ENDOCRINOLOGY AND DIABETES – DELIVERING CARE IN THE TWENTY-FIRST CENTURY

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INTRODUCTION

This symposium addressed some of the major challenges to developing appropriate, high quality care for patients with endocrine disease. Common themes running throughout the symposium were the need for a good evidence base for treatment, continuous audit and the need for adequate resources. For common diseases (such as thyroid disease and diabetes) the main challenges will be the ability to manage large numbers of patients and to be able to respond to changes in management policies as new evidence appears. Rarer conditions provide no less challenge: there is a clear need for centres specialising in pituitary disease, and for expensive treatments (such as human growth hormone treatment and assisted fertility) there are challenges in assessing the cost effectiveness of treatment and ensuring equity of care.

SESSION 1

Delivery of care for common endocrine syndromes: thyroid disease

Chairman: A.D. Toft, NHS consultant, Endocrine Clinic, Royal Infirmary, Edinburgh

Thyrotoxicosis is one of the commonest endocrine conditions with a prevalence of 2·7% in women in the UK.[1] Treatment options have changed little in 50 years, and continue to rely on anti-thyroid drugs, radioiodine treatment and surgery. However, significant geographical variation exists in the preference for various treatments: radioiodine is used more commonly in the US than in the UK, and the UK avoids surgery more than the rest of Europe. Part of this variation underlines the fact that no particular treatment is ideal and that none guarantees restoration of euthyroidism: anti-thyroid drugs carry the risk of agranulocytosis and rashes; radioiodine treatment is contraindicated in young women who may be pregnant or may have young children at home, and in patients with Graves' ophthalmopathy which may rapidly deteriorate following radioiodine.

Professor Jayne Franklyn presented evidence that a further risk of thyrotoxicosis is increased mortality following radioiodine treatment.[2] In a cohort of 7,209 subjects treated with radioiodine for thyrotoxicosis between 1950 and 1990; significantly increased standardised mortality was found as shown in Table 1.

TABLE 1

Cause of death	SMR	p
All cause mortality	1·13	<0·001
Circulatory disease	1·2	<0·001
Cardiovascular disease	1·2	<0·001
Cerebrovascular disease	1·4	<0·001

Furthermore, all categories of cardiovascular diseases (rheumatic, hypertensive, ischaemic, etc.) were significantly increased. The excess mortality affected all age groups and was greatest immediately after treatment had ended, with the majority of the effect evident within one year. Evidence of a dose effect was shown with larger doses of radioiodine having a greater effect on mortality, suggesting that either radioiodine itself, or that more severe thyrotoxicosis (which requires larger cumulative doses) increases cardiovascular risk. This implies that more aggressive management of hypertension or atrial fibrillation (AF) may be justified in these patients, although further prospective trials would be required to demonstrate this.

Subclinical hyperthyroidism (TSH suppressed below the lower end of the reference range with a normal fT4 and T3) is common and the optimum treatment remains controversial. In a study of 1,210 subjects over 60 years of age 6·3% of men and 5·5% of women had TSH levels below 0·5.[3] On follow-up this was persistent in 87·5% for TSH <0·05 and in only 24% for TSH between 0·05 and 0·5. In a separate study with 2,007 subjects over 60 years of age 12% had subclinical hyperthyroidism.[4] In over ten years of follow-up there was a cumulative incidence of AF of 28% in subjects with subclinical hyperthyroidism and 11% in those without.

A further study of 1,191 subjects over 60 years of age with follow-up of ten years showed that subclinical hyperthyroidism resulted in higher mortality rates, most deaths being caused by circulatory disease.[5] Furthermore, survival was graded by TSH: those with the lowest TSH having a ten year survival rate of approximately 55% while those with normal TSH had a 65% survival rate. Intriguingly, those subjects with subclinical hypothyroidism (an elevated TSH less than ten, with normal fT4 and T3) had higher survival than normal euthyroid subjects.

