DM

Continuing education

EDITORIAL

The initiation of insulin therapy in patients with Type 2 diabetes has long been regarded as the 'bread and butter' of the clinical practice of diabetology, although this has increasingly been undertaken in a primary care setting over recent times. However, this relative straight-forward procedure has become increasingly controversial, with hotly contested views of the best way to commence insulin in such patients.

The pharmaceutical industry has driven much of the recent developments, and the launch of insulin glargine and its rapid uptake as the initiating insulin of choice by many in Type 2 diabetes has been an impressive exercise in commercial enterprise. However, it is the remit of *Continuing Education* (CE) to appraise critically the evidence base for each advocated insulin initiation regime in this setting, and to establish the effectiveness and safety, as well as the durability of each approach.

The articles chosen by the editorial panel for short citations as Today's Evidence in the Diabetes Journal Watch are two comparative studies of insulin initiation in Type 2 diabetes, both studies being sponsored by the pharmaceutical industry. They are helpful contributions to the literature and yet have important limitations. Indeed, the results of both studies are predictable, and the study sponsor can be rapidly guessed from reading the study design.

The Cochrane systematic review of insulin therapy in Type 2 diabetes was published in late 2004 and was cited in the previous issue of CE. However, it is unlikely that you will see the results featuring in any commercial advertising! Hopefully, I have wetted your appetite for Simon Page's important Today's Evidence paper on this topic. He has appraised the evidence for each approach, and concludes on the importance of tailoring insulin therapy to the individual patient, rather than taking a 'one size fits all' approach. Importantly, he highlights that the patient may also have a view. For the clinician to provide the best advice, we need the best evidence, and studies of insulin initiation in Type 2 diabetes need to last longer than 6 months, so that the durability of each insulin regimen can be established.

Another important contemporary issue in diabetology in the UK is the ongoing recruitment crisis for specialist registrars and consultants in diabetes and endocrinology. Although there has been much wringing of hands in private, this issue has been little explored in the literature. Kathy Higgins and Eleanor Scott have provided a Learning and Teaching Section article on the recruitment crisis, defining the problem, the cause of the problem and its potential solutions.

As an educational supervisor in diabetes and endocrinology, one of the most striking changes over recent years has been the lack of attraction of the specialty to graduates trained in the UK. Indeed, no UK-trained graduates have been appointed to the South Trent Specialist Registrar rotation in Diabetes and Endocrinology over the past 3 or 4 years. This has partly been a reflection of the fact that no UK-trained graduates have been applying for the posts. Frankly, something has gone badly wrong.

The fact that candidates are appointed to National Training Number (NTN) Specialist Registrar posts does not attest to the quality of the candidates. On a number of occasions, the candidates appointed have reached only the minimum requirements, and those on the interviewing panel are mindful that there is a clinical service to be run, and thus appointments need to be made. In contrast, the historical position of the specialty was to attract the most academically able candidates.

Another difficulty is that the training system for specialist registrars adopted over recent years does not usually incorporate a robust appraisal of trainees. The record of in-training assessment (RITA) process is usually a formality, and the consultant appointment committee has become the most rigorous assessment of the completion of specialty training. Hence, candidates may hold a Certificate of Completion of Specialist Training (CCST) in the specialty, and yet not be shortlisted or appointed by consultant appointment committees.

So how do we take this forward? Kathy and Eleanor make a number of important suggestions, including:

- Exposure of junior medical trainees to enthusiastic senior figures in the specialty, who enjoy their clinical practice.
- The option of opting out of acute general medicine as a Consultant Physician in Diabetes and Endocrinology.
- The wider availability of flexible working patterns, which may be particularly attractive to female colleagues.

As the Co-ordinating Editor, I am very aware that the readership is not just UK based, and I would be interested in the experiences of colleagues elsewhere on how recruitment in the specialty is being addressed. Or is this just a local issue? If there are important lessons elsewhere, these need to be rapidly flagged up in the UK setting.

The rest of the supplement explores a range of relevant day-to-day issues in clinical diabetes practice. We have two Clinical Practice Question articles, the first by Marie-France Kong and Michael Horowitz looking at the recent evidence in the diagnosis and management of diabetic gastroparesis, and the second by Donald Whitelaw on the management of diabetes during Ramadan. This year Ramadan will begin on about 4 October, so now is very much the time to plan ahead for patients who intend to fast. If you believe that your patients do not intend to fast during the holy month, then there is even more reason to read the article!

There are also two Horizons articles. Mark Walker and Doug Turnbull have provided an important update on mitochondrial DNA disease, most commonly associated with the MIDD syndrome (maternally inherited diabetes and deafness) and the

MELAS phenotype (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes). Lee Kennedy and Eric Khoo have explored new therapeutic options for the treatment of obesity in patients with Type 2 diabetes. This incorporates an introduction to Rimonabant, a selective endocannabinoid antagonist, which has demonstrated promising results over 12 months in patients with overweight patients with hypertension, dyslipidaemia and Type 2 diabetes. This agent is likely to be available in the UK during 2006, and it will be of interest to see whether the reality lives up to the current promise.

Finally, the Diabetes Journal Watch contains the usual assortment of key citations which may change clinical practice either now or in the not too distant future. With regard to weight issues, there is a Cochrane review of the current therapeutic options in Type 2 diabetes, and one hopes that the studies of Rimonabant will be of better methological design than those with previous agents. Another Cochrane review explores the α-glucosidase inhibitors in patients with Type 2 diabetes. This ties in with an article on postprandial hyperglycaemia which appeared in the January 2005 issue of CE, and the Cochrane review concludes that Acarbose has no impact upon morbidity or mortality, but improves glycaemic control, albeit with no benefit at a dose greater than 50 mg thrice daily.

The management of diabetes at the time of an acute myocardial infarction (AMI) has also been explored in previous issues, and it is thus appropriate that the DIGAMI 2 study receives a more detailed citation than is the norm. Essentially, the study did not demonstrate that acutely introduced, long-term insulin therapy improved survival in Type 2 diabetic patients with an AMI. However, the study did reaffirm the importance of tight long-term glycaemic control post AMI, and appears to indicate that tight glycaemia itself is more important than insulin therapy being used to achieve it.

Feedback is always welcomed, and should be directed to myself at ian.lawrence@uhl-tr.nhs.uk. I hope that you agree that we are not 'ducking' the key issues in contemporary diabetes practice, and we endeavour to provide a measured response to new and emerging evidence. The reality is that the best evidence should lead to the best care for people with diabetes.

Competing interests

Dr Lawrence has received either speaker honoraria, payment to attend advisory boardsor sponsorship to attend academic meetings from various pharmaceutical companies including Eli Lilly, Novo Nordisk and Sanofi Aventis.

Ian Lawrence for the Editorial Panel

TODAYS' EVIDENCE

Insulin initiation in Type 2 diabetes

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Your department has recently employed a new Diabetes Specialist Nurse (DSN) who has moved from a similar department elsewhere in the country. She rapidly realizes that the insulin-starting regimen in Type 2 diabetes differs between the two departments. Her impression was that the regimen that she used in her previous department worked well but her new colleagues are equally convinced of the efficacy of their insulin starter regimen.

She approaches you with the following questions:

- How strong is the evidence for continuing metformin and/or sulphonylureas when starting insulin?
- Does the published evidence favour a bedtime basal insulin start or twice daily insulin?
- Which starting regimen is most weight neutral?
- Are there any long-term data comparing different insulin starting regimens?
- Is bedtime basal insulin just a staging post to either twice daily or basal bolus insulin therapy?

Introduction

Disease progression is a central feature of the natural history of Type 2 diabetes requiring a staged pharmacological approach to management. Diet and oral hypoglycaemic agent (OHA) monotherapy progresses to combination OHA therapy and then to insulin. The longer a patient has Type 2 diabetes the greater the likelihood that insulin will be required. In the United Kingdom Prospective Diabetes Study (UKPDS) 53% of patients initially treated with sulphonylureas required insulin therapy at 6 years, rising to almost 80% at 9 years [1,2].

Insulin initiation is therefore a common 'bread and butter' issue for units involved in diabetes care. It is perhaps surprising that more evidence is not available to guide clinicians and nurse specialists in how best to achieve an effective transfer to insulin therapy. Indeed, the National Institute for Clinical Excellence (NICE) diabetes management guidelines [3] comment that 'local experience, patient preference and relative costs should inform the choice of insulin type and regimen as there is little research evidence in this area'.

What are the options and what is the evidence?

The ever increasing range of OHAs and insulins provide a large number of possible options for introducing insulin therapy (see Table 1). Commonly used regimens are shown in italics.

Table 1 Options for insulin initiation in Type 2 diabetes

Insulin addition (conventional or analogue) to continued OHA therapy
Basal insulin
Twice daily premixed insulin
Prandial insulin
Basal bolus insulin
Insulin substitution (conventional or analogue)
Basal insulin
Twice daily premixed insulin
Prandial insulin
Basal bolus insulin

Table 2 Summary points from the recent Cochrane review of clinical trials of insulin initiation in Type 2 diabetes

Trials were of short duration (weight mean duration 10 months).
Trial methodology quality was low.
No studies assessed diabetes-related morbidity, or mortality.
There was no significant difference in diabetes control comparing twice daily insulin regimens with or without oral hypoglycaemic therapy.
Insulin/OHA combinations had an insulin-sparing effect with an overall 43% reduction in daily insulin doses compared with insulin monotherapy.
Treatment regimens combining metformin with insulin were associated with less weight gain than insulin monotherapy or combination therapy with sulphonylureas.
The only regimen which was statistically less effective was insulin monotherapy using once daily NPH insulin.

The recent Cochrane review of insulin initiation trials [4] is a meta-analysis of 20 randomized controlled studies of 1811 participants, with mean age 59.8 years and mean duration of diabetes of 9.6 years. Short-term clinical outcomes were compared between different insulin monotherapy regimens (one, two or more insulin injections) and combination insulin/OHA in insulin-naive patients. Key points from their analysis are summarized in Table 2.

The overall conclusion of the Cochrane review was that regimens using either a single bedtime dose of NPH with continued OHA therapy, or insulin monotherapy, administered as a twice daily or multiple daily injections, achieved similar improvements in glycaemic control during the first few months of therapy. The frequency of hypoglycaemic was similar in 13 of 14 studies for which comparative data were available and there were no differences in quality of life-related issues. It is likely, therefore, that the regimens that the DSN has experienced in either of the institutions in which she has worked are similarly effective as a means of introducing insulin.

Metformin

An important observation from the Cochrane review was the importance of continued metformin therapy as a central component of the OHA–insulin regimen. Overall, OHA–insulin combination therapy resulted in significantly less weight gain compared with insulin monotherapy or insulin–sulphonylurea regimens, provided that the NPH injection was administered at bedtime and metformin was included in the OHA regimen. This, together with the cardiovascular benefits associated with metformin therapy reported in the UKPDS [5], provides strong grounds to recommend the inclusion of metformin in all regimens on transfer to insulin, provided there are no contraindications or intolerable side-effects. This is also in line with current NICE guidance [3].

Sulphonylureas

Combination therapy with sulphonylurea (SU) and insulin results in a significant insulin sparing effect (~50%) which is more potent than that associated with metformin (29%) [4]. However, weight gain and hypoglycaemia risk are similar to insulin monotherapy. Given the short duration of published insulin initiation trials, it is also unclear whether continued SU therapy will contribute to long-term glucose control. Given the progressive β-cell failure of Type 2 diabetes, long-term benefits of SU therapy cannot be taken for granted. Consideration should be given to stopping SU therapy if prandial insulin therapy is added to a basal insulin–OHA regimen (see below) or if a switch to twice daily premixed insulin is advised, to facilitate insulin dose titration.

A simple approach

The addition of basal insulin to OHA offers a simple introduction to insulin therapy. Traditionally, NPH insulin has been the basal insulin of choice and there is evidence to suggest this is best given as a bedtime injection in combination with continued OHA (usually SU and metformin) therapy. In the Cochrane review this was associated with a lower pooled weighted mean difference of HbA_{1c} of 0.3% compared with insulin monotherapy [4].

Recent data suggest that basal analogues may offer advantages with this approach. Riddle and colleagues compared bedtime NPH insulin with bedtime glargine in a randomized open-label multicentre trial in 756 overweight patients with Type 2 diabetes [6]. The Treat to Target trial incorporated simple dose-adjustment algorithms based on the fasting glucose to optimize glycaemic control. After 24 weeks' fasting glucose and HbA_{1c} were similarly improved in both groups and an impressive ~60% achieved the target HbA_{1c} of < 7%. However, more patients receiving glargine achieved this without documented nocturnal hypoglycaemia compared with NPH insulin (33.2% vs. 26.7%; $P < 0.05$). A meta-analysis comparing insulin glargine with NPH insulin in Type 2 diabetes has confirmed a consistent reduction in the incidence of overall symptomatic, nocturnal and severe nocturnal hypoglycaemia in Type 2 diabetes [7].

In a further study, once daily glargine plus OHA (metformin and glimeparide) was compared with twice daily premixed insulin monotherapy in 371 insulin-naive patients with poor glycaemic control (HbA_{1c} 7.5–10% at entry) [8]. Both groups used dose adjustment algorithms to optimize glucose control. After 24 weeks, the mean HbA_{1c} decrease from baseline was significantly better in the glargine plus OHA group and more

patients achieved the target HbA_{1c} of < 7% without confirmed nocturnal hypoglycaemia (45% vs. 28.6%; $P = 0.0013$). Whilst this trial favours the use of supplemental basal insulin over twice daily premixed insulin monotherapy, the authors acknowledge that continued metformin (for reasons summarized above) might improve the effectiveness of the premixed insulin regimen.

These recent trials suggest that the option of adding basal insulin to continued OHA therapy (including metformin) is a simple and effective means of introducing insulin therapy in patients with Type 2 diabetes. However, because of their short duration and the progressive nature of Type 2 diabetes, it is not clear whether this simple initiation regimen will prove durable in maintaining longer-term glycaemic control. Clinical experience suggests not and, in a recent review article, Riddle [9] proposed that the early use of basal insulin could act as a platform for the transition to a basal bolus regimen. Initially, if glycaemic targets were not being met, a prandial insulin injection could be added before the largest meal of the day. Further prandial injections would be added with other meals to achieve optimal control of both fasting and prandial glucose levels. This approach will ultimately lead to a basal bolus regimen, which will not be appropriate for all patients with Type 2 diabetes. As with so many aspects of diabetes management, an approach tailored to each patient's circumstances is required.

Whether glargine should be used as the basal insulin of choice in Type 2 diabetes remains unclear. A recent economic evaluation of insulin glargine concluded that, whereas its use was cost effective in Type 1 diabetes due to the higher frequency of hypoglycaemia, it was of borderline cost effectiveness in Type 2 diabetes [£32 508–£43 411 per quality adjusted life year (QALY)] [10]. Where addition of basal insulin is the preferred means of insulin initiation, bedtime NPH insulin in combination with OHA is preferred as first-line therapy, with insulin glargine reserved for patients who experience troublesome nocturnal hypoglycaemia. This approach is in accordance with NICE recommendations [11].

Twice daily premixed insulin

Switching to twice daily premixed insulin is the other commonly used strategy used to initiate insulin therapy in Type 2 diabetes. This approach is recommended by the European Diabetes Policy Group [12], ideally in combination with metformin, which provides both improved glycaemic control and insulin dose sparing [13].

