidism is associated with impairment of offspring IQ, the rationale to increase the thyroxine dose for women treated with thyroxine on the diagnosis of pregnancy by 25 μg and to measure thyroid function two weeks later was questioned. An alternative approach, suggested by Professor Tony Weetman in discussion, was to check the thyroid function when pregnancy was diagnosed and to adjust the thyroxine dose accordingly.

SOMETHING FOR EVERYONE

The final session covered some key practical aspects of diabetes and endocrinology. Dr John Bevan, University of Aberdeen, reported the data by Colao et al.[18] on the treatment of macroprolactinomas – prolactin-secreting pituitary adenomas that exceed 1 cm in size. The report states that as long as there was no visible tumour (or at least a 50% reduction in size) and the cabergoline dose was 0.5 mg/week or less, then 40% of patients with macroprolactinomas remain in remission on cessation of drug treatment, supporting periodic trials of treatment withdrawal. This may be potentially useful, as Dr Bevan then updated us on the recent Medicines and Healthcare products Regulatory Agency (MHRA) advice that patients to be treated with cabergoline or bromocriptine should have a baseline echocardiogram and surveillance echocardiogram every six to 12 months, because of the small risk of valvular fibrosis or regurgitation. Quinagolide, a non-ergot derivative, does not have the same risk so it is being increasingly used as a first-line treatment. We received further practical advice from Professor Tony Weetman, University of Sheffield, regarding thyroid nodules. He advised that fine needle aspiration (FNA) should be carried out on all new nodules and, if benign (cytology: thy2), a repeat at six months is sufficient to exclude malignancy.[19] Other key points were that nodules that do not increase in size can still be malignant, and the presence or absence of multiple nodules should not alter our threshold for FNA.

Finally, Professor Brian Frier, University of Edinburgh, reminded us of the driving regulations for people with diabetes; in particular, the need to advise all insulin-treated patients to test their blood sugar every time they drive – in a recent study 48% did not do so and only half of patients with Type 1 diabetes had discussed driving with their healthcare team.[20]

CONCLUSION

The day was indeed 'something for everyone', ranging from the translation of molecular biology into new therapies to the practical management of common endocrine- and diabetes-related problems that we see in

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everyday clinical practice. As practising endocrinologists, we also learned how manipulation of endocrine systems will play an increasing role in the management of the general medical patient.

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REFERENCES

1 Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. *Ann Intern Med* 2004; 141:764–70.
2 Souverein PC, Berard A, Van Staa TP et al. Use of oral glucocorticoids and risk of cardiovascular and cerebrovascular disease in a population based case-control study. *Heart* 2004; 90:859–65.
3 Filipsson H, Monson JP, Koltowska-Haggstrom M et al. The impact of glucocorticoid replacement regimens on metabolic outcome and comorbidity in hypopituitary patients. *J Clin Endocrinol Metab* 2006; 91:3954–61.
4 Liu X, De Scheerder I, Desmet W. Dexamethasone-eluting stent: an anti-inflammatory approach to inhibit coronary restenosis. *Expert Rev Cardiovasc Ther* 2004; 2:653–60.
5 Small GR, Hadoke PW, Sharif I et al. Preventing local regeneration of glucocorticoids by 11β-hydroxysteroid dehydrogenase type 1 enhances angiogenesis. *Proc Natl Acad Sci USA* 2005; 102:12165–70.
6 Brenta G, Danzi S, Klein I. Potential therapeutic applications of thyroid hormone analogs. *Nat Clin Pract Endocrinol Metab* 2007; 3:632–40.
7 Scanlan TS. Sobetirome: a case history of bench-to-clinic drug discovery and development. *Heart Fail Rev* 2009; in press. Epub ahead of print.
8 Holman RR, Paul SK, Bethel MA et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; 359:1577–89.
9 Nathan DM, Buse JB, Davidson MB et al. Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 2009; 52:17–30.
10 Evans JM, Ogston SA, Emslie-Smith A et al. Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin. *Diabetologia* 2006; 49:930–6.
11 Huang ES, Meigs JB, Singer DE. The effect of interventions to prevent cardiovascular disease in patients with type 2 diabetes mellitus. *Am J Med* 2001; 111:633–42.
12 Van den Berghe G, Baxter RC, Weekers F et al. The combined administration of GH-releasing peptide-2 (GHRP-2), TRH and GnRH to men with prolonged critical illness evokes superior endocrine and metabolic effects compared to treatment with GHRP-2 alone. *Clin Endocrinol (Oxf)* 2002; 56:655–69.
13 Van den Berghe G, Wouters P, Weekers F et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001; 345:1359–67.
14 Brunkhorst FM, Engel C, Bloos F et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; 358:125–39.
15 Metzger BE, Lowe LP, Dyer AR et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008; 358:1991–2002.
16 Rowan JA, Hague WM, Gao W et al. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med* 2008; 358:2003–15.
17 Allan WC, Haddow JE, Palomaki GE et al. Maternal thyroid deficiency and pregnancy complications: implications for population screening. *J Med Screen* 2000; 7:127–30.
18 Colao A, Di Sarno A, Cappabianca P et al. Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. *N Engl J Med* 2003; 349:2023–33.
19 Oertel YC, Miyahara-Felipe L, Mendoza MG, Yu K. Value of repeated fine needle aspirations of the thyroid: an analysis of over ten thousand FNAs. *Thyroid* 2007; 17:1061–6.
20 Graveling AJ, Warren RE, Frier BM. Hypoglycaemia and driving in people with insulin-treated diabetes: adherence to recommendations for avoidance. *Diabet Med* 2004; 21:1014–9.

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