Whether these effects can be extrapolated to patients taking thyroxine replacement treatment requires clarification. Around 0·8% of the population take

thyroxine, and for those over 60 (the population with greatest cardiovascular risk) the proportion is 3·6%. Of these patients, around 20% will have TSH <0·5 and therefore may be at increased cardiovascular risk. Further studies are currently underway to examine this.

Thyrotoxicosis is well known to reduce bone mineral density and increase fracture risk.[6] Professor Franklyn presented data showing that fracture mortality was doubled in patients with treated thyrotoxicosis even 20 years following radioiodine.[2] For patients taking thyroxine replacement resulting in a suppressed TSH, bone mineral density is reduced. This may increase fracture risk and provides a further reason to avoid subclinical hyperthyroidism in these patients.

KEYPOINTS

- Cardiovascular mortality is increased following radioiodine treatment for thyrotoxicosis
- Cardiovascular mortality is increased in subclinical thyrotoxicosis
- It remains unknown whether this applies to those with suppressed TSH production while on thyroxine replacement

Given the potentially increased morbidity and mortality of over- or under-replacement with thyroxine, a key task is to identify those that are on thyroxine replacement and ensure regular monitoring of thyroid function takes place. Professor Roland Jung presented data on local experience of a computer database and recall system similar to a number of automated thyroid registers operated throughout Scotland. Of a catchment population of 380,000 in Tayside, 9,544 (2·5%) are enrolled with this database and 97·5% are successfully followed up at least annually. Patients are referred by endocrinology consultants or by general practitioners (GPs), patient details stored on a database and a recall letter sent both to the GP and patient to arrange for TFTs to be checked; the results are then extracted from the local biochemistry computer system. The database has grown rapidly particularly in the last four years as GPs are required to have mechanisms to audit the management of hypothyroidism: many find this is most simply and inexpensively done by referring patients to the thyroid register. As a result, the balance of patients has changed (currently approximately 2,000 with post-ablative hypothyroidism and 6,000 with primary hypothyroidism) and the number requiring follow-up has increased, despite no new resources being made available to run the service. Cogent to Professor Franklyn's presentation was the fact that in this database in 1991 58·8% of patients had a suppressed TSH, and currently patients are being reviewed and doses of replacement thyroxine reduced. The system costs £30,000/year with each recall costing £5 for administrative costs and £1·75 for biochemistry costs. The estimated costs of arranging this in primary care would be greater (around 50% more expensive) and possibly less efficient: it is estimated that local GP practices lose between 26% and 50% of patients from annual follow-up.

KEYPOINTS

- Management of large numbers of patients with thyroid problems requires information technology support
- This provides the opportunity to audit quality and to respond rapidly to new evidence
- Centralising follow-up improves cost efficiency

SESSION 2

Delivery of 'hi-tech' endocrine care

Chairman: J.S. Bevan, NHS Consultant, Department of Endocrinology, Aberdeen Royal Infirmary, Aberdeen

The importance of growth hormone deficiency is undoubted in children but remains controversial in adults. Professor Sönksen highlighted the fact that adult growth hormone deficiency is associated with increased cardiovascular mortality, reduced quality of life (as many as 43% may have clinical depression), increased central obesity and reduced lean body mass, reduced physical performance and increased cholesterol as well as reduced HDL cholesterol concentrations.[7] Treatment with growth hormone may restore quality of life, and Professor Sönsken offered a number of vivid anecdotes and patient perspectives to illustrate the point. However, although growth hormone may reduce central obesity and reduce cholesterol and LDL fractions, no data are available to demonstrate a benefit in mortality. Furthermore, patient response is heterogeneous and the high cost of treatment (currently between £3,000 and £6,000/year) and a lack of agreed funding in some health authorities makes the decision of whether or not to offer treatment a difficult one.