The Cochrane review demonstrated that this approach was as good (or as bad) as the basal insulin–OHA combination regimen in terms of the expected improvements in glucose control, hypoglycaemia and weight gain, the latter especially if combined with metformin. A recent 28-week parallel group study in 233 insulin-naive patients with Type 2 diabetes compared the biphasic insulin analogue BIAsp (30/70) with the addition of basal analogue insulin (Glargine) plus continued OHA [14]. Both treatment arms included metformin with a dose range of 1500–2550 mg daily and a small percentage of patients continued with a thiazolidinedione. Regular insulin dose titration was employed based on home blood glucose measurements. Insulin secretagogues and acarbose were discontinued during the run-in period. After 28 weeks, HbA_{1c} levels were significantly lower in the biphasic analogue group (6.91%) compared with the glargine group (7.41%; $P < 0.01$) with largest reductions being achieved in those patients with initial HbA_{1c} levels over 8.5%. The provision of both basal and prandial insulin using biphasic insulin improved breakfast and evening meal prandial glucose control compared with the peakless profile of glargine. Episodes of mild hypoglycaemia, weight gain and daily insulin doses were higher in the biphasic group. Similar data have been reported in a trial showing small advantages with biphasic insulin lispro 25/75 plus metformin when compared with daily glargine plus metformin [15].

The fact that the best response occurred in those patients with the highest HbA_{1c} (and by inference the worst β-cell function) suggests that premixed biphasic insulin should be considered preferentially in patients with the worst glycaemic control ($HbA_{1c} > 8.5\%$) at referral for insulin initiation.

Prandial insulin

There are limited data on the initiation of insulin using three (or more) injections of rapid-acting insulin at mealtimes. This approach can work well. Feinglos *et al.* (1997) reported an improvement in HbA_{1c} from 9.7% to 7.1% with the addition of mealtime injections of insulin lispro in 25 insulin-naive patients previously treated with SU alone [16]. No alternative insulin regimen was used in this 'proof of concept' study. However, the Cochrane review [4] did not report clear advantage in multidose insulin regimens which would justify the greater educational input and patient commitment that more complex insulin regimens would require to deliver effective dose titration.

Current recommendations

It is clear from the above discussions that a 'one size fits all' solution to the issue of insulin initiation in Type 2 diabetes is not available. Either the addition of basal insulin to OHAs or twice-daily premixed insulin plus metformin appears to be both effective and safe. Whether one or other approach is adopted as the primary method in a particular unit is a matter for local discussion and agreement and will depend as much, if not more, on availability of resources, including DSN time and expertise, and the effective use of dose titration algorithms as on considerations of which initial insulin regimen is best. Of course, the patient may also have a view!

Based on the above data, it is reasonable to consider the addition of a basal insulin injection as the preferred option where an early transition to insulin therapy is planned (HbA_{1c} < 8%), a recommendation supported by data from the Treat to Target Trial [6]. Where control has already deteriorated to HbA_{1c} levels of ≥ 8.5%, a twice-daily biphasic insulin regimen with continued metformin would be preferred.

Whichever regimen is selected, it is important to remember the progressive nature of Type 2 diabetes and the fact that the initial insulin regimen is unlikely to provide long-term stable control. Intensification of insulin therapy will be required if optimal glycaemic targets are to be maintained over time. The issue of whether bedtime basal insulin is just a staging post to either twice daily or basal bolus insulin therapy remains unclear, but further data will be provided when the results of the ongoing Treating to Target in Type 2 diabetes (4T) trial become available.

Future issues

Unlike in the USA, thiazolidinediones are not approved for use in combination with insulin therapy in Britain. Many diabetologists are, in fact, using the glitazones in combination with insulin and sometimes metformin in a 'triple therapy' combination [17]. There is emerging evidence that this approach can be effective [18] and, if more widely adopted, it will open up a whole new set of issues around transfer of patients from OHAs to insulin. The impending availability of inhaled insulin will present yet more challenges and the inevitable need for more research if we are to understand how best to manage the transfer from tablet to insulin therapy in Type 2 diabetes.

Competing interests

S.P. has received reimbursement for attending symposia and for organizing education.

References

1 Wright A, Burden AC, Paisey RB, Cull CA, Holman RR for the UK Prospective Diabetes Study Group. Sulfonylurea inadequacy. Efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the UK Prospective Diabetes Study (UKPDS 57). *Diabetes Care* 2002; **25**: 330–336.

2 Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylureas, metformin or insulin in patients with type 2 diabetes. *JAMA* 1999; **281**: 2005–12.

3 *Management of Type 2 Diabetes*. Blood glucose (Guideline G) at http://www.nice.org.uk (last accessed 15 June 2005).

4 Goudswaard AN, Furlong NJ, Valk GD, Stolk RP, Rutten GEHM. Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes (Review). *Cochrane Database System Rev* 2004; Issue 4, Art no. CD003418.pub2.

5 UK Prospective Diabetes Study (UKPDS) Group. UKPDS 34. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; **352**: 854–865.

6 Riddle MC, Rosenstock J, Gerich J on behalf of the Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003; **26**: 3080–3086.

7 Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Zhengning L, Salzman A. Reduced hypoglycaemic risk with insulin glargine. *Diabetes Care* 2005; **28**: 950–955.

8 Janka HU, Plewe G, Riddle MC, Kliebe-Ffrisch C, Schweitzer MA, Yki-Jarvinen H. Comparison of basal insulin added to oral agents versus twice-daily pre-mixed insulin therapy for type 2 diabetes. *Diabetes Care* 2005; **28**: 254–259.

9 Riddle MC. Making the transition from oral to insulin therapy. *Am J Med* 2005; **118**: 14S–20S.

10 Warren E, Weatherley-Jones E, Chilcott J, Beverley C. Systematic review and economic evaluation of a long acting insulin analogue, insulin glargine. *Health Technol Assessment* 2004; **8**: 45.

11 NICE Technology Appraisal Guidance No. 53. *Guidance on the Use of Long-Acting Insulin Analogues for the Treatment of Diabetes—Insulin Glargine*. Available at http://www.nice.org.uk (last accessed 15 June 2005).

12 European Diabetes Policy Group. A desktop guide to type 2 diabetes mellitus. *Diabet Med* 1999; **16**: 716–730.

13 Aviles-Santa L, Sinding J, Raskin P. Effects of metformin in patients with poorly controlled, insulin-treated type 2 diabetes mellitus. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1999; **131**: 182–188.

14 Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P *et al.* Initiating insulin therapy in type 2 diabetes. A comparison of biphasic and basal insulin analogs. *Diabetes Care* 2005; **28**: 260–265.

15 Malone JK, Kerr LF, Campaigne BN, Sachson RA, Holcombe JH; Lispro Mixture-Glargine Study Group. Combined therapy with insulin lispro Mix 75/25 plus metformin or insulin glargine plus metformin: a 16-week, randomized, open-label, crossover study in patients with type 2 diabetes beginning insulin therapy. *Clin Therapeutics* 2004; **26**: 2034–2044.

16 Feinglos MN, Thacker CH, English J, Bethel MA, Lane JD. Modification of postprandial hyperglycemia with insulin lispro improves glucose control in patients with type 2 diabetes. *Diabetes Care* 1997; **20**: 1539–1542.

17 Higgs ER, Krentz AJ on behalf of the Association of British Clinical Diabetologists. ABCD position statement on glitazones. *Pract Diabetes Int* 2004; **21**: 293–295.

18 Poulsen MK, Henriksen JE, Hother-Nielsen O, Beck-Nielsen H. The combined effect of triple therapy with rosiglitazone, metformin, and insulin aspart in type 2 diabetic patients. *Diabetes Care* 2003; **26**: 3273–3279.

What's new in the journals?

Today's Evidence: initiation of insulin in Type 2 diabetes

Janka HU, Plewe G, Riddle MC, Kliebe-Frisch C, Schweitzer MA, Yki-Järvinen H. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for Type 2 Diabetes. *Diabetes Care* 2005; **28**: 254–259.

This 24-week study compared two insulin initiation regimens in 371 insulin-naive patients with Type 2 diabetes and poor glycaemic control (HbA_{1c} 7.5–10.5%), who were receiving metformin and sulphonylurea therapy. Patients were randomized to receive either once-daily insulin glargine plus glimepiride and metformin (glargine plus OHA) or 30% regular/70% isophane insulin (30/70 premixed insulin) twice daily without OHA. The insulin dosage was titrated to target fasting blood glucose (FBG) < 5.6 mmol/l (both insulins) and pre-dinner blood glucose < 5.6 mmol/l (30/70: premixed insulin). Glycaemic control improved in both groups: glargine plus OHA 8.85%

vs. 7.15%, and 30/70 premixed insulin 8.83% vs. 7.49%. However, the mean between-treatment HbA_{1c} difference of −0.34% ($P < 0.0005$) significantly favoured the glargine plus OHA group. Patients treated with glargine and OHA also experienced less confirmed hypoglycaemic episodes (mean 4.07 vs. 9.87/patient year, $P < 0.0001$), while weight gain was similar in both groups (1.4 kg vs. 2.1 kg, $P = 0.0805$). This study is in keeping with the findings of the recent Cochrane review of insulin initiation in Type 2 diabetes, but most clinicians in the UK who use premixed insulins in this setting do not discontinue metformin.

Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P *et al.* for the INITIATE Study Group. Initiating insulin therapy in Type 2 Diabetes. A comparison of biphasic and basal insulin analogs. *Diabetes Care* 2005; **28**: 260–265.

This 28-week study compared two insulin initiation regimens in 233 insulin-naive patients with Type 2 diabetes and poor glycaemic control ($HbA_{1c} \geq 8.0\%$), who were receiving > 1000 mg/day metformin alone or in combination with other oral hypoglycaemic agents (OHA). There was a 4-week run-in period where metformin therapy was optimized to 1500–2550 mg/day, and insulin secretagogues and α-glucosidase inhibitors were discontinued, but thiazolidinediones were continued in the form of pioglitazone (up to 30 mg daily). Patients were randomized to receive either once-daily insulin glargine plus metformin ± pioglitazone (glargine plus OHA) or 30% soluble insulin aspart/70% insulin aspart crystallized with protamine (Novomix 30) twice daily plus metformin ± pioglitazone (Novomix 30 plus OHA). The insulin dosage was titrated to target fasting blood glucose (FBG) 4.4–6.1 mmol/l (both insulins) and pre-dinner blood glucose 4.4–6.1 mmol/l (Novomix 30 plus OHA). Glycaemic control improved in both groups: glargine plus OHA 9.77% vs. 7.41%, and Novomix 30 plus OHA 9.70% vs. 6.91%. However, the overall reduction in HbA_{1c} significantly favoured the Novomix 30 plus OHA group: –2.79% vs. 2.36% ($P < 0.01$). Patients treated with glargine and OHA experienced less minor hypoglycaemic episodes (0.7 vs. 3.4 episodes/year, $P < 0.05$), while weight gain was greater in the Novomix 30 plus OHA group (5.4 kg vs. 3.5 kg, $P < 0.01$). This study demonstrates that Novomix 30 plus OHA is more effective than insulin glargine plus OHA at improving glycaemic control over 6 months, but the insulin glargine group did not receive an insulin secretagogue. One-third of both groups received pioglitazone, which is not licensed with insulin in the UK.

Insulin pump therapy

McMahon SK, Airey FL, Marangou DA, McElwee KJ, Carne CL, Clarey AJ *et al.* Insulin pump therapy in children and adolescents: improvements in key parameters of diabetes management including quality of life. *Diabet Med* 2005; **22**: 32–38.

This study looked at the impact of insulin pump therapy (CSII) on key parameters of diabetes management including quality of life in children and adolescents with Type 1 diabetes mellitus (T1DM). All patients started on insulin pump therapy were prospectively followed before and after institution of insulin pump therapy. Data collected included age, duration of diabetes, HbA_{1c}, anthropometric data and episodes of severe hypoglycaemia defined as hypoglycaemia resulting in coma or convulsion. A subset of patients also completed the Diabetes Quality of Life Instrument (DQOL) and Self-Efficacy for Diabetes Scale (SED) questionnaires to assess quality of life. At the time of analysis, 100 patients had been managed with insulin pump therapy. The mean age when starting pump therapy was 12.5 (3.9–19.6) years. Duration of therapy ranged from 0.2 to 4.0 years (mean 1.4 years, median 1.5 years). HbA_{1c} decreased from 8.3 ± 0.1% prior to pump therapy to 7.8 ± 0.1% ($P < 0.0001$). Episodes of severe hypoglycaemia decreased from 32.9 to 11.4 per 100 patient years. Components of quality of life measures showed improvement on pump treatment. BMI standard deviation scores (z scores) did not increase.

Kaufman F. Intensive management of type 1 diabetes in young children. *Lancet* 2005; **345**: 9461.

This is a comment on intensive management in children, the main article being from Weinzimer in *Paediatrics*. Sixty-five children with a mean age of 4.5 and mean duration of diabetes of 1.8 years were started on continuous subcutaneous insulin infusion (CSII) and followed for 162 patient years. Forty-one percent of children were looked after by carers, the rest by their mothers. Glycaemic control improved, HbA_{1c} falling from 7.4% (SD 1.0%) to 7.0% (0.9%). The improvement was sustainable over 3 years. Episodes of severe hypoglycaemia decreased by 53%, the biggest reduction in the 3–5 years age group. There were almost no episodes of diabetic ketoacidosis. At present the HbA_{1c} target for young children is greater than for adults (< 8.0%) due to the risk of hypoglycaemia, whilst the author feels that with CSII and insulin analogues, it may be possible to lower these targets and minimize the risk of long-term complications.

Oral hypoglycaemic therapy for Type 2 diabetes

Ahrén B, Gomis R, Standl E, Mills D, Schweizer A. Twelve- and 52-week efficacy of the dipeptidyl peptidase IV inhibitor LAF237 in metformin-treated patients with Type 2 Diabetes. *Diabetes Care* 2004; **27**: 2874–2880.

This randomized, placebo-controlled trial of 107 metformin-treated patients with Type 2 diabetes investigated the efficacy of the dipeptidyl peptidase IV inhibitor LAF237 over 12 weeks, with there being a 40-week extension in patients completing the core study. Glycaemic control improved with LAF237 (50 mg once daily), HbA_{1c} falling from 7.7% to 7.1% over 12 weeks, with fasting plasma glucose (FPG) falling by 2.2 mmol/l ($P < 0.0001$). There was no change in the HbA_{1c} of the placebo group, but FPG decreased 1.2 mmol/l ($P < 0.01$). Forty-two out of 56 patients (75%) continued LAF237, and 29 out of 51 continued placebo (56.9%) for the 40-week extension, with the improved HbA_{1c} being maintained in the LAF237-treated patients [the between group difference in HbA_{1c} after 1 year was −1.1% ($P < 0.0001$)]. There were no differences in body weight or lipid parameters, and the incidence of adverse events

was similar in both groups, with no problems from nausea or vomiting associated with LAF237. This is the first study demonstrating 1-year efficacy of this new oral agent for the treatment of Type 2 diabetes.

van de Laar FA, Lucassen PL, Akkermans RP, van de Lisdonk EH, Rutten GE, van Weel C. α-Glucosidase inhibitors for patients with Type 2 Diabetes. Results from a Cochrane systematic review and meta-analysis. *Diabetes Care* 2005; **28**: 166–175.

This systematic review included 41 studies of α-glucosidase inhibitors (AGIs), which were randomized controlled trials of at least 12 weeks' duration in patients with Type 2 diabetes. The majority of the studies used Acarbose (30 Acarbose, seven Miglitol, one Voglibose and three combined). There was no evidence for an effect on morbidity or mortality, but AGIs improved glycaemic control (HbA_{1c} decreased 0.77% with Acarbose, and 0.68% with Miglitol). With Acarbose doses > 50 mg thrice daily, the impact on glycaemia was no greater, but the occurrence of side-effects increased. Acarbose decreased the body mass index by 0.17 kg/m^2, but there was no impact on lipids. Compared with sulphonylurea therapy, AGIs seemed inferior regarding glycaemic control, but they reduced fasting and post-load insulin levels. The authors state that a previous meta-analysis of seven trials demonstrating that Acarbose reduced the incidence of myocardial infarctions in patients with Type 2 diabetes was subject to publication bias, heterogeneity, detection bias and confounding factors.

