

# Diabetes and Endocrinology Symposium: Clinical challenges and expert advice

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O Pereira

Specialist Registrar in Diabetes and Endocrinology, Aberdeen Royal Infirmary

Correspondence to O Pereira,  
Department of Diabetes and  
Endocrinology, Aberdeen Royal  
Infirmary, Foresterhill,  
Aberdeen AB25 2ZN, UK

tel. +44 (0)845 4566000 bleep 3883  
e-mail olivia.pereira@nhs.net

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## INTRODUCTION

This symposium focused on common challenges faced in diabetes and endocrinology. Topics included subclinical hyperthyroidism, delayed puberty, adrenal incidentaloma, hirsutism, autonomic neuropathy and diabetic foot. It included perspectives from an editor about the most recent publications in peer-reviewed diabetes journals which have changed clinical practice. The Sydney Watson Smith Lecture, delivered by Professor Peter Butler, (University of California, Los Angeles) described the advances and limitations in the field of islet cell and stem cell transplantation. The symposium also covered the importance of psycho-educational interventions to induce behaviour change in order to improve diabetes self-management.

## SESSION 1

**Subclinical hyperthyroidism** This affects 1–3% of the population and is associated with a three-fold risk of atrial fibrillation over ten years. Several observational studies have shown that it is associated with an increased mortality. Whether subclinical hyperthyroidism warrants treatment on prognostic grounds alone remains unknown. Treatment would be recommended in the presence of atrial fibrillation. A proportion of people have low thyroid-stimulating hormone as part of the normal ageing process rather than endogenous thyroid disease. Professor Simon Pearce, of Newcastle University, mentioned that these patients therefore warrant a period of observation and enquiry to look into other causes.<sup>1</sup>

**Short stature/delayed puberty** Late puberty accompanied by short stature is a common reason for referral to an endocrinologist. Constitutional delay of puberty is common in boys. Pathological causes include chronic systemic illness, a range of endocrine disorders and Turner's syndrome in girls. The emotional and psychological consequences of pubertal delay need to be addressed. Treatment with androgen/oestrogen is given with the intention to reproduce a physiological growth pattern and induce and maintain changes in secondary sexual development at a physiological age and tempo.

**Adrenal incidentaloma** The incidence of adrenal adenomas increases with age and is rare in subjects <40 years. These are mostly benign and non-functioning. Biochemical

tests are helpful to determine functionality, and the term 'subclinical Cushing's' should be avoided. There is a 40% chance of malignancy in tumours >6 cm in size. Adrenalectomy is recommended for adrenal adenomas >4 cm. Younger patients with smaller tumours might prefer the surgical option. The development of functionality and malignancy during follow-up is rare. Patients are generally followed up for four years, although more data are needed as computed tomography scanning exposes patients to the risk of radiation. Novel adrenal biomarkers need evaluation.

## SESSION 2

**Clinical hot topics from the diabetes journals – perspectives from an editor** Professor Richard Donnelly (University of Nottingham) discussed this under three headings:

1. Glycaemic control and vascular complications in type 2 diabetes – the risk–benefit balance: The post UKPDS (United Kingdom Prospective Diabetes Study) data analysis showed that intensively treated patients accrued statistically significant benefit in all-cause mortality ten years later, compared with the conventional group termed the 'Legacy Effect'. A troubling finding from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial was that, compared with standard therapy, intensive therapy (achieved using thiazolidinediones, sulfonylureas, metformin and insulin) was associated with a significantly increased risk of death from any cause.<sup>2</sup> The ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial showed that intensive control reduced the incidence of major macrovascular and microvascular events primarily because of a reduction in the incidence of nephropathy.<sup>3</sup> Lowering of blood pressure resulted in a reduction in the risks of major vascular events and death.
2. New technologies and treatment options: The mechanism of and role for glucagon-like peptide (GLP)-1 agonists and dipeptidyl peptidase-4 inhibitors was discussed. These increase the scope for combination treatment with the added benefit of weight reduction. Dual  $\alpha/\gamma$ -peroxisome-proliferator activated receptor (PPAR) agonists, which combine the profile of a glitazone and fibrate, are under development. Bariatric surgery in

obese type 2 diabetes mellitus is also becoming increasingly popular. Despite the fact that these new treatments provide more options and flexibility, there is a need for long-term trials and safety data.