KEYPOINTS

- Human growth hormone (hGH) is expensive
- Replacement in deficient individuals improves quality of life
- There is currently no evidence that it improves mortality rates in adults

This difficulty was addressed by the next speaker, Dr Andrew Walker. Focusing on the need to make the best

use of the limited resources available, Dr Walker outlined the steps required in making an economic appraisal of new and expensive treatments. Using the number of quality-adjusted life years (QALYs) gained from treatment allows different treatments to be compared and the opportunity cost of not providing treatment measured. However, making such measurements is an inexact science subject to several assumptions about the disability caused by disease, the indirect costs of disease and treatment effectiveness. Thus, using the example of growth hormone treatment, the cost per QALY varies between £27,000 and £11,000 per year. This compares with the cost of the use of ACE inhibitors in Type 2 diabetes of £5,137/QALY and annual retinal screening for diabetic subjects compared to three-yearly screening with a cost of £34,082/QALY.

KEYPOINTS

- Limited resources should be allocated equitably
- This requires a measurement of cost-effectiveness; QALYs are a good way of assessing this
- QALY calculations are inexact and subject to a degree of uncertainty

Adult growth hormone deficiency normally follows pituitary surgery, and Professor John Wass focused on measuring the quality of surgery. Success following surgery (as measured by biochemical 'cure' in secretory tumours, or prevention of recurrence in non-secreting adenomas) varies greatly between tumour types and even within tumour types. Thus, the best reported long-term cure results are 91% in acromegaly,[8] 79% in microprolactinomas[9] and 74·1% for Cushing's disease.[10] Part of this variation between tumour types reflects different behaviour of these tumours. Thus, experienced surgeons tend to operate more radically on tumours with an inherently high recurrence rate with a consequently higher rate of post-operative pituitary hormone deficiency. To illustrate the point, TSH deficiency occurs post-operatively in 5% of patients with acromegaly, 0% for microprolactinomas and 25·8% for Cushing's disease.

Tumour size also has a significant effect: in acromegaly cure rates of 91% are reported for microadenomas, but only 48% are cured with macroadenomas, even in the best surgical hands.[8] However, there is considerable variation between surgeons in reported series: for example, variations for growth hormone secreting microadenomas lies between 39%[11] and 91%.[8]

This point was amplified by Mr Michael Powell. Approximately 500–640 patients present each year with pituitary tumours within the UK. To train and maintain competence, a surgeon requires approximately 40–50 patients/year from estimates of operative workload within the centres with the best surgical results. Within the UK this translates as between ten and 16 specialist pituitary surgical centres, with perhaps one or two within Scotland based on population and its dispersion. Each unit would require at least two neurosurgeons to allow for continuous service during holiday or leave.

Audit of outcomes is an essential component for each centre – a practice which is rare within the UK at the moment. The estimated cost of maintaining an audit database for this purpose is £26,000 per year (£22,000 for a part-time specialist nurse, £1,000 for computing equipment, £1,000 for software and £2,000 for information technology expertise), although no resources are currently available from the NHS in most centres to implement this. Finally, Mr Powell urged endocrinologists referring patients for pituitary surgery to refer only to centres where outcome data are audited and known.

KEYPOINTS

- Success rates in pituitary surgery vary widely between individuals and units
- The best results are obtained by the most experienced surgeons
- Published outcome results are not widely available
- Pituitary surgery should be organised into supra-regional centres

SESSION 3

Delivery of care for infertility

Chairman: N.D.C. Finlayson, President of the Royal College of Physicians of Edinburgh; J. Mills, Honorary Senior Lecturer in Obstetrics and Gynaecology, University of Dundee

Professor Roger Gosden began the session by scanning the horizon for advances in fertility treatment. In the UK, 1% of births are due to assisted reproduction. However, demographic changes mean more women defer starting a family until later in life, often when their own oocyte supply is becoming exhausted. The number of live births thus falls with age, and women over 40 have approximately a 5% chance of a live birth, even with assisted reproduction (Figure 1). Under these circumstances donor eggs are normally used to increase fertility, but as the supply is limited and even older women normally have some eggs remaining, a number of approaches to use the patient's own eggs were explored.