Masoudi FA, Inzucchi SE, Wang Y, Havranek EP, Foody JM, Krumholz HM. Thiazolidinediones, metformin and outcomes in older patients with diabetes and heart failure. An observational study. *Circulation* 2005; **111**: 583–590.

In North America, both metformin and thiazolidinediones (TZD) are commonly used to treat diabetes in patients with heart failure in spite of strong warnings from the Food and Drug Administration against this practice. The authors undertook a retrospective cohort study of 16 417 Medicare beneficiaries with diabetes discharged post-hospital with the main discharge diagnosis being heart failure. Crude 1-year mortality rates were lower among those treated with a TZD (30.1%) or metformin (24.7%) compared with those receiving neither drug (36%, $P < 0.0001$ for both comparisons). In multivariate models, treatment with either a TZD [hazard ratio (HR) 0.87, 95% CI 0.80, 0.94) or metformin (HR 0.87, 95% CI 0.78, 0.97) was associated with lower risk of death. Admissions for all causes did not differ for either agent. However, there was a higher risk of readmission for heart failure with a TZD (HR 1.06, 95% CI 1.00, 1.09) and a lower risk with metformin (HR 0.92, 95% CI 0.92, 0.99). This observational study is reassuring, but TZD therapy should not be used in diabetic patients with heart failure.

Management of Type 2 diabetes

Young RJ, Taylor J, Friede T, Hollis S, Mason JM, Lee P *et al.* Pro–Active Call Center Treatment Support (PACCTS) to improve glucose control in Type 2 Diabetes. *Diabetes Care* 2005; **28**: 278–282.

This randomized controlled trial of Pro-Active Call Centre Treatment Support (PACCTS) employed trained, non-medical telephonists to provide guidance regarding glycaemic management in 591 patients with Type 2 diabetes. The telephonists were supported by specially designed software and a diabetes nurse, and telephoned according to a protocol with the frequency of calls being proportional to the last HbA_{1c} reading. Compared with usual care, HbA_{1c} improved by 0.31% ($P = 0.003$) overall in the PACCTS patients over 12 months, with the improvement being 0.49% in patients with a baseline $HbA_{1c} > 7.0\%$. Medication increased more in the PACCTS group than in usual care ($P = 0.002$). In this urban caucasian population of Salford, PACCTS is effective at improving glycaemic control in Type 2 diabetes, and is worthy of further study and wider evaluation.

Cardiovascular risk and Type 1 diabetes

Tesfaye S, Chaturvedi N, Eaton SEM, Ward JD, Manes C, Ionescu-Tirgoviste C *et al.* for the EURODIAB Prospective Complications Study Group. Vascular risk factors and diabetic neuropathy. *N Engl J Med* 2005; **352**: 341–350.

The authors set out to identify the risk factors associated with development of distal symmetric neuropathy in Type 1 diabetes using the EURODIAB cohort. From 1172 patients without neuropathy at baseline, 276 developed new-onset neuropathy over the course of approximately 7 years' follow-up (23.5%). They found that the cumulative incidence of neuropathy was associated with the duration of diabetes, glycaemic control (both current and change during follow-up), smoking, body mass index and presence of cardiovascular disease as well as presence of other diabetes-related complications. They also noted that hypertension, though not an independent risk factor for development of distal symmetrical neuropathy, was an independent risk factor in development of autonomic neuropathy. Whilst this was an epidemiological study, it identified several modifiable risk factors worthy of further interventional research.

Myocardial infarction

Malmberg K, Rydén L, Wedel H, Birkeland K, Bootsma A, Dickstein K *et al.* for the DIGAMI 2 Investigators. 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**: 650–661.

Patients with diabetes have a worse prognosis post acute myocardial infarction (AMI) compared with their non-diabetic counterparts. However, the first DIGAMI study demonstrated improved survival with an insulin-based management of diabetes both acutely and long-term. The DIGAMI 2 study compared three different management strategies of diabetes in patients presenting with an AMI.

- Group 1, acute insulin–glucose infusion followed by long-term insulin therapy
- Group 2, acute insulin–glucose infusion followed by standard diabetes management
- Group 3, 'routine metabolic management according to local practice'.

The investigators recruited 1253 patients with Type 2 diabetes, the median study duration being 2.1 years. At randomization, HbA_{1c} was 7.2%, 7.3% and 7.3% in groups 1, 2 and 3, respectively, whilst blood glucose was 12.8 mmol/l, 12.5 mmol/l and 12.9 mmol/l, respectively. Blood glucose levels fell in all groups over the initial 24 h, but more so in groups 1 and 2. Multiple-dose insulin therapy (≥ 3 doses/day) was given to 42% group 1, but also 15% group 2 and 13% group 3. At the end of follow-up, glycaemic control was similar in each group ($HbA_{1c} \approx 6.8\%$). There was no difference in the primary end-point of mortality difference between groups 1 and 2 [hazard ratio (HR) 1.03, 95% CI 0.79, 1.34), nor the secondary end-point of mortality between groups 2 and 3 (HR 1.23, 95% CI 0.89, 1.69). There were also no significant differences in non-fatal reinfarctions or strokes among the three groups. The implementation of the DIGAMI 2 study had a number of limitations, including the study being underpowered to demonstrate the end-points (the study was stopped prematurely due to slow patient recruitment rate), non-adherence to glycaemic targets and the widespread use of insulin in group 3 (14% received an insulin–glucose infusion, and 41% had extra insulin injections in the acute phase). However, the overall 2-year mortality of 18.4% is impressive, and is the lowest reported long-term mortality in a cohort of diabetic patients with an AMI. Furthermore, the updated HbA_{1c} and blood glucose were significant and independent mortality predictors: an increase in HbA_{1c} by 2% or blood glucose by 3 mmol/l was associated with an increase in mortality by 20%. The DIGAMI 2 study thus confirms the importance of glycaemic control, but did not demonstrate that acutely introduced, long-term insulin therapy improves survival in Type 2 diabetic patients presenting with an AMI.

The CREATE-ECLA Trial Group Investigators. Effect of glucose–insulin–potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction. *JAMA* 2005; **293**: 437–446.

This study investigated the effect of high–dose glucose–insulin–potassium (GIK) infusion on mortality in patients with ST-elevation myocardial infarction (STEMI). The trial involved 20 201 patients worldwide who were randomized to receive GIK infusion for 24 h plus usual care (n = 10 901) or to receive usual care alone (n = 10 110). Main outcome measures were mortality, cardiac arrest, cardiogenic shock and reinfarction at 30 days. They showed a lack of benefit in any of these outcomes and, in particular, showed a lack of benefit in mortality in those with diabetes, a pre-specified subgroup.

Diabetic foot

Cruciani M, Lipsky BA, Mengoli C, de Lalla F. Are granulocyte colony-stimulating factors beneficial in treating diabetic foot infections? A meta-analysis. *Diabetes Care* 2005; **28**: 454–460.

This systematic review of the literature incorporates five randomized trials with a total of 167 patients treated with granulocyte colony-stimulating factor (G-CSF) as adjunctive therapy for diabetic foot infections. The investigators administered various G-CSF preparations parenterally for between 3 and 21 days. It appears that adjunctive G-CSF therapy does not hasten the clinical resolution of diabetic foot infection or ulceration, but is associated with a reduced rate of amputation and other surgical procedures. The numbers needed to treat (NNT) to prevent amputation is 8.6 and to prevent surgical intervention is 4.5, and in view of the small NNT, the authors suggest that G-CSF should be considered in treating diabetic foot infections, particularly in patients with limb-threatening infections.

Depression

Timonem M, Laakso M, Jokeleinan J, Rajala U, Meyer-Rochow V, Keinänen-Kiukaanniemi S. Insulin resistance and depression: cross sectional study. *BMJ* 2005; **330**: 17–18.

Depression is more common in people with diabetes. The authors examined the correlation between insulin resistance (defined with a qualitative insulin sensitivity check index) and the severity of depressive symptoms with Beck's depression inventory in 491 Finnish patients aged 65 years. As expected, there were significant differences between patients with diabetes (DM), impaired glucose tolerance (IGT) and normal glucose tolerance (NGT) according to body mass index (BMI) (30.4 ± 4.4 vs. 28.3 ± 4.3 vs. 29.6 ± 4.7 in the DM, IGT and NGT groups, respectively) and waist–hip ratio (WHR) (74, 60 and 57, respectively). They found a negative correlation between insulin sensitivity and depression (Spearman correlation coefficient $r = -0.13$, $P = 0.004$). The correlation was most evident in patients with IGT. Patients with DM and IGT had higher depression scores than those with NGT, with a statistically significant difference between those with IGT and NGT. This relationship remained after adjustment for BMI, WHR, alcohol consumption and physical activity. The cause for this link is unknown, although the authors suggest a link with counter-regulatory hormones associated with depression.

Diabetes and primary care

Hippisley-Cox J, O'Hanlon S, Coupland C. Association of deprivation, ethnicity, and sex with quality indicators for diabetes: population based survey of 53 000 patients in primary care. *BMJ* 2004; **329**: 1267–1269.

The National Service Framework (NSF) for diabetes sets standards of care, implementation of which is included in the General Medical Services (GMS) contract. This primary care study determined the impact of sex, ethnicity and social deprivation on indicators of care. Patients (n = 54 180) from 237 practices (a diabetes prevalence of 3%) were included using the general practice database QRESEARCH. Adjusted for age and sex, patients from less affluent areas were less likely to have records for measures including BMI, smoking, HbA_{1c} and microalbuminuria. Whilst patients from high ethnicity areas were more likely to have details of smoking and neurology testing, creatinine and cholesterol levels were less likely to be recorded. There was also some sex disparity, with women less likely to have BP, cholesterol and microalbumin records.

The authors conclude that practices in areas of high deprivation and high ethnicity will find it harder to meet targets in the new GMS contract and that women are less likely than men to receive adequate care for diabetes. Furthermore, these practices are probably less likely to attract adequate resources.

Surgery for obesity

Sjöström L, Lindroos A-K, Peltonen M, Torgerson J, Bouchard C, Carlsson B *et al.* for the Swedish Obese Subjects Study Scientific Group. Lifestyle, diabetes and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 2004; **351**: 2683–2693.

The authors investigated the metabolic changes 2 years and 10 years post obesity surgery (gastric banding, vertical banded gastroplasty or gastric bypass) in obese subjects enrolled into the Swedish Obese Subjects (SOS) Study. The control group was obtained by matching the subjects with others who did not undergo surgery on the basis of sex, age, anthropometric, metabolic and psychosocial factors. The control group received 'usual care' for their obesity. Approximately 25% of each group were lost to follow-up after 10 years, but data were available on more than 600 patients in both groups. Follow-up data at 2 years were not available in 8.2% of the surgically managed subjects and 18.5% of the controls, yielding data from 1845 surgically treated subjects and 1660 controls. Weight loss was greater in the surgical group at both 2 and 10 years (23% weight loss vs. 1% weight gain, and 16% weight loss vs. 2% weight gain, respectively). The primary outcome in the SOS study was overall mortality, and the authors inform us that the study is on-going with respect to this. However, more patients 'recovered' from diabetes in the surgical group after 10 years (36% vs. 13%), and the development of diabetes was similarly reduced in the surgical group (7% vs. 24%). The results at 2 years were more impressive, presumably relating to a regain of some of the lost weight over the intervening 8 years in the surgical group. Beneficial effects on lipids were also demonstrated, and, whilst the incidence of hypertension was not affected, the 'recovery' from hypertension was statistically greater in the surgically treated group at 10 years.

The Cochrane Library

Norris SL, Zhang X, Avenell A, Gregg E, Schmid CH, Lau J. Pharmacotherapy for weight loss in adults with type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2005; **1**: CD004096.

In this systematic review, the authors searched MEDLINE and EMBASE for randomized, controlled trials where pharmacotherapy was used as the primary strategy for weight loss among adults with Type 2 diabetes. Using this methodology, sufficient data for analysis were available for fluoxetine, orlistat and sibutramine. Twenty-two studies were included in the review, with a total of 296 participants for fluoxetine, 2036 for orlistat and 1047 for sibutramine. Weight reduction for fluoxetine was 5.1 kg [95% confidence interval (CI) 3.3, 6.9) at 24–26 weeks of follow-up, 2.0 kg (95% CI 1.3, 2.8) for orlistat at 12–57 weeks of follow-up and 5.1 kg (95% CI 3.2, 7.0) for sibutramine at 12–52 weeks of follow-up. The pooled reduction for HbA_{1c} was 0.5% (95% CI 0.3, 0.6) for orlistat (follow-up 24–57 weeks); sibutramine 0.5% (95% CI −0.2, 1.3, follow-up 12–52 weeks); fluoxetine 1.0% (95% CI 0.4, 1.5) at 8–16 weeks, 1.0% (95% CI 0.6, 1.4) at 24–26 weeks, and one study with a follow-up of 52 weeks demonstrated an HbA_{1c} reduction of 1.8% (95% CI −0.2, 3.8). The authors comment that many of the studies were of poor methodological quality and that the study populations were almost exclusively those with poorly controlled glycaemia and few were receiving insulin.

LEARNING AND TEACHING SKILLS

The recruitment crisis in diabetes and endocrinology

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Defining the problem

For some years there has been an undercurrent of discontent expressed by consultants within the specialty that the number and quality of applicants for national training number (NTN) posts is suboptimal and that there are insufficient good candidates for consultant jobs, leaving posts unfilled. This has been of largely informal and anecdotal concern, although it has reached national significance with discussions held within the Association of British Clinical Diabetologists (ABCD) [1] and the Specialist Advisory Committee at the Royal College of Physicians (RCP). In order constructively to take these issues further it would seem prudent to examine what evidence there is of a problem.

Applicants for NTN posts

It has been difficult to find national statistics on this. Several Deaneries publish data on the 'overall competition ratio' (OCR) for Specialist Registrar (SpR) jobs in different specialties in their region. This figure is basically derived from the number of applicants per SpR job advertised. However, these data are not comprehensive or easily comparable between deaneries as different years are published. The West Midlands Deanery (http://www.wmdeanery.org) has published data

Table 1 Data compiled from West Midlands deanery website. 'Overall competition ratios' (total applications/positions offered) for acute medical specialties within the West Midlands deanery for the past 7 years (http://www.wmdeanery.org)

	Year						
	1998	1999	2000	2001	2002	2003	2004
Diabetes/endocrine	17	32	7	7	7	2	13
Cardiology	—	49	14	8	12	3	8
Elderly medicine	3	16	13	4	6	5	1
Renal	—	6	4	4	10	12	—
Respiratory	9	8	8	3	5	5	5

showing the competition for SpR jobs on a yearly basis from 1998 to date (Table 1). It is clear that the number of applicants for NTN posts within Diabetes and Endocrinology (D&E) has declined considerably since 1999, going from 32 applicants per job to two in 2003. Whilst this is not necessarily representative of every region, it does give some insight into what has been happening and confirms the perception of a decline in the number of applicants. This decline, however, is a change that has been mirrored in other acute general medical specialties in this region, including cardiology and geriatrics, although numbers remain fairly stable in renal and respiratory medicine. To gain a more national view on this, looking at recent OCR data from some other deaneries (Table 2), it would appear that overall competition for D&E SpR jobs is currently similar to most other acute medical specialties, with the exception of cardiology, where competition appears to be high. So this is not necessarily a problem that is unique to D&E.