3. The current concern about insulin therapies and cancer risk: Based on existing data there is no solid evidence, but there was a concern raised about insulin glargine and breast cancer risk, which requires investigation.

**Sydney Watson Smith Lecture** Professor Peter Butler provided insight into novel approaches to restore beta cells in patients with diabetes. Pancreatic transplantation is limited by the shortage of organ donors, operative morbidity and the need for immunosuppression. Islet cell transplantation requires three donors; insulin independence if achieved, is short-lived as it undergoes attrition. It is also associated with significant morbidity. There has been progress in the field of human embryonic stem cell transplantation, but this approach has important limitations.<sup>4</sup> In order to provide a cure, the embryonic stem cells need to maintain their ability to proliferate. A major challenge is to control the proliferative activity of the cells. Loss of cell cycle control can result in neoplastic cell growth. Another challenge is to protect the resulting beta cells from rejection, thereby avoiding the need for immunosuppression. B cell mass remains relatively constant through different ages by the formation of new B cells from endogenous pancreatic progenitors.<sup>5</sup> In type 1 diabetes, B cells show increased apoptosis and evidence of autoimmune damage. One approach to restore beta cell mass would be to promote this B cell regeneration and suppress accelerated beta cell apoptosis.

### SESSION 3

**Hirsutism** Management of hirsutism was presented from an endocrinologist's as well as a dermatologist's point of view. Hirsutism is a very common and distressing symptom. Mild and long-standing hirsutism requires little if any investigation. Measurement of total testosterone is the most important screening test. In patients with a short history or if testosterone levels are >5 nmol/L, more extensive investigation of adrenal and ovarian function is required. The mainstay of treatment is the use of anti-androgens in combination with dietary management (in obese subjects) and efficient cosmetic measures. Non-

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systemic approaches include simple hair removal, electroepilation, laser hair removal and topical eflornithine, although not all are readily available on the NHS.

### SESSION 4

**How do experts manage childhood/adolescent diabetes?**

Clinicians often report poor levels of training in communication skills to discuss behaviour change. There is good evidence that motivational interviewing can help improve quality of life and glycosylated haemoglobin.<sup>6</sup> The talking diabetes training programme has been developed at Cardiff University and is now being evaluated in a multi-centre randomised trial in 26 centres. Results are expected in late 2009.

**Diabetic autonomic neuropathy** This unfortunately goes unrecognised until well advanced, and five-year survival is 50% on diagnosis. Therefore, simple assessment tools to detect subclinical diabetic autonomic neuropathy are needed. Novel techniques such as dynamic pupillometry<sup>7</sup> and spectral analysis of heart rate variability can be useful tools. Intensive multifactorial intervention can improve outcome.

**Diabetic foot** Foot screening identifies patients at high risk of developing foot ulceration. A narrow spectrum high-dose antibiotic for two weeks is recommended, depending on the severity of the ulcer.<sup>8</sup> Flucloxacillin is the first choice for diabetic foot infections. Negative pressure wound therapy is useful for moist ulcers. Offloading remains the cornerstone of the management of neuropathic foot ulceration and Charcot's foot, while vascular intervention should be considered for any vascular problems. There is limited evidence that bisphosphonates have any benefit for Charcot's foot, although there may be some relief in symptoms.

### CONCLUSION

The symposium provided an interactive and informative overview of common challenges faced in clinical practice that are still uncertain. It also drew our attention to the need for improving our communication skills to improve self-management. The key themes focused on the application of medical evidence to improve clinical practice and provided insight into the limitations of transplantation for the cure of type 1 diabetes.

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