One method is to identify the embryos with the best chance of giving rise to a live birth. By prolonging culture to the 8 or 16 cell blastocyst stage, one or two cells can be removed and karyotyped using fluorescent *in situ* hybridisation to identify chromosome abnormalities.[12]

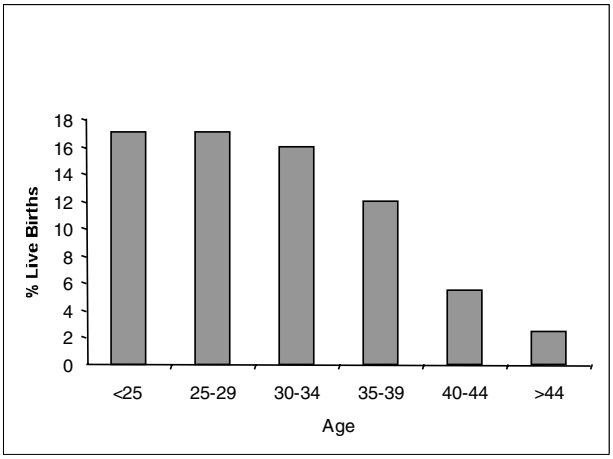

FIGURE 1
Live births per cycle of IVF.

This identifies only 26% of embryos with a normal diploid karyotype, 27% with non-viable or chaotic karyotypes and 47% mosaics. By selecting more vigorous embryos the number transferred is reduced and limits the risk of multiple births. In the future, it is anticipated that the use of screens for genomic and mitochondrial genetic integrity, the ability to profile the embryonic mRNA and protein complement will increase the ability to select the most favourable embryos for implantation.

Another method to reduce the use of donor eggs is cytoplasmic transfer.[13] This experimental technique uses the patient's oocyte, but increases the chance of fertilisation and implantation by transplantation of 10–15% of donor egg cytoplasm (avoiding donor nucleus) to the recipient egg and inducing fusion into a single egg by passing a small electrical current through the egg. A potential concern is that the formed egg is mosaic for mitochondria, although whether this has clinical implications is unknown.

In vitro oocyte maturation is a method avoiding the use of donor eggs and is simpler, cheaper and potentially safer.[14] By harvesting a few immature eggs after a normal cycle, or following minimal pharmacological stimulation, the egg is matured *in vitro* over 36 hours by stimulating the IP_3 signalling pathway, promoting oocyte maturation and extrusion of the polar body. Pregnancy rates from this technique are around 20% currently.

A number of experimental techniques are also being explored, including germ cell engineering. In premature ovarian failure an immature oocyte may be transplanted with the nucleus of a somatic cell from the same subject. Following electrofusion into a single cell the oocyte may be induced to mature and emits a polar body restoring the oocyte to a normal haploid state ready for fertilisation. A potential concern surrounding such techniques is that genomic imprinting is lost. Imprinting involves setting switches for around 50 genes that are either on (activating surrounding genes) or off (inhibiting genes). Normally, these genes are involved in growth and carry a distinct pattern of switches which are opposite in the oocyte and sperm, but are essential for normal orderly development to take place. Genes are switched off by methylation of CpG islands and switched on by demethylation which allows histones to disaggregate around these genes, exposing naked DNA to the transcription machinery. However, these imprinted patterns are lost with the use of somatic cells, and also in embryonic stem cells; this may limit use of this technology both in reproductive and transplantation medicine in the future.

Finally, the topic of fertility preservation was discussed. For men, sperm can be stored prior to spermatotoxic chemotherapy regimens, thawed and used for fertilisation later. However, for boys, such preservation of fertility is not currently possible, although animal studies indicate that this may be feasible in the near future.[15] In the mouse, spermatogonia harvested from immature animals mature normally and produce viable sperm when transplanted into a testis rendered azoospermic by ablative chemo- or radiotherapy. A trial in humans is currently underway and offers the prospect of preserving fertility even in pre-pubertal boys.