Demonstrating a decline in the quality of NTN candidates is much harder to substantiate. One of the main indicators would be demonstrating that the specialty is not appointing candidates to NTN posts after holding interviews. Looking at the data available on the deanery websites, this is not currently the case, as numbers of posts available match up with number of appointments made, the assumption being, therefore, that these candidates are considered of suitable quality by the appointing committee.

Applicants for consultant posts

Information relating to this has recently been published in the RCP newsletter [2]. Further, more detailed information is available on the RCP website (http://www.rcplondon.ac.uk/professional/spr/spr_prospect04.htm). Looking at the number of applicants per D&E consultant post recently there has been a mean of 2.9 per post. This is actually comparable to the national average of 3.1 for all medical specialties, although there is noticeably more competition per post in cardiology (5.4), gastroenterology (6.0), renal (4.1) and respiratory (3.4). Although D&E has had consultant expansion over the last few years (2001–2003), this has been less than that of most other acute medical specialties at 6.6% compared with 9–15%, and the specialty has actually had a marked increase over the same years in the number of trainees gaining Certificates of Completion of Specialist Training (CCST) (Table 3). Despite this, a

Table 2 'Overall competition ratios' across acute medical specialties in four deaneries. Data compiled from information available on North-western Deanery website (http://www.careers.pgmd.man.ac.uk) (North–west), London Deanery website (http://www.londondeanery.ac.uk) (London), Eastern deanery website (http://www.easterndeanery.org) (Eastern) and West midlands deanery website (http://www.wmdeanery.org) (West Mid)

	2001		2003		
	North–west	West Mid	Eastern	London	West Mid
Cardiology	26	8	7	22	3
Diabetes/endocrine	14	7	9	3	2
Gastroenterology	9	—	3	3	—
Elderly	—	—	—	2	—
Renal	6	4	4	4	12
Respiratory	8	3	4	5	5

Table 3 Numbers of Certificates of Completion of Specialist Training being awarded per year in the acute medical specialties. Data compiled from information available in JCHMT newsletter No. 8 (January 2005) (http://www.jchmt.org.uk/pubnews08.asp)

	1998	1999	2000	2001	2002	2003	2004
Cardiology and GIM	15	33	41	48	36	37	46
Diabetes/endocrine and GIM	35	39	33	57	44	45	38
Gastroenterology and GIM	59	74	48	62	33	67	59
Geriatrics and GIM	50	52	60	70	72	90	56
Renal and GIM	14	23	13	16	14	24	18
Respiratory and GIM	32	54	49	46	49	47	44

third of D&E appointments committees have been cancelled due to unsuitable or insufficient applicants for the job. Even when appointment committees were held, 11% of D&E posts were not filled after interview. This would suggest that although the specialty is actually getting applicants, there is a problem with their quality, so that appointments are not being made and jobs are having to be re-advertised. This inability to fill consultant posts appears to be a problem unique to D&E and does not seem to be mirrored to the same extent in the other major acute general medical specialties.

What is the cause of the problem?

Applicants for NTN posts

A reduction in the competition for NTN posts is a problem affecting all acute general medical specialties and is likely to have been the result of the recent expansion in NTN. An alternative explanation could be that the acute general medical specialties are no longer attracting senior house officers (SHOs), who are preferring instead to train in general practice, the surgical specialties, or dropping out of practising medicine altogether. Whatever the reason, when it comes to attracting available SHOs, D&E is clearly in direct competition with all other specialties and if it is to improve the number and quality of applicants for NTN posts then some knowledge of what attracts/dissuades them from the specialty is of value. A recent study by Higgins attempts to address this [3]. In order to find out why D&E was failing to attract applicants in Leicester a questionnaire was sent to all local medical SHOs. Surprisingly, 46% of them had considered pursuing a career in D&E. The main features that were putting them off were the lack of interventional procedures and care of the diabetic foot. Involvement in acute general medicine did not appear to be a factor determining career choice at this stage, although 43% did not want to practice general medicine at consultant level. Attractive features included working as part of a multidisciplinary team (MDT), being a clinic-based specialty, and the fact it was considered intellectually stimulating. The potential for research also figured highly. Importantly, 30% of those who were considering it as a career had done an SHO job in the specialty, whereas only 6% of those who were not considering it had.

To explore this in more detail, we sent a questionnaire to all SpR in Leicester, Nottingham, Sheffield and Leeds. When asked what had inspired them to chose the specialty, the strongest and most repeated free text responses were 'charismatic and/or enthusiastic consultants'; 'great registrars'; that the specialty contained an 'interesting case mix', and was appreciated for being a 'clinic-based specialty' and 'working as part of team'. The main positive features of the job now that they were SpR were the 'interesting and intellectually stimulating case mix', and 'working in a supportive, multidisciplinary team'. The negative features were overwhelmingly the commitment to acute general medicine on-call/shift work, and this was perceived to impact negatively on their training in the specialty, including getting to clinics. In addition, it was felt that consultant colleagues were disillusioned. Ninety percent of respondents had attended diabetes/endocrine clinics as an SHO prior to entering the specialty.

From this it would appear that exposure to the specialty as an SHO is a key deciding factor in choosing it as a career. For those that were considering, or had chosen it, the clinic-based multidisciplinary nature of the job was an attractive component. Acute general medical involvement is clearly a contentious issue, with almost half of medical SHOs not wishing to do it as a consultant, and SpR clearly struggling to enjoy and train in the specialty because of the burden of acute general medicine and shift work.

A decline in the quality of applicants for NTN posts is difficult to qualify. In order to apply for an NTN, doctors have demonstrated their professional ability in terms of general professional training and obtaining their MRCP. So unless there is criticism over the ability of these processes to weed out poor-quality doctors then it should not be a problem with their clinical competence. Due to the overall lack of competition for jobs within the specialty it is not currently necessary for SHOs to improve their CV by doing anything more than the basic general professional training and, as a result, it is unusual now for applicants for NTN to have experience of research, audit or case reports. Hence recent applicants do not have the same quality of CV as applicants 10–20 years ago. It is likely that the perception of a fall in quality of candidates is a result of loss of competition, so that candidates do not need to enhance their career prospects by developing a broader interest in the specialty prior to SpR training.

Applicants for consultant posts

Given that SpR training takes 5–7 years, the lack of recent competition for consultant posts is likely to reflect a mismatch in workforce planning between the number of training posts 10 or more years ago, and predicted consultant vacancies. This may be because there have been unanticipated retirements and lateral movement of established consultants into other posts, such as postgraduate deans, medical directors. The other situation is that despite passing their CCST, the candidates for consultant posts are not considered to be adequately qualified for the post being advertised and are being discounted, in many cases, prior to interview. It is possible that the specialty is appointing doctors to NTN posts that on paper and at interview appear to have the skills to do the job, but are proving disappointing as SpR so that there is a mismatch between established consultants' expectations of trainees and what is being delivered. Indeed, this is supported by the data suggesting that at consultant level available trainees are not being appointed [2]. If this is the case, what aspects of established consultant expectations are unfilled?

Anecdotally, trainees are currently perceived as being less experienced, less committed to their jobs, unwilling to take appropriate responsibility, and do not ensure continuity of

patient care. The consultant/SpR relationship has been eroded due to a whole variety of factors that have recently changed working practice—an increased number of trainees, the European Working Time Directive, shift work patterns, increasing consultant workload, the 'New' consultant contract, Shipman, the Bristol Enquiry, clinical governance and revalidation. This has meant that SpR rarely work for one consultant and instead several SpR are shared amongst several consultants for outpatient work, in-patient work and educational supervision. Cancelling clinics due to acute medical commitments on the part of both the SpR and consultant is commonplace and it is all too easy to perceive that because less time is spent working with each other as part of a team, SpR are not involved or committed to their training or providing good patient care, and that consultants are less willing to be involved in training. In addition to these problems, the greater share of acute general medicine undertaken by D&E consultants and SpR, as colleagues in other specialties have gradually been opting out, has significantly compounded the problem. Perhaps this is too hastily put down to deficiencies in individuals rather than accepting this as a 'cultural' problem as a result of dramatic changes in the profession over the last 10 years. It is simply not designed to produce the same type of doctor that for decades was believed to be the gold standard.

Another anecdotal problem is that an increasing number of trainees seem to have suboptimal communication skills. This may be more noticeable as a result of the more rigorous assessment and appraisal techniques utilized, particularly with 360° evaluation now commonplace, but also could represent changing public demands for information, and a culture of willingness of patients to complain if they feel they have not received this information appropriately. In addition, due to the rapid expansion in the number of NTN posts, many current SpR are non-UK graduates and some, whilst knowledgeable and diagnostically astute, struggle to communicate to the level currently expected by today's patients.

What does the future hold and how do we address the problem?

NTN posts

It appears that in order to be attracted into the specialty, exposure as an SHO is really important. D&E probably therefore needs to be volunteering its SHO posts into foundation programmes and highlighting the problems facing the specialty to organizers of medical rotations to ensure it is fairly represented. Whilst they are doing a D&E post, SHOs should be welcomed enthusiastically into the team and made to feel an integral part of it. They need to have exposure to specialty clinics to ensure that they see the positive side of the specialty and the areas that consultants and SpR feel enthusiastic about, as enthusiasm is a strong motivator. The specialty needs to be very careful that covering the general medical ward and seeing in-patient diabetes (often diabetic foot problems) is not their only exposure to it, and that shift work patterns do not limit their ability to attend clinics as these are both likely to dissuade them. Within the diabetes team they need to feel that they are useful and care should be taken that they are not made to feel inadequate by diabetes specialist nurses, podiatrists, etc., who readily override SHO decisions. In addition, the opportunity for research is well perceived by medical SHOs. Given the recruitment crisis simultaneously affecting academic medicine, exposure to enthusiastic clinical academics and the extensive, exciting research possibilities that currently exist in D&E may help both to recruit SHOs into the specialty and improve the quality of NTN applicants.

Consultant posts

The negative impact that acute general medicine and shift work has on D&E trainees and consultants should not be underestimated. It negatively affects trainees experience in the specialty and has significantly eroded the consultant/SpR training relationship so that trainees are no longer 'making the grade' as consultants. D&E needs to have equality in acute general medicine along with all other medical specialties. D&E trainees should not be subjected to more acute general medicine in their training than that required by other specialties to dually accredit. The balance needs to be corrected so they are doing more specialty training and not being used as general dogsbodies to shift the voluminous, often non-specific illnesses that currently get admitted under the auspices of acute general medicine. Consultants need more contact with their SpR to work closely with them, developing their clinical and professional skills. With the development of NTN in acute general medicine and the growth of this as a stand alone specialty, we should, as with other specialities, be allowed to opt out.

Currently, up to 70% of British medical students are female [2]. Nationally, 41% of NTN in our specialty are female, more than the 'interventional procedure' specialties of cardiology (15%) and gastroenterology (25%) [2]. From our SpR survey a third of current SpR intend to work part time as a consultant, and all of these are female. This is likely to affect the specialty's ability to fill NTN and consultant posts in the future, and also likely to reduce those willing to do acute general medicine. If D&E were to be really proactive as a specialty, to ensure it gets a greater share of good-quality trainees in the future, it should be looking at ways to appeal to women. This would involve greater acceptance and incorporation of flexible working practices, to include part-time working, family friendly hours and working from home. As a clinic-based specialty, with no interventional procedures to disrupt the routine of a working day, it is already attracting more women than some other acute medical specialties and is ideally suited to be able to accommodate such changes. The current acute medical shift system for SpR, in reality, does not fit well into this and D&E involvement in it needs to be at the very least equal to other specialties. The advent of acute medicine as a stand-alone specialty, if it is allowed to take the burden of acute medicine away from D&E,

has the potential to make D&E a very attractive specialty in the future. Incidentally, many male colleagues are also likely to appreciate such flexible working practices.

Conclusion

In summary, many of the changes seen are due to the recent expansion in NTN and consultant posts. The issues of quality probably reflect the major changes that have taken place in working practices and training over the last decade. In order to improve the situation the specialty needs to try to make accessible the features of the job that make it attractive, whilst employing strategies to attract applicants in what is currently a buyer's market. To ensure trainees meet the standards expected of consultants it needs to consider ways of increasing time/interaction with them whilst working within the limitations of modern working practices. This could be eased in part by ensuring the balance is redressed between specialty training and the seemingly excessive involvement in acute general medicine. Looking to the future, the majority of doctors will be female and in order to ensure the specialty does not remain a 'poor relation' it needs to be proactive in creating a training structure and consultant job that is attractive to female applicants. The specialty has numerous features that would suit those seeking flexible working patterns, but shift work and modern acute general medical demands override this. The challenge is how this is addressed.

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Competing interests

None to declare.

References

1 Daggett P. Where have all the trainees gone? *ABCD Newsletter*. Spring 2004; Issue 4.
2 Coward R. Mind the gap! Too many specialist registrars for consultant vacancies? *College Commentary* Jan./Feb. 2005.
3 Higgins KS. Diabetes and endocrinology as a career? *Diabet Med* 2005; **22**: 955–956.

CLINICAL PRACTICE QUESTION

Diabetic gastroparesis

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Please consider the following case scenario

A 35-year-old woman with a 17-year history of Type 1 diabetes complains of postprandial 'fullness', nausea and intermittent vomiting of 6 months' duration. She has long-standing poor glycaemic control with unexplained hypoglycaemia and hyperglycaemia, particularly postprandially. Her most recent HbA_{1c} is 8.9% in spite of the use of basal bolus insulin therapy. She has lost 3 kg over the previous 6 months, currently weighing 55 kg and having a body mass index of 19 kg/m^2. She also has background retinopathy, renal impairment (serum creatinine being 125 μmol/l) with her liver function tests and lipid profile being unremarkable. Urinalysis has shown proteinuria for the past couple of years, whilst blood pressure is 130/70, with her receiving angiotensin-converting enzyme inhibition therapy. A screen for coeliac disease antibodies has been previously negative, and urinary tract infection and pregnancy have been excluded. She is reviewed in clinic by one of the specialist registrars, and she reports that her symptoms have not been helped by either metoclopramide or cyclizine. The Specialist Registrar thus seeks out your advice:

- What is the prevalence of gastroparesis in diabetic patients?
- Is diabetic gastroparesis more common in any particular group of patients?
- Should empirical treatment of the patient's postprandial 'fullness', nausea and vomiting continue, or are specific investigations for gastroparesis warranted?
- What therapeutic options are available other than antiemetics?
- Do novel therapies for diabetic gastroparesis have anything to offer this patient?

What is the prevalence of gastroparesis in diabetic patients?

Gastroparesis was once considered a rare complication of diabetes mellitus, occurring occasionally in patients who had long-standing Type 1 diabetes complicated by symptomatic autonomic neuropathy [1]. Over the last 20 years or so numerous studies have resulted in an increased knowledge of gastric motor function in humans and it is now recognized that delayed gastric emptying represents a frequent, and clinically important, complication of diabetes mellitus.

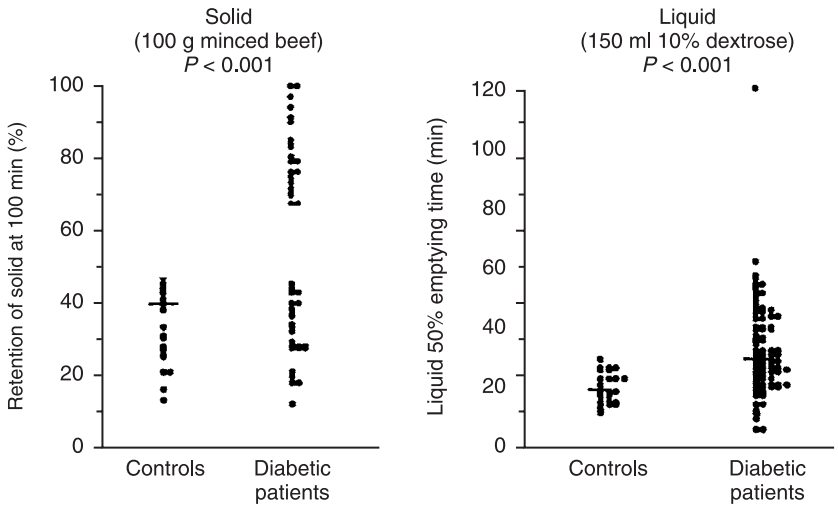

Figure 1 Gastric emptying of solid (100 g minced beef) and liquid (10% dextrose) in both normal subjects and patients with diabetes mellitus. Horizontal lines represent median values. Gastric emptying is delayed in about 50% of patients. Reproduced from Horowitz M, Maddox AF, Wishart JM, Harding PE, Chatterton BE, Shearman DJC. Relationships between oesophageal transit and solid and liquid gastric emptying in diabetes mellitus. *Eur J Nucl Med* 1991; **19**: 229–234, with kind permission from Springer Science and Business Media.

Cross-sectional studies have established that gastric emptying of solid, or nutrient liquid, meals is abnormally slow in some 30–50% of out-patients with long-standing Type 1 [2] or Type 2 [3] diabetes (Fig. 1). In most of these studies radionuclide techniques were used to measure gastric emptying. Early studies, using insensitive barium contrast techniques to quantify gastric emptying, underestimated the prevalence. The reported prevalence of delayed gastric emptying is highest when gastric emptying of both solid and nutrient-containing liquids (or semisolids) is measured, either simultaneously or separately, reflecting the relatively poor correlation between gastric emptying of solid and liquid meal components in diabetes. In many cases the magnitude of the delay in gastric emptying is relatively modest (Fig. 1), and a distinction should perhaps be made between 'gastroparesis' and 'delayed gastric emptying', with a diagnosis of gastroparesis restricted to those patients in whom gastric emptying is grossly delayed.

A previous misconception was that gastroparesis is inevitably associated with both intractable upper gastrointestinal symptoms and a poor prognosis [1]. While upper gastrointestinal symptoms occur frequently and affect quality of life adversely in patients with diabetes, the concept that upper gastrointestinal symptoms are a direct result of delayed gastric emptying [4] is oversimplistic. In particular, the relationship between upper gastrointestinal symptoms and the rate of gastric emptying is relatively weak; some patients with marked delay in gastric emptying may have few or no upper gastrointestinal symptoms (Fig. 2), and severe symptoms may remit spontaneously. Delayed gastric emptying should therefore be regarded as a marker of disordered gastric motility and not as the direct cause of symptoms. Although the available information is limited, delayed gastric emptying per se does not appear to be associated with a poor prognosis [5].

In view of the demonstrated effect of acute hyperglycaemia on gastric emptying, as discussed below, it should be recognized that while the prevalence of delayed gastric emptying during euglycaemia has not been formally evaluated, it will almost certainly be less than that reported in previous studies in

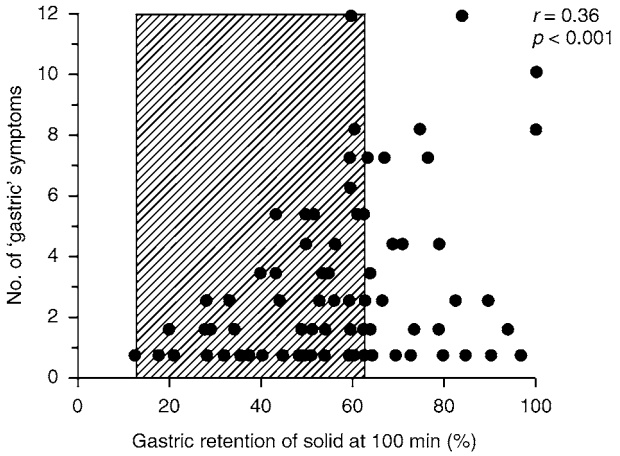

Figure 2 The relationship between symptoms (total score) referable to delayed gastric emptying and gastric emptying of a solid (minced beef) meal. The normal range for gastric emptying is shown in the shaded area. Reproduced from Horowitz M, Maddox AF, Wishart JM, Harding PE, Chatterton BE, Shearman DJC. Relationships between oesophageal transit and solid and liquid gastric emptying in diabetes mellitus. *Eur J Nucl Med* 1991; **19**: 229–234, with kind permission from Springer Science and Business Media.

which blood glucose concentrations were not stabilized during measurements of gastric emptying. There is evidence that the blood glucose concentration also affects perception of gastrointestinal sensations in diabetes mellitus. For example, in patients with Type 1 and Type 2 diabetes the perception of postprandial fullness is related to the blood glucose concentration [6]. An important role for hyperglycaemia in the aetiology of gastrointestinal symptoms is also supported by cross-sectional, epidemiological studies. The mechanism(s) by which hyperglycaemia affects gut perception/symptoms is currently unknown.

It is now recognized that gastric emptying is a major determinant of postprandial glycaemia, accounting for at least 35% of the variance in peak postprandial glucose levels after oral glucose (75 g) in both healthy individuals and patients with Type 2 diabetes [6]. In Type 1 patients with gastroparesis, as

would be predicted, it has been shown that less insulin is initially required to maintain euglycaemia after a meal when compared with those with normal gastric emptying. All patients with Type 1 diabetes, and insulin-treated Type 2 diabetes, need to co-ordinate carbohydrate absorption with insulin delivery, and this may be particularly difficult in Type 1 patients with gastroparesis. It is, however, not known whether asymptomatic patients with suboptimal glycaemic control (particularly unexplained hyperglycaemia or hypoglycaemia) should be screened routinely for disordered gastric emptying. Nor is it known whether treatment of Type 1 patients who have gastroparesis with prokinetic drugs improves glycaemic control.

Is diabetic gastroparesis more common in any particular group of patients?

Evaluation of cardiovascular autonomic function has usually been employed as a surrogate marker of the function of the abdominal vagus, as there is a lack of tests to assess gastrointestinal autonomic function directly. The prevalence of disordered gastric emptying/gastric motility is higher in patients with cardiovascular autonomic neuropathy than in those without [7,8], but the correlation between disordered motility with abnormal cardiovascular autonomic function (either parasympathetic or sympathetic) is relatively weak [7,8]. Although this may be interpreted as evidence for selective autonomic impairment of the gastrointestinal tract, other factors, such as hyperglycaemia, appear to be important.

Acute changes in the blood glucose concentration, both hyperglycaemia and hypoglycaemia, have a substantial, and reversible, effect on gastric motility, in both healthy subjects and patients with diabetes [6]. Marked hyperglycaemia (blood glucose concentration about 15 mmol/l) slows gastric emptying in uncomplicated Type 1 patients, as well as those with autonomic neuropathy [9]. It is not known whether the response to hyperglycaemia is dependent on the rate of gastric emptying during euglycaemia, previous (long-term) glycaemic control or autonomic nerve function. Cross-sectional studies suggest that an inverse relationship between the rate of gastric emptying and the blood glucose concentration also exists in Type 2 patients [3]. Changes in the blood glucose concentration within the normal postprandial range also influence gastric emptying and motility [10,11]; emptying of solids and liquids is slower at blood glucose of 8 mmol/l than 4 mmol/l in both healthy subjects and patients with Type 1 diabetes [10]. In patients with Type 1 diabetes, gastric emptying is accelerated markedly during hypoglycaemia [12]; this response is also evident in patients with autonomic neuropathy [13] and likely to be important in the counter-regulation of hypoglycaemia. The effect of hypoglycaemia on gastric emptying in patients with severe gastroparesis has not been evaluated.

The prevalence of delayed gastric emptying is weakly associated with the duration of known diabetes [8], which may be attributable to an increased prevalence of autonomic neuropathy, and appears to be higher in females than males for uncertain reasons. The latter is also the case in patients with functional dyspepsia. A number of electrolyte abnormalities may affect gastric motility. *Helicobacter pylori* infection does not appear to affect gastric emptying in diabetes. Dyspeptic complaints and delayed gastric emptying occur frequently in patients with chronic renal failure.

Should empirical treatment of the patient's nausea and vomiting continue, or are specific investigations for gastroparesis warranted?

Vigorous attempts should be made to optimize glycaemic control, although at this time the benefit of this approach has not been established. Nevertheless, attempts should be made to maintain blood glucose levels close to the euglycaemic range.

The decision of when to evaluate diabetic patients for delayed gastric emptying is not always easy because, as discussed, upper gastrointestinal symptoms occur frequently in patients with diabetes, but are not strongly predictive of disordered gastric emptying or motility. In any diabetic patient who presents with upper gastrointestinal symptoms, a comprehensive history and examination should be performed. It should be recognized that there are many causes of gastroparesis apart from diabetes (Table 1), and these should be excluded. Although gastroparesis may be pharmacologically induced, in some patients it may not be feasible to withdraw medication that could slow gastric emptying. It is also not known whether the magnitude of the response to drugs which slow gastric emptying (such as anticholinergic medications) is influenced by the rate of gastric emptying or the blood glucose concentration; this issue may potentially have relevance to the use of pramlintide and exenatide, which have recently been approved by the Food and Drug Administration (FDA) and improve

Table 1 Causes of gastroparesis

Transient delayed gastric emptying
Drugs, e.g. morphine, anticholinergics, nicotine, dopaminergics
Electrolyte abnormalities—hyperglycaemia, hypokalaemia, hypomagnesaemia
Hypothyroidism, hyperthyroidism, hypopituitarism, Addison's disease
Postoperative ileus
Viral gastroenteritis
Herpes zoster
Critical illness
Pregnancy
Chronic gastric stasis
Diabetes mellitus
Idiopathic/functional dyspepsia
Gastro-oesophageal reflux
Atrophic gastritis
Post-surgical, e.g. vagotomy
Liver disease
Anorexia nervosa and bulimia nervosa
Spinal cord disease
Central nervous system disease, brain stem lesions, Parkinson's disease
Autonomic degeneration
Progressive systemic sclerosis
Heart/lung transplantation

glycaemic control, at least in part, by slowing gastric emptying. It is reasonable to give an empirical trial of prokinetic therapy for about 4 weeks, but it should be recognized that there is a substantial placebo response. If symptoms fail to improve, appropriate investigations to identify other causes of upper gastrointestinal symptoms should be performed. Upper gastrointestinal endoscopy should be performed to exclude gastric outlet, or duodenal, obstruction as well as mucosal disorders. The prevalence of reflux oesophagitis may be increased in patients with diabetic gastroparesis. Gastric emptying should be measured if symptoms fail to improve (as this enables therapy to be targeted), or recur following the cessation of therapy. Scintigraphic measurement of gastric emptying is the optimum technique for assessment of gastric motility. It is relatively easy to perform and non-invasive; the radiation dose approximates that received from a single abdominal radiograph. Measurement of gastric emptying should ideally be done during euglycaemia, but at a minimum with regular blood glucose monitoring. Unfortunately, there is a lack of standardization of scintigraphic techniques with substantial variation between different centres, particularly in relation to the volume and composition of the test meal and the calculation of gastric emptying rates. This renders comparisons between studies performed in different centres difficult and usually dictates the need for each laboratory to have access to an appropriate control range.

Scintigraphic breath tests have recently been used to quantify solid and/or liquid gastric emptying; these are cheaper and simpler than external scintigraphy and, with the use of stable isotopes, avoid the use of irradiation [7]. However, studies in patients with diabetes are limited and additional validation of these methods in patients with gastroparesis, particularly those in whom gastric emptying is markedly delayed, is required before their use can be advocated. Nonetheless, it seems likely that scintigraphic breath tests will prove to be useful as a screening test for gastroparesis.

What therapeutic options are available other than antiemetics?

It is logical to suggest a dietary intake of small, low-fibre and low-fat meals, with homogenized solid foods and increased nutrient liquids, but it has not been established that such an approach is useful.

At present, the use of prokinetic drugs (mainly domperidone, metoclopramide and erythromycin) forms the mainstay of therapy. In general, these drugs all provide dose-related improvements in gastric emptying, although their mechanisms of action differ, involving stimulation of $5HT_4$ receptors (metoclopramide), dopamine receptor blockade (domperidone and metoclopramide) and stimulation of motilin receptors (erythromycin) [14]. Unfortunately, cisapride, which has been subjected to the most comprehensive studies and appears to have the most diffuse gastrointestinal effects, is no longer licensed for use in the UK because of reports of cardiac arrhythmias, including deaths. Whether drug combinations are synergistic has not been adequately assessed.

The response to prokinetic therapy, i.e. the magnitude of acceleration in gastric emptying, tends to be greater when gastric emptying is more delayed. Relatively few studies have evaluated the effects of prolonged (> ~8 weeks) prokinetic therapy. A beneficial effect on quality of life has also been reported in some studies, but this issue has not been evaluated widely. In general, there is a poor correlation between effects on symptoms and gastric emptying [15]. Furthermore, there is little information as to whether the symptomatic response differs between patients with and without delayed emptying; it is likely that some patients with normal gastric emptying also respond to prokinetic therapy. Because comparisons between the prokinetic drugs are limited, it is difficult to give confident therapeutic recommendations. Erythromycin is the most potent drug when given intravenously (in doses of < 3 mg/kg), and may be particularly useful in the initial phase of management. When used orally, erythromycin may have greater efficacy as a suspension, rather than as a tablet, but is probably less effective than when given intravenously. The gastric motor response to erythromycin is also critically dependent on the dosage. It has recently been demonstrated, in both healthy subjects and patients with diabetes [16,17], that the effect of erythromycin on gastric emptying is attenuated markedly during hyperglycaemia; this effect is likely to be evident with other prokinetic drugs. Metoclopramide has the advantage of being available for parenteral (including subcutaneous) use and having central antiemetic properties. Domperidone has a low prevalence of adverse effects and can be used in relatively high doses.

Treatment of symptomatic gastroparesis is certainly not uniformly satisfactory, particularly in the subgroup of patients who have intractable bouts of nausea and vomiting lasting a number of days. If symptoms are refractory to prokinetic therapy, placement of a feeding jejunostomy may be required to maintain nutrition. In most cases surgery is not recommended [14] as this may be associated with deterioration as well as a high risk of nosocomial infections. The unpredictable clinical course in cases of gastroparesis associated with severe symptoms also argues against the use of aggressive therapy. If surgery is performed, this should be done in specialized centres.

Do any novel therapies for diabetic gastroparesis have anything to offer this patient?

Dopamine antagonists, such as levosulpiride [18], and $5HT_4$ agonists which do not affect cardiac function, such as tegaserod, are currently in development. Treatment with levosulpiride for 6 months has been reported to improve both gastric emptying and glycated haemoglobin in Type 1 patients with delayed gastric emptying [18], but these observations require confirmation. Since administration of erythromycin is associated with the risks of long-term antibiotic use and, possibly, diminished efficacy, potent motilides which lack antibiotic activity have been developed. The outcome of a study using one of these drugs in a large cohort of Type 1 patients with

upper gastrointestinal symptoms was, however, disappointing. The use of phosphodiesterase inhibitors such as sildenafil, which may accelerate gastric emptying in animal models of diabetes, is currently being evaluated.

Gastric electrical stimulation therapy, using either neural electrical stimulation at a high frequency (which probably stimulates vagal sensory nerves and may suppress the vomiting centre [19]) or gastric electrical pacing [in which electrical stimulation of cholinergic motor neurones approximates the physiological frequency (approx. 3 cycles/min)], is being evaluated as a therapy. In the absence of persuasive data a device which uses the former approach has been approved by the FDA; a few centres in the UK also offer the high-frequency stimulation device in refractory cases.

It has recently been reported that botulinum toxin injection of the pylorus may improve symptoms in patients with diabetic gastroparesis—the outcome of placebo-controlled trials is awaited.