KEYPOINTS

- The demand for fertility services is increasing but the supply of donor oocytes remains a limiting factor
- A number of emerging treatments to limit the dependence on donor oocytes include embryo selection, cytoplasmic transfer, *in vitro* maturation and germ cell engineering
- New techniques for fertility preservation are becoming available

Professor Alan Templeton next addressed the question of whether current methods of fertility treatment are distributed equitably within the UK. Again this drew attention to the variation in outcome between units, and emphasised the need for audit and for success rates to be easily available. Current guidelines which Professor Templeton helped to draw up[16] suggest the NHS in Scotland should be prepared to fund fertility treatment for couples where the following criteria apply:

- woman 38 or younger;
- infertility for >3 years;
- neither partner has previously been sterilised;
- no child living at home; and
- less than three previous embryo transfers (from whatever source).

The treatment offered should include three NHS funded cycles of IVF with up to two fresh and one frozen embryo transfers. Intracytoplasmic sperm injection (ICSI) or microepididymal sperm aspiration (MESA) should be available if locally advised. *In vitro* fertilisation with donated eggs should be available, if advised. For all IVF, the cost of drugs should be borne by the NHS and no more than two embryos should be transferred to reduce the triplet rate. Partners should be seen together at first visit.

For endometriosis, IVF should be offered for severe ovarian disease as this offers the greatest chance of a live birth. However, for mild peritoneal disease, some studies suggest that laparoscopic laser therapy may double the pregnancy rate,[17] although this finding has not been confirmed.

A number of ineffective or redundant procedures were advised against, including the correction of a varicocoele (surgically or non-invasively), menstrual temperature charts, post-coital tests and testosterone treatment for male infertility.

KEYPOINTS

- National guidelines have been established to ensure equity of access to fertility services in the UK
- The procedures covered include IVF, ICSI and MESA
- Embryo transfer should be limited to two to reduce multiple births
- Ineffective treatments and procedures should no longer be offered

SESSION 4

Delivery of care for common endocrine syndromes: Type 2 diabetes

Chairman: R.W. Newton, Consultant Physician, Ninewells Hospital, Dundee

Dr Ken Paterson reviewed the changing demographics of Type 2 diabetes and the implications this will have for diabetes services in the UK.

The original 1985 WHO criteria for the diagnosis of diabetes included either a fasting blood glucose of ≥7·8 mmol/L or a glucose ≥11·1 mmol/L two hours after a 75 g glucose load (the two hour oral glucose tolerance test). In most subjects, diabetes was diagnosed on the two hour glucose value, although this has a coefficient of variation (CV: standard deviation/mean*100) of 17%, whereas the fasting glucose has a CV of only 6%. However, in most high risk populations studied, such as the Pima Indians of North America, microvascular complications such as diabetic retinopathy develop significantly at a fasting glucose of 6·8. In 1997, the American Diabetic Association proposed changing the diagnostic criteria to a fasting glucose ≥7·0 mmol/L. This was estimated to reduce the prevalence of diabetes by 10%, but by allowing simpler screening it was hoped ascertainment would be increased, and with it the detected prevalence. In 1999 the WHO adopted the lower threshold of 7·0 mmol/L for fasting glucose, but retained the two hour glucose tolerance test value of 11·1 mmol/L. $HbA1_c$ remains a valuable indicator of glycaemic control and predicts microvascular complications and, more weakly, macrovascular complications and mortality. However, variability between laboratories, analytical methods and equipment and the lack of a suitable calibration standard prevent its use as a diagnostic test for diabetes.