There are uncontrolled data to suggest that pancreatic transplantation, which is known to have beneficial effects on autonomic function, may improve both gastric emptying and symptoms [20]. If this proves to be the case, it would also provide additional evidence for a role of chronic glycaemic control in the aetiology of gastroparesis.

Practice points

1. Disordered gastric emptying occurs frequently in patients with diabetes; in 30–50% of out-patients with long-standing Type 1 or Type 2 diabetes gastric emptying is delayed, although the magnitude of this delay is modest in many cases.
2. Upper gastrointestinal symptoms occur frequently and affect quality of life adversely in patients with diabetes.
3. The relationship between symptoms and the rate of gastric emptying is relatively weak.
4. Gastroparesis does not always reflect irreversible autonomic nerve damage.
5. Acute changes in blood glucose concentration have a substantial effect on gastric motor function and, probably, upper gastrointestinal symptoms.
6. Gastric emptying is slower during hyperglycaemia when compared with euglycaemia and accelerated during insulin-induced hypoglycaemia.
7. Variations in the blood glucose concentration within the normal postprandial range also affect gastric emptying; emptying is slower at a blood glucose concentration of 8 mmol/l when compared with 4 mmol/l.
8. The blood glucose concentration may influence the response to prokinetic drugs.
9. Disordered gastric emptying is likely to contribute to poor glycaemic control, particularly in Type 1 diabetes.

Competing interests

None declared.

References

1 Rundles RW. Diabetic neuropathy. *Medicine* 1945; **19**: 111–160.
2 Horowitz M, Harding PE, Maddox A, Maddern GJ, Collins PJ, Chatterton BE *et al.* Gastric and oesophageal emptying in insulin-dependent diabetes mellitus. *J Gastroenterol Hepatol* 1986; **19**: 97–113.
3 Horowitz M, Harding PE, Maddox AF, Akkermans LM, Chatterton B, Shearman DJ. Gastric and oesophageal emptying in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 1989; **19**: 151–159.
4 Kassander P. Asymptomatic gastric retention in diabetics: gastroparesis diabeticorum. *Ann Intern Med* 1958; **19**: 797–812.
5 Kong M-F, Horowitz M, Jones KL, Wishart JM, Harding PE. Natural history of diabetic gastroparesis. *Diabetes Care* 1999; **19**: 503–507.
6 Rayner CK, Samsom M, Jones KL, Horowitz M. Relationships between upper gastrointestinal motor and sensory function with glycemic control. *Diabetes Care* 2001; **19**: 371–381 (Review).
7 Ziegler D, Schadewaldt P, Pour Mirza A, Piolot R, Schommartz B, Reinhardt M *et al.* [^{13}C]Octanoic acid breath test for non-invasive assessment of gastric emptying in diabetic patients; validation and relationship to gastric symptoms and cardiovascular autonomic function. *Diabetologia* 1996; **19**: 823–830.
8 Horowitz M, Maddox AF, Wishart JM, Harding PE, Chatterton BE, Shearman DJC. Relationships between oesophageal transit and solid and liquid gastric emptying in diabetes mellitus. *Eur J Nucl Med* 1991; **19**: 229–234.
9 Fraser R, Horowitz M, Maddox A, Chatterton B, Harding P, Dent J. Hyperglycaemia slows gastric emptying in type 1 diabetes mellitus. *Diabetologia* 1990; **19**: 675–680.
10 Schvarcz E, Palmer M, Aman J, Horowitz M, Stridsberg M, Berne C. Physiological hyperglycaemia slows gastric emptying in normal subjects and patients with insulin-dependent diabetes mellitus. *Gastroenterology* 1997; **19**: 60–66.
11 Jones KL, Kong MF, Berry MK, Rayner CK, Adamson U, Horowitz M. The effect of erythromycin on gastric emptying is modified by physiological changes in the blood glucose concentration. *Am J Gastroenterol* 1999; **19**: 2074–2079.
12 Schvarcz E, Palmer M, Aman J, Lindkvist B, Beckman KW. Hypoglycaemia increases the gastric emptying in patients with type 1 diabetes mellitus. *Diabet Med* 1993; **19**: 660–663.
13 Russo A, Stevens JE, Chen R, Gentilcore D, Burnet R, Horowitz M *et al.* Insulin-induced hypoglycaemia accelerates gastric emptying of solids and liquids in longstanding type 1 diabetes. *J Clin Endocrinol Metab* in press.
14 Samsom M, Smout AJPM, Goozen HG. Medical and surgical treatment of gastroparesis. *Gastroenterol Int* 1998; **19**: 169–176.
15 McHugh S, Lico S, Diamant NE. Cisapride vs metoclopramide. An acute study in diabetic gastroparesis. *Dig Dis Sci* 1992; **19**: 997–1001.
16 Petrakis IE, Vrachassotakis N, Sciacca V, Vassilakis SI, Chalkiadakis G. Hyperglycaemia attenuates erythromycin-induced acceleration of solid-phase gastric emptying in idiopathic and diabetic gastroparesis. *Scand J Gastroenterol* 1999; **19**: 396–403.
17 Jones KL, Berry M, Kong M-F, Kwiatek MA, Samsom M, Horowitz M. Hyperglycaemia attenuates the gastrokinetic effect of erythromycin and affects the perception of postprandial hunger in normal subjects. *Diabetes Care* 1999; **19**: 339–344.
18 Melga P, Mansi C, Ciuchi E, Giusti R, Sciaba L, Prando R. Chronic administration of levosulpiride and glycemic control in IDDM patients with gastroparesis. *Diabetes Care* 1997; **19**: 55–58.
19 Tougas G, Huizinga JD. Gastric pacing as a treatment for intractable gastroparesis—shocking news? *Gastroenterology* 1998; **19**: 598–601.
20 Gaber AO, Oxley D, Karas J, Cardoso S, Hathaway D, Shokouh-Amiri MH *et al.* Changes in gastric emptying in recipients of combined pancreas-kidney transplants. *Dig Dis* 1991; **19**: 437–443.

Suggested reading

Horowitz M, Samsom M, eds. *Gastrointestinal Function in Diabetes Mellitus*. Chichester: John Wiley & Sons 2004. 349 pp. ISBN 0-471-89916-X.

Horowitz M, O'Donovan D, Jones KL, Feinle C, Rayner CK, Samsom M. Gastric emptying in diabetes: clinical significance and treatment. *Diabet Med* 2002; **19**: 177–194.

Kong M-F, Macdonald IA, Tattersall RB. Gastric emptying in diabetes. *Diabet Med* 1996; **13**: 112–119.

HORIZONS

Mitochondrial diabetes

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Case history

A 62-year-old lady attends the diabetic clinic with a history of non-insulin-dependent diabetes and long-standing deafness. Her diabetes is managed with a sulphonylurea, but on enquiry you find her son also has diabetes and deafness. Probing the family history a little further, you discover that her sister has cognitive impairment and bowel problems, her niece has diabetes, cardiomyopathy and strokes, whilst her great nephew had a stroke-like episode at the age of 10 years. Since all the relatives are on the maternal side of the family you suspect that her diabetes and deafness may be due to a mitochondrial DNA defect. You remember a previous talk on this issue at Diabetes UK and consider the following questions:

1. What is mitochondrial DNA disease?
2. Why is mitochondrial DNA disease only transmitted down the maternal line?
3. Is it mitochondrial DNA disease—how do I test for it?
4. Why do patients with mtDNA disease develop diabetes?
5. How should the diabetes be managed?
6. Should other family members be tested?

What is mitochondrial DNA disease?

Mitochondria are found in all nucleated cells, are the principal generators of cellular ATP by oxidative phosphorylation and are the only location of extrachromosomal DNA within the cell. The mitochondrial genome comprises a multicopy, circular dsDNA molecule (16.6 kb in humans), which encodes 13 essential polypeptides of the oxidative phosphorylation system and the necessary RNA machinery (two rRNAs and 22 tRNAs) for their translation within the organelle. The remaining protein subunits that make up the electron-transferring respiratory chain complexes and ATP synthase, together with those required for mitochondrial DNA (mtDNA) maintenance, are nuclear encoded, synthesized on cytoplasmic ribosomes and specifically targeted and sorted to their correct location. Consequently, ATP synthesis is under the dual genetic control of both the nuclear and mitochondrial genomes.

Pathogenic mtDNA mutations are common causes of genetic disease and, although it is difficult to determine accurately the true incidence of patients with mtDNA disease, recent estimates suggest at least in 1 in 6500 is affected by mtDNA disease, with at least as many asymptomatic carriers and individuals at risk of developing symptoms [1]. The clinical features of patients with mtDNA are notoriously variable, with patients being affected at any age and severity, ranging from a mild eye movement disturbance in late life to fatal lactic acidosis in childhood [2].

It is important to realize that diabetes is extremely common in these patients. Diabetes may be the only presenting symptom, but frequently manifests in association with deafness—the so called MIDD syndrome (maternally inherited diabetes and deafness) [3]. In some patients, the diabetes may also be associated with other clinical features prominent in mitochondrial disease, such as myopathy or cardiomyopathy.

Why is mitochondrial DNA disease only transmitted down the maternal line?

Mitochondria are present at high numbers in the oocytes, whereas there are relatively few mitochondria in sperm; these tend to be lost during the process of fertilization or eliminated. Thus the assumption is that the mitochondrial genome is strictly transmitted through the maternal line [4] and that mtDNA lineages are therefore clonal. The recent identification of a patient harbouring paternal mtDNA in muscle has challenged this model [5], but subsequent studies of other patients with mitochondrial myopathies have not shown any evidence of paternal transmission [6,7], even when assisted reproduction techniques were applied [8]. From a clinical genetic perspective we believe that advice should be clear, i.e. mitochondrial DNA disease is maternally transmitted and therefore all maternally related family members are at risk of developing disease.

Is it mitochondrial DNA disease?

The investigation of patients with possible mtDNA disease should be relatively straightforward—after all, the genome is

tiny and is transmitted only down the maternal line. In spite of this, the diagnosis of mtDNA disease is made difficult by several characteristics unique to mitochondrial genetics, including the presence of multiple copies of mtDNA (polyploidy) in individual organelles and cells. Homoplasmy describes the situation when all copies of the mitochondrial genome within a cell are identical, and heteroplasmy when there is a mixture of two or more mitochondrial genotypes. The value of these terms is apparent when we consider mtDNA mutations that lead to disease. Some mutations appear to affect all copies of the mitochondrial genome, whereas the overwhelming majority of pathogenic mutations are present only in a subset of mtDNA copies and are termed heteroplasmic. In the presence of heteroplasmy, there is a threshold level of mutation load that is important for the expression of a respiratory chain defect and hence disease symptoms. The level of heteroplasmy can vary markedly between tissues in an individual, complicating the investigation and diagnosis of mtDNA disease.

The situation is further complicated because not all maternally transmitted diabetes is due to mtDNA defects. We conducted a comprehensive search for mtDNA mutations by sequencing the entire mitochondrial genome in patients with maternally inherited diabetes [9]. Importantly, we detected mtDNA mutations only in those patients with maternally inherited diabetes plus other features of mitochondrial disease (e.g. sensory neural deafness, myopathy) in the patient or other family members. Patients that satisfy these criteria are highly likely to carry an mtDNA mutation and should be considered for further investigation.

The most common pathogenic mtDNA mutation causing diabetes is the 3243A→G *MTTL1* gene mutation which is associated with both the MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) [10] and MIDD [3] phenotypes. This mutation has been reported to be the cause of between 0.1 and 1% of hospital patients with diabetes, although this number is very dependent on both populations and clinical screening for associated features [11,12]. Despite affected tissues demonstrating high mutant loads, the level of the 3243A→G mutation may be very low or even absent in blood with longitudinal studies showing the level to decrease over time, presumably due to positive selection against cells harbouring high mutant loads [13]. In addition to testing for the mutation in a blood sample, we recommend that a urine sample should also be collected to isolate the urinary epithelial cells and that routine testing for the 3243A→G mutation be performed in this tissue [14,15]. If this test is negative, then mutation screening should be extended to other mtDNA mutations, but only if there is strong evidence of mtDNA disease. Several different mtDNA point mutations and mtDNA rearrangements have been documented in patients with diabetes, so knowing which mutation to screen first is a further hurdle. If the clinical features are predominantly diabetes and myopathy, we would advocate screening the sample for the 14709T→C *MTTE* gene mutation [16]. If this is negative, then it would be worth seeking advice from a diagnostic centre with a major interest in mtDNA disease. Our strategy would be to consider seeking further evidence of mtDNA disease such as cytochrome *c* oxidase (COX)-deficient muscle fibres on a needle muscle biopsy followed by direct sequencing of the mitochondrial genome if clinical suspicion is strong [17].

This patient (and all maternal family members) has the 3243A→G MELAS mutation which is present at > 70% mutant loads in urinary epithelial cells from affected family members.

Why do patients with mtDNA disease develop diabetes?

The generation of ATP by the mitochondria within the pancreatic β-cell is a key step in coupled glucose-stimulated insulin secretion. Substrate oxidation within the mitochondria generates ATP, and it is the increased ATP to ADP ratio within the β-cell that leads to closure of the K^+ ATP channel, the depolarization of the cell membrane and the ultimate secretion of insulin.

It is assumed that comparable mechanisms contribute to the development of impaired insulin secretion and diabetes in patients with mitochondrial DNA mutations. As in other tissues, once the level of heteroplasmy for the mtDNA mutation in the β-cells exceeds a given threshold there will be impairment of respiratory chain function and decreased insulin secretion. We recently measured the levels of heteroplasmy in individual β-cells and whole islets from post mortem tissue from a patient who had mitochondrial diabetes due to the 3243A→G mutation [18]. Surprisingly, we found comparatively low levels of heteroplasmy within the β-cells, certainly well below the threshold for impaired respiratory chain function in other tissues. We also found that the islets overall were smaller than those in healthy non-diabetic subjects, in keeping with a decreased β-cell mass. This led us to conclude that either the threshold for impaired respiratory chain function and decreased insulin secretion is particularly low in β-cells, or those cells with a high mutant load are removed, leading to decreased β-cell mass and insulin secretion.

Our understanding of the situation might be helped by the observations made using a mouse model of mitochondrial diabetes [19]. The investigators found that when the mice first developed diabetes, the key defect in the β-cells was an impairment of stimulus-secretion coupling from otherwise normal sized islets. However, as the animals aged, there was a loss of β-cells with markedly impaired respiratory function which led to a decreased β-cell mass and worsening of the diabetes. Thus, current knowledge from human and animal-based studies would suggest that the decreased insulin secretion in mitochondrial diabetes is likely to result from a combination of mechanisms that include decreased coupled insulin secretion and decreased β-cell mass.

There is currently great interest in the potential role of impaired mitochondrial function in the development of insulin resistance [20]. However, clinical experience and evidence from a limited number of clinical studies suggest that patients with the 3243A→G mutation and diabetes tend to have normal or increased sensitivity to the action of insulin.

How should the diabetes be managed?

Patients can present as a classical case of Type 2 diabetes, or as a Type 1 diabetic patient requiring immediate insulin therapy. However, autoimmune markers (islets cell antibodies and GAD) are almost always negative. In the case of MIDD, due to the 3243A→G mutation, deafness precedes the development of diabetes, which most commonly develops during middle age. Patients presenting with Type 2 diabetes are managed in the standard way through a combination of lifestyle modification and oral hypoglycaemic therapy as required. Most patients respond well to sulphonylurea therapy, reflecting the fact that impaired β-cell function rather than insulin resistance is the major defect. As a general rule, metformin should be avoided because of the risk of exacerbating lactic acidosis, although we have used it successfully and safely for over 10 years in an obese patient whose mitochondrial disease is limited to MIDD. For those patients that require insulin therapy at diagnosis or after tablet failure, standard insulin regimes can be used to suit individual needs. Patients are at risk of large and small vessel diabetic complications and therefore require the usual high standards of diabetes care and risk factor management.

Should other family members be tested?

There is very little information to guide the clinician in this area. In families with inherited disease there is a balance between confidentiality and concern about a diagnosis vs. the early detection of preventable complications. In our experience of this family and others, the family is only too aware that there is 'something running in the family' and are keen to reach a diagnosis. Disappointingly, there is no specific treatment for mtDNA disease but, especially for patients with the 3243A→G mutation, careful follow-up is helpful. Many of the clinical features associated with this syndrome, such as deafness, diabetes and migraine, are common in the general population and should be treated appropriately. Deafness may be marked, but many patients do extremely well with a digital hearing aid. The deafness is usually most marked at high frequency and the hearing aid will need programming to ensure optimum hearing is obtained. In some patients the hearing loss is very profound and cochlear implants are required. Migraine is a common feature in these patients and may be associated with stroke-like episodes. Active therapy of the migraine attacks is important and prophylactic therapy to prevent attacks may be appropriate if the attacks are frequent. Cardiomyopathy is an important cause of death in these patients and all patients should have ECG and echocardiographs once a year to detect rhythm disturbances or cardiac hypertrophy. If evident, we recommend involvement of an experienced cardiologist at an early stage.

Competing interests

None declared.

References

1 Schaefer AM, Taylor RW, Turnbull DM, Chinnery PF. The epidemiology of mitochondrial disorders—past, present and future. *Biochim Biophys Acta* 2004; **1659**: 115–120.

2 Taylor RW, Turnbull DM. Mitochondrial DNA mutations in human disease. *Nat Rev Genet* 2005; **6**: 389–402.

3 van den Ouweland JWM, Lemkes HHPJ, Ruitenbeek K. Mutation in mitochondrial $tRNA^{Leu(UUR)}$ gene in a large pedigree with maternally transmitted type II diabetes mellitus and deafness. *Nat Genet* 1992; **1**: 368–371.

4 Giles RE, Blanc H, Cann HM, Wallace DC. Maternal inheritance of human mitochondrial DNA. *Proc Natl Acad Sci USA* 1980; **77**: 6715–6719.

5 Schwartz M, Vissing J. Paternal inheritance of mitochondrial DNA. *N Engl J Med* 2002; **347**: 576–580.

6 Filosto M, Mancuso M, Vives-Bauza C, Vila MR, Shanske S, Hirano M *et al.* Lack of paternal inheritance of muscle mitochondrial DNA in sporadic mitochondrial myopathies. *Ann Neurol* 2003; **54**: 524–526.

7 Taylor RW, McDonnell MT, Blakely EL, Chinnery PF, Taylor GA, Howell N *et al.* Genotypes from patients indicate no paternal mitochondrial DNA contribution. *Ann Neurol* 2003; **54**: 521–524.

8 Marchington DR, Scott Brown MS, Lamb VK, van Golde RJ, Kremer JA, Tuerlings JH *et al.* No evidence for paternal mtDNA transmission to offspring or extra-embryonic tissues after ICSI. *Mol Hum Reprod* 2002; **8**: 1046–1049.

9 Choo-Kang AT, Lynn S, Taylor GA, Daly ME, Sihota SS, Wardell TM *et al.* Defining the importance of mitochondrial gene defects in maternally inherited diabetes by sequencing the entire mitochondrial genome. *Diabetes* 2002; **51**: 2317–2320.

10 Goto Y, Nonaka I, Horai S. A mutation in the tRNA(Leu)(UUR) gene associated with the MELAS subgroup of mitochondrial encephalomyopathies. *Nature* 1990; **348**: 651–653.

11 Newkirk JE, Taylor RW, Howell N, Bindoff LA, Chinnery PF, Alberti KG *et al.* Maternally inherited diabetes and deafness: prevalence in a hospital diabetic population. *Diabet Med* 1997; **14**: 457–460.

12 Odawara M, Sasaki K, Yamashita K. Prevalence and clinical characterisation of Japanese diabetes mellitus with an A-to-G mutation at nucleotide 3243 of the mitochondrial $tRNA^{Leu(UUR)}$ gene. *J Clin Endocrinol Metab* 1995; **80**: 1290–1294.

13 Rahman S, Poulton J, Marchington D, Suomalainen A. Decrease of 3243A→G mtDNA mutation from blood in MELAS syndrome: a longitudinal study. *Am J Hum Genet* 2001; **68**: 238–240.

14 Shanske S, Pancrudo J, Kaufmann P, Engelstod K, Jhung S, Lu J *et al.* Varying loads of the mitochondrial DNA A3243G mutation in different tissues: implications for diagnosis. *Am J Med Genet* 2004; **130A**: 134–137.

15 McDonnell MT, Schaefer AM, Blakely EL, McFarland R, Chinnery PF, Turnbull DM, Taylor RW *et al.* Noninvasive diagnosis of the 3243A>G mitochondrial DNA mutation using urinary epithelial cells. *Eur J Hum Genet* 2004; **12**: 778–781.

16 McFarland R, Schaefer AM, Gardner JL, Lynn S, Hayes CM, Barron MJ *et al.* Familial myopathy: new insights into the T14709C mitochondrial tRNA mutation. *Ann Neurol* 2004; **55**: 478–484.

17 Taylor RW, Schaefer AM, Barron MJ, McFarland R, Turnbull DM. The diagnosis of mitochondrial muscle disease. *Neuromuscul Disord* 2004; **14**: 237–245.

18 Lynn S, Borthwick GM, Charnley RM, Walker M, Turnbull DM. Heteroplasmic ratio of the A3243G mitochondrial DNA mutation in single pancreatic beta cells. *Diabetologia* 2003; **46**: 296–299.

19 Silva JP, Kohler M, Graff C, Oldfors A, Magnuson MA, Berggren PO, Larsson NG. Impaired insulin secretion and beta-cell loss in tissue-specific knockout mice with mitochondrial diabetes. *Nat Genet* 2000; **26**: 336–340.

20 Lowell BB, Shulman GI. Mitochondrial dysfunction and type 2 diabetes. *Science* 2005; **307**: 384–387.

CLINICAL PRACTICE QUESTION

Management of diabetes during Ramadan

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Please consider the following case scenario

A 45-year-old male Moslem patient attends your clinic. He has Type 2 diabetes treated with twice daily premixed insulin and also takes metformin 500 mg after each meal. His glycaemic control is suboptimal, HbA_{1c} being 8.4%. He is overweight and has hypertension, but no other diabetes-related complications. He reminds you that the holy month of Ramadan will begin shortly and asks your advice regarding appropriate adjustments to his treatment while he is fasting.

His 41-year-old wife, who has accompanied him to clinic, also has Type 2 diabetes; she takes gliclazide 80 mg twice daily and rosiglitazone 4 mg once daily. She too seeks your advice regarding management of diabetes during Ramadan.

- What advice should you give to this couple?
- What factors need to be taken into consideration before offering advice?
- What evidence is available to guide management?
- Are there any circumstances in which you should modify your advice?

Background

The holy month of Ramadan is one of the most important events in the Islamic calendar. Individuals are required to observe a total fast (i.e. taking in neither solids nor fluids) during the hours of daylight for 1 month. The precise dates for commencement and completion are defined by observations of the moon; this year (2005), Ramadan will begin on about 4 October. Because Ramadan is defined by the lunar calendar it falls a little earlier each year and may therefore take place during any season. The end of Ramadan is celebrated with the feast of Eid-al-Fitr. In most countries the maximum daily duration of fasting is about 18 h, depending on the season and distance from the equator.

The prevalence of diabetes is high in many Moslem countries, and correspondingly so among Moslems living in the west. Thus in the UK, especially in urban areas with large Moslem communities, issues surrounding the management of diabetes during Ramadan are increasingly pertinent.

What factors need to be taken into consideration before offering advice?

There has been considerable debate over the past three decades as to whether fasting at all is safe for Moslems with diabetes, with conflicting and sometimes rather didactic views put forward [1–10], often unsupported by any evidence base. As a result, many people do not seek medical advice, fearing that this will be unfavourable: they may expect to be discouraged from fasting or to take precautions such as increasing blood glucose monitoring or applying additional dietary restraint. A reduction in diabetic clinic attendances during Ramadan is also recognized, though not only for these reasons [11].

It is prudent therefore to assume that the patient seeking advice intends to fast unless presented with overwhelming evidence against so doing. Professional support and guidance, even when fasting may be inadvisable, will always be safer than covert fasting against advice. In practice, serious hazard to diabetic patients from fasting during Ramadan appears to be extremely rare, although potential problems include dehydration, hyperglycaemic and hypoglycaemic crises, and retinal vein occlusion [11,12]. Hospitalization rates have usually been said not to rise, although the largest observational study to date did report an increase in hypoglycaemic episodes requiring hospital admission [13].

It is a common aim of diabetes management to achieve blood glucose concentrations as near normal as is compatible with the avoidance of hypoglycaemia. This should remain true during Ramadan. In the absence of specific advice, priority understandably tends to be given to avoidance of (daytime) hypoglycaemia; this is particularly undesirable during Ramadan as its occurrence will necessitate breaking the fast for that day. Some indication of diurnal patterns of glycaemic control, which may be available from home blood monitoring records, is therefore valuable.

It is important to establish the patient's usual pattern of activity during Ramadan. Most individuals will take breakfast before dawn and will dine after dusk; some will have a light snack or meal at dusk to end their fast, especially if Ramadan falls during the winter period, with a later evening meal. Most people in employment continue to work as usual, although the working day may be shortened [11,14]. Some may return to bed for part of the daylight fasting period; occasionally a pattern analogous to that of night workers prevails.

The size of the predawn and postdusk meals often increases to compensate for the omission of the midday meal, although this varies between individuals. Although Ramadan is intended to be a time for abstention and spiritual contemplation, a pattern of 'malfasting' is recognized featuring a cluster of unhealthy behaviours which tend to favour hyperglycaemia [2,14,15]. These include a more sedentary habit, altered sleep pattern and compensatory overeating/gorging at the permitted meals between dusk and dawn.

What evidence is available to guide management?

Interest in this subject has grown in recent years, particularly in countries with predominantly Moslem populations. Guidance derived from a review of published data is available [6] and a number of studies have evaluated the safety of oral hypoglycaemic agents and insulins. Some of these have suffered from methodological problems and few include data from western Moslem communities. Nonetheless, results have been largely reassuring, despite some evidence of unrecognized mild hypoglycaemia [7,16].

While there are case reports of adverse health effects of fasting during Ramadan, there is some evidence that where malfasting behaviours are avoided, beneficial effects on glycaemic control can be achieved. Most studies have in fact reported little overall change in glycaemic control when assessed by HbA_{1c} or fructosamine [4,8,9,16], while there are conflicting data regarding weight change and lipids [6,8,15,17], with some evidence that there may be differences between diabetic and non-diabetic individuals.

That less may in fact change during Ramadan than was previously believed is suggested by evidence from a recent observational study of over 12 000 subjects [13]. At least half of these reported no change in hypoglycaemic medications or doses, physical activity, sleep duration, or overall intake of food and fluids. Where changes were made in patients with Type 2 diabetes, severe hypoglycaemic episodes were associated with adjustments in therapy and physical activity. Meanwhile, severe hyperglycaemia was related to changes in food (especially sugar) intake.

A number of smaller observational studies have given support to the emerging view that for most people with Type 2 diabetes fasting during Ramadan is safe [7,8,15]. Earlier injunctions that all diabetic patients should refrain from fasting have more recently been replaced by advice only that those with Type 1 diabetes should not fast, although even this can be challenged [4]. Since many people will choose to fast regardless of medical advice, clinicians must be prepared to offer constructive support and to advise rather on how best to fast than whether to fast.

A general set of pragmatic rules can be proposed (see Table 1):

- Drugs (including insulin) taken at mealtimes should be omitted where the relevant meal is not taken.
- Drugs with a low propensity for hypoglycaemia can be continued otherwise unchanged.
- Drugs with potential to induce hypoglycaemia should be used with appropriate adjustment to dose and/or timing.

Hence it will often be appropriate to reduce a morning dose of premixed insulin but to increase the evening dose; sometimes usual doses can simply be reversed. It is usually prudent to advise increased blood glucose monitoring. This can be particularly difficult to implement in Ramadan as many people are reluctant to perform capillary testing while fasting [4].

Table 1 Recommended modification to hypoglycaemic therapy during Ramadan (references cited where published evidence is available)

(a) Drugs likely to require dose or timing change:
Insulins
Premixed human insulins
Human soluble insulin
Human isophane/NPH insulin (if taken at other than bedtime)
Oral hypoglycaemic agents
Long-acting sulphonylureas (glibenclamide [19], glimepiride [10], chlorpropamide)
(b) Drugs unlikely to require adjustment (other than omission where the relevant meal is not taken):
Insulins
Rapid-acting analogue insulins [20,21]
?Premixed analogue insulins [22]
Long-acting insulin analogues
Bedtime isophane/NPH insulin
Oral hypoglycaemic agents
Short-acting sulphonylureas (including tolbutamide, glipizide; probably gliclazide if taken in two equal doses)
Meglitinide analogues (repaglinide [9,23], nateglinide)
Metformin
α-glucosidase inhibitors (acarbose)
Thiazolidinediones (pioglitazone and rosiglitazone)

Are there any circumstances in which you should modify your advice?

Children (under the age of 12 years) are not required to fast during Ramadan, although there are reports of young people participating successfully in the fast [16]. Exemption is also made for ill health and pregnancy. Nonetheless, many people make strenuous efforts to observe the fast despite the potential for exemption.

Women with diet-treated diabetes in pregnancy (gestational or pregestational) who are otherwise healthy can probably be permitted to fast, although the risk of ketosis may be increased [18]. The pragmatic policy in my department is to dissuade all pregnant women taking insulin from attempting to observe the fast. There is very little evidence to guide clinicians here and the prevailing view is one of caution [6].

Those with acute illness may need to interrupt their fast for only a few days; people unable to fast during Ramadan are permitted to make up fasting days at another time.

Increasing interest in this area is resulting in the emergence of a growing body of data, all pointing towards a relaxation in strictures against fasting and providing useful guidance in the safer use of hypoglycaemic therapies during Ramadan. There remain very few published reports from western countries with immigrant Moslem populations, where incongruity in language, culture and religion between patients and health professionals will often present additional challenges.

Key points

- Most Moslems will wish to fast during Ramadan and clinicians need to be prepared to provide appropriate support.

• Simple pragmatic advice can be given, based on knowledge of the action of the different drug therapies.
• This advice should be tailored according to individual patients' customs.
• Ramadan fasting for most patients with diabetes is probably safe.
• There is as yet limited high-quality systematic research in this area, with little relating directly to Moslems living in western countries.

Competing interests

None to declare.