One of the largest demographic changes affecting most of the developed world is the increase in the ageing population. For Type 2 diabetes, incidence rates are relatively constant at 1% per annum from age 20 to age 80. Between now and 2016 it is estimated that the larger aged population will increase the number of Type 2 diabetic patients by 6,400 between the ages of 55–74 and 2,400 in those over 75. By 2036 the corresponding increases will be 7,400 and 10,000 based on current ascertainment rates and assuming no significant changes in lifestyle. In some ethnic communities the effect of age will be more pronounced. Indo-Asian and Afro-Caribbean subjects have a three- to five-fold increased risk of developing Type 2 diabetes while the population is relatively young: in the Indo-Asian population 43% are under 16 years old and only 3% are older than 65; the corresponding rates for the Caucasian population are 20% and 16%.

Another potent risk factor for developing Type 2 diabetes is obesity. The relative risk by body mass index (mass in kg/{height in m}^{2} :BMI) is shown in Table 2.[18] The frequency distribution of BMI is also shown in Table 3.

Obesity has a strong socio-economic gradient, with obesity being 50% more prevalent in the lowest groups compared with the highest. Furthermore, obesity is currently increasing in the adult population (16–64 years of age) by 3% from 1995–8, and also in the child population: currently in 4–11 year olds, 4·6% of boys and 7% of girls are overweight, and 0·4% of boys and 1·3% of girls are obese. Obesity in childhood is strongly correlated with adulthood obesity, and the current evidence therefore suggests that obesity is likely to increase rather than decline.

Exercise is known to reduce the risk of Type 2 diabetes, as shown in Table 4. However, 25% of men and 38% of women describe themselves as inactive, and exercise is less common in groups at highest risk of developing diabetes, such as lower socio-economic groups and ethnic populations.

TABLE 2

BMI	Relative risk of Type 2 diabetes
<23	1
23–25	2·7
25–30	7·6
30–35	20·1
>35	38·8

TABLE 3

BMI	Male %	Female %
<25	44	53
25–30	40	30
>30	16	17

TABLE 4

Hours of exercise per week	Relative risk of Type 2 diabetes
<0·5	1
0·5–2	0·89
2–4	0·87
4–7	0·83
>7	0·71

Worldwide, the current prevalence of Type 2 diabetes is 3–4% in the UK, up to 10% in the US and parts of Europe and as high as 20% in American African, Mexican and Hispanic populations. The most important rise in Type 2 diabetes will be in Africa and Asia, however, where incidence has increased three-fold from 5% to 14% in 15 years. In China, incidence is currently increasing five-fold, and in the Middle East two-fold. These changes in developing nations are due to a combination of increased life expectancy, increased obesity and reduced malnutrition, increased urbanisation with reduced activity and increased fat consumption.

With these considerations of rising numbers of diabetic patients worldwide, the question of how effective, quality care can be coordinated, even at a local level, is vexing. This is a particular concern as no additional resources or staff are presently available, and the National Service Framework for diabetes, which will determine standards and resources and which was originally due to be implemented in April 2002, has been delayed by one year. Addressing whether the future of most diabetic care lay within hospital clinics or in GPs' surgeries, Dr Miles Fisher argued for exclusive hospital care, while Dr Colin Kenny argued for GP care. The main thrust of the arguments was that a centralised and specialised hospital clinic could offer the most streamlined and experienced service, whereas the counter argument was that hospital care was expensive, incurred additional costs for patients in travelling and missing work and failed to take account fully of the patients' social and family environment.

The implications for each service were explored – for patients to be seen three monthly, by 2016 each GP list of 4,500 patients would require to generate an additional 14 slots per week, while each average diabetic clinic would require an additional 600 clinic slots. However, the consensus view (perhaps shared even by the advocates of each argument) was that diabetes requires care integrated between both settings. The real challenge ahead is to ensure that this integration takes place effectively and will require additional staffing, information technology support and, inevitably, additional finance to ensure effective care.

KEYPOINTS

- Changes in population demographics and lifestyle will increase the prevalence of Type 2 diabetes dramatically in the coming decades
- Ensuring effective and high quality care to these patients will need increased staffing and finance
- Care will require to be integrated between primary, secondary and tertiary care, and this will require effective information technology support

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