References

1 Barber SG, Fairweather S, Wright AD, Fitzgerald MG, Malins JM. Muslims, Ramadan and diabetes mellitus. *BMJ* 1979; **ii**: 46–47 (Letter).
2 Sulimani RA, Famuyiwa FO, Laajam MA. Diabetes mellitus and Ramadan fasting: the need for a critical appraisal. *Diabet Med* 1988; **5**: 589–591.
3 Rashed AH. The fast of Ramadan. *BMJ* 1992; **304**: 521–522.
4 Ahmed AF, Saleem Y, Abuaisha H. Ramadan fasting and insulin-dependent diabetes mellitus: effect on clinical and biochemical control. *Int Diab Digest* 1993; **4**: 88–89.
5 Omar MAK, Motala AA. Fasting in Ramadan and the diabetic patient. *Diabetes Care* 1997; **20**: 1925–26 (Letter).
6 Azizi F, Siahkolah B. Ramadan fasting and diabetes mellitus. *Int J Ramadan Fasting Res* 1998; **2**: 8–17.
7 Uysal AR, Erdogan MF, Sahin G, Kamel N, Erdogan G. Clinical and metabolic effects of fasting in 41 type 2 diabetic patients during Ramadan. *Diabetes Care* 1998; **21**: 2033–34 (Letter).
8 Yarahmadi S, Larijani B, Bastanhagh MH, Pajouhi M, Baradar Jalili R, Zahedi F *et al.* Metabolic and clinical effects of Ramadan fasting in patients with type II diabetes. *J Coll Physicians Surg Pak* 2003; **13**: 329–332.
9 Sari R, Balci MK, Akbas SH, Avci B. The effects of diet, sulphonylurea and repaglinide therapy on clinical and metabolic parameters in type 2 diabetic patients during Ramadan. *Endocr Res* 2004; **30**: 169–177.
10 The Glimepiride in Ramadan (GLIRA) Study Group. The efficacy and safety of glimepiride in the management of type 2 diabetes in Muslim patients during Ramadan. *Diabetes Care* 2005; **28**: 421–422.
11 Davidson JC. Muslims, Ramadan and diabetes mellitus. *BMJ* 1979; **ii**: 1511–1512 (Letter).
12 Alghadyan AA. Retinal vein occlusion in Saudi Arabia: possible role of dehydration. *Ann Ophthalmol* 1993; **25**: 394–398.
13 Salti I, Bénard E, Detournay B, Bianchi-Biscay M, Le Brigand C, Voinet C *et al.* A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the Epidemiology of Diabetes and Ramadan 1422/2001 (EPIDIAR) study. *Diabetes Care* 2004; **27**: 2306–2311.
14 Khatib FA, Shafagoj YA. Metabolic alterations as a result of Ramadan fasting in non-insulin-dependent diabetes mellitus patients in relation to food intake. *Saudi Med J* 2004; **25**: 1858–1863.
15 Laajam MA. Ramadan fasting and non-insulin-dependent diabetes: effect on metabolic control. *East Afr Med J* 1990; **67**: 732–736.
16 Salman H, Abdallah MA, Abanamy MA, Al Howasi M. Ramadan fasting in diabetic children in Riyadh. *Diabet Med* 1992; **9**: 583–584 (Letter).
17 Akanji AO, Mojiminiyi OA, Abdella N. Beneficial changes in serum apo A-1 and its ratio to apo B and HDL in stable hyperlipidaemic subjects after Ramadan fasting in Kuwait. *Eur J Clin Nutr* 2000; **54**: 508–513.
18 Felig P, Lynch V. Starvation in human pregnancy: hypoglycaemia, hypoinsulinaemia and hyperketonaemia. *Science* 1970; **170**: 990–992.
19 Belkhadir J, El Ghomari H, Klöcker N, Mikou A, Nasciri M, Sabri M. Muslims with non-insulin dependent diabetes fasting during Ramadan: treatment with glibenclamide. *BMJ* 1993; **307**: 292–295.
20 Akram J, De Verga V and the Ramadan Study Group. Insulin lispro (Lys(B28), Pro(B29)) in the treatment of diabetes during the fasting month of Ramadan. *Diabet Med* 1999; **16**: 861–866.
21 Kadiri A, Al Nakhi A, El Ghazali S, Jabbar A, Al Arouj M, Akram J *et al.* Treatment of type 1 diabetes with insulin lispro during Ramadan. *Diabetes Metab* 2001; **27**: 482–486.
22 Mattoo V, Milicevic Z, Malone JK, Schwarzenhofer M, Ekangaki A, Levitt LK *et al.* A comparison of insulin lispro Mix25 and human insulin 30/70 in the treatment of type 2 diabetes during Ramadan. *Diabetes Res Clin Pract* 2003; **59**: 137–143.
23 Mafauzy M. Repaglinide versus glibenclamide treatment of type 2 diabetes during Ramadan fasting. *Diab Res Clin Pract* 2002; **58**: 45–53.

HORIZONS

New options for drug treatment of obesity in patients with Type 2 diabetes

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Consider the following case scenario

Your patient is 56 years old, and has had Type 2 diabetes for 4 years. He takes metformin 850 mg thrice daily, gliclazide 160 mg twice daily, and lisinopril 10 mg per day for hypertension. Glycaemic control has deteriorated over the past 6 months, with fasting blood glucose between 10 and 15 mmol/l. He is thirsty much of the time, and passes urine frequently. Although he is generally fit, the patient complains that he has been very tired recently. He is a non-smoker and drinks only modest amounts of alcohol. HbA_{1c} is 10.5%, indicating very poor glycaemic control. There are no diabetic complications, although microalbuminuria has been noted intermittently during the past 2 years. He has had a weight problem since his early 20s, and is now heavier than he has ever been—body mass index (BMI) is 31.4 kg/m^2. He is aware of the need

for tight glycaemic control but would really like to avoid insulin treatment if possible, particularly since he knows that his weight would almost certainly increase.

He would like to know if there are any drugs that might help him lose weight and thus avoid having to go on to insulin:

- What drugs are available? What benefits should he expect and what side-effects should he be warned about?
- If he receives drug treatment to help him lose weight, how should his diabetes be managed?
- He has heard about a new drug, rimonabant, that is being tested and would like to know whether this is likely to be suitable for him?

Background

The number of obese individuals in the world is projected to increase to 300 million by 2025. Currently, 50% of the European population is overweight or obese, and 30% is obese. There is an intimate relationship between body weight and diabetes risk. For every kg increase in body weight above the recommended range, the relative risk of developing diabetes increases by 9%. Weight loss and weight management are important measures to prevent diabetes and to improve control of hyperglycaemia and other risk factors in those who have diabetes. Lifestyle management (diet and exercise) is always the first step and the mainstay of any regimen. However, used alone these measures are often disappointing. Drug therapy to help with weight loss has a place in patients who are at high risk. Orlistat and sibutramine are currently the most widely studied and used drugs and their use can undoubtedly lead to modest weight loss and improvement of metabolic parameters [1]. The range of available drugs is increasing, and this will heighten debate about the relative merits and indications for each therapy.

Orlistat

Orlistat is a gastrointestinal lipase inhibitor that decreases digestion and absorption of fat from the gut by about 30%. Its use in many patients is limited by gastrointestinal side-effects but it is a very safe drug. Use up to 4 years has now been reported [2], and in this large cohort of patients at high risk of diabetes, decreased incidence of new diabetes (6.2% vs. 9.0% with placebo) was reported in association with modest weight loss. It is possible that orlistat has benefits beyond those of weight loss—decreased free fatty acid levels and improved insulin sensitivity have been reported recently [3], and there is a suggestion that incretin levels are increased after feeding when orlistat is used. In a meta-analysis, Li *et al.* [1] reported the mean weight loss over 12 months' treatment to be 2.89 kg [95% confidence interval (CI) 2.27, 3.51].

Sibutramine

Sibutramine is a centrally acting inhibitor of the uptake of serotonin and noradrenaline. In a review of 29 clinical trials, Arterburn and colleagues [4] reported a mean weight reduction over 12 months of 4.45 kg (95% CI 3.62, 5.29), reinforcing the results from an earlier meta-analysis [5]. There was a modest improvement in lipid profile but, to date, no evidence relating to decreased morbidity or mortality. Reviewing data from eight trials, Vettor *et al.* [6] combined data on 1093 patients with diabetes, 552 of whom were treated with sibutramine. On average, weight deceased by 5.6 kg and waist circumference by 5.3 cm compared with placebo. Weight loss was accompanied by improved blood glucose and HbA_{1c}. Pulse rate and diastolic blood pressure were slightly increased, but there was no difference in systolic pressure. A 12-month randomized trial [7] of sibutramine in metformin-treated patients confirmed that the two drugs could be combined effectively. Decreased leptin and resistin, along with increased adiponectin, have been documented with sibutramine treatment [8]. Sibutramine appears to be safe for medium-term treatment so long as blood pressure is monitored and the drug is not given to patients with heart disease. These considerations, along with recent case reports of memory impairment and cardiomyopathy related to the drug, temper our view about its use for extended periods.

Rimonabant

The appetite-stimulating effect of marijuana (*Cannabis sativa*), and its major active component Δ^9-tetrahydrocannabinol, are well documented. The role of the endogenous cannabinoid system in regulating energy homeostasis has been extensively studied. Administration of endogenous cannabinoids, such as anandamide, to animals increases appetite and food intake. The effects are mediated through G protein-coupled receptors, of which two subtypes (CB1 and CB2) have been described. The central nervous system effects of cannabinoids are mediated through the cannabinoid receptor type 1 (CB1). Mice with genetically disrupted CB1 receptors are hypophagic, and of low body weight [9]. CB1-positive neurones collocate with several other neurone types that may be important in the central regulation of food intake: corticotrophin-releasing hormone-positive neurones in the paraventricular nucleus; neurones positive for the cocaine amphetamine regulated transcript (CART) in the arcuate nucleus; melanin-concentrating hormone (MCH) and orexin-containing neurones in the lateral hypothalamus. Leptin decreases hypothalamic levels of endocannabinoids. Furthermore, the CB1 receptor is expressed in adipocytes and agonists of this receptor stimulate lipogenesis. Administration of a CB1 antagonist to animals enhances adipocyte expression of adiponectin and thus decreases insulin resistance [10]. Animal work also suggests that CB1 blockade leads directly to increased thermogenesis in skeletal muscle [11]. Recent work [12] demonstrates that activation of hepatic CB1 receptors increases expression of transcription factors and key enzymes involved in hepatic lipogenesis. Thus, a variety of central and peripheral action may combine to mediate the effect of CB1 antagonism to decrease food intake and increase energy expenditure.

Initial animal studies with the selective CB1 antagonist rimonabant confirmed its potential as an antiobesity agent. For example, studies in diet-induced obese mice [13] demonstrated that the drug led to hypophagia and decreased circulating levels of insulin, free fatty acids and leptin. Thus, experimental studies in both animals and humans have confirmed the potential of this drug in treating obesity and metabolic syndrome, and in promoting smoking cessation. The very recent publication of the first clinical trial of the drug in overweight and obese patients was therefore most welcome [14]. The RIO (rimonabant in obesity)-Europe trial was a multicentred, randomized, placebo-controlled study involving 1507 men and women who had either a BMI above 30 kg/m^2 or a BMI of > 27 kg/m^2 in association with poorly controlled dyslipidaemia or hypertension. Patients were randomized to receive either placebo, or rimonabant at a dose of either 5 mg or 20 mg per day, and followed up for 1 year. All patients received dietary advice and were asked to adhere to a hypocaloric (600 kcal/day) diet. Patients taking placebo lost an average of 1.8 kg, while those taking 5 mg rimonabant per day lost 3.4 kg, and those taking 20 mg per day lost 6.6 kg. At the higher dose, waist circumference was decreased, and insulin sensitivity improved. The results were highly significant statistically. The most frequent side-effects were mood disturbances, nausea and vomiting, dizziness and anxiety.

A problem with many studies of treatment of obesity is that a considerable proportion of people do not complete treatment, leading to difficulties with interpretation. Only 61% of patients recruited completed the schedule for the RIO-Europe study. Our view of this mode of study should also be tempered by the documented beneficial effects of cannabinoids which have anti-inflammatory and neuroprotective effects and may help prevent or slow progression of conditions such as multiple sclerosis and Parkinson's disease [15].

Management of diabetes and blood pressure

Published evidence on how best to manage diabetes in patients who are using drugs to help with weight loss is surprisingly lacking. For our patient, we would make sure that he had received advice on adherence to a hypocaloric diet, and that he was strongly advised to take regular exercise in a form that suited his physical fitness and preferences. Carrying on with his metformin may expose him to increased risks of gastrointestinal side-effects if he chose to take orlistat, although we have seen patients successfully treated with the combination of the two. Serious consideration should be given to stopping his gliclazide, or at least changing to a shorter-acting insulotropic drug. Two possible approaches to this that might help to withdraw the drug without sacrificing glycaemic control are a short spell of intensive control with insulin prior to withdrawal, and use of a hypocaloric diet that is relatively restricted in carbohydrate. If hypoglycaemic drugs are withdrawn, he may need to intensify monitoring of his diabetes. If realistic goals are set, this can improve compliance with dietary and other measures. Sibutramine is not contraindicated as long as his blood pressure is well controlled and closely monitored for the duration of his treatment.

Other drugs and new drugs

Rimonabant is not yet widely available and, in most countries, the only drugs available for treatment of obesity are orlistat and sibutramine. However, there are drugs in common use that have a favourable effect on food intake and energy balance, although they are not specifically licensed for weight management. Fluoxetine and sertraline are centrally acting serotonin reuptake inhibitors, and have been shown to lead to decreases in body weight equivalent to that achieved by sibutramine [1,16]. The centrally acting sympathomimetic agents phentermine and diethylpropion are no longer available on prescription in the UK, but are still widely used in many countries. Bupropion, widely used to help with smoking cessation, also has beneficial effects in relation to eating behaviour and has been proposed as an agent to help with weight loss [17].

Topiramate is a drug licensed for use in refractory epilepsy in combination with other anticonvulsants, and the drug may have actions peripherally on adipose tissue as well as centrally [18]. Zonisamide is another anticonvulsant drug, used in the treatment of refractory partial seizures, and has been shown to be of benefit in inducing weight loss [1]. A novel pharmacological approach is delaying the rate of gastric emptying, thus reducing food absorption without affecting energy expenditure [19]. Finally, there is a great deal of interest currently in glucagon-like peptide-1 (GLP-1) analogues such as exenatide and liraglutide, and agents that prolong the half-life of incretins by inhibiting the enzyme dipeptidyl peptidase-4 (DPP-4) [20]. The incretins stimulate insulin secretion, delay gastric emptying, induce satiety and may have a role in maintaining β-cell mass.

Practice points

- Increased adiposity is the major risk factor for metabolic syndrome and diabetes and should be considered as the primary treatment goal in many patients.
- Drug therapy to assist with weight loss or weight maintenance should be considered in high-risk patients along with diet and exercise.
- With an effective weight-reducing regimen, consideration should be given to stopping or reducing oral hypoglycaemic drugs, at least on a temporary basis.
- Orlistat and sibutramine, when used according to recommendations, are safe agents and their use is associated with modest weight loss and improved glycaemic control.
- Amongst new approaches to pharmacological treatment of obesity, the CB1 antagonist rimonabant, GLP-1 agonists and DPP-4 inhibitors show particular promise for the management of the overweight patient with diabetes.

Search strategy

We used Medline 1996 to search under the following categories: rimonabant; cannabinoid and obesity; cannabinoid and diabetes; sibutramine; orlistat and diabetes. We used these searches and the recently published Cochrane review (see Further reading) to identify articles of potential relevance. Of the 743 articles identified, 115 were selected for detailed review.

Competing interests

None declared.

References

1 Li Z, Maglione M, Tu W, Mojica W, Arterburn D, Shugarman LR *et al.* Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med* 2005; **142**: 532–546.

2 Torgerson Jarl S, Hauptman J, Boldrin Mark N, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004; **27**: 155–161.

3 Kelley David E, Kuller Lewis H, McKolanis Therese M, Harper P, Mancino J, Kalhan S. Effects of moderate weight loss and orlistat on insulin resistance, regional adiposity, and fatty acids in type 2 diabetes. *Diabetes Care* 2004; **27**: 33–40.

4 Arterburn David E, Crane Paul K, Veenstra David L. The efficacy and safety of sibutramine for weight loss: a systematic review. *Arch Intern Med* 2004; **164**: 994–1003.

5 Kim Su H, Lee Young M, Jee Sun H, Nam Chung M. Effect of sibutramine on weight loss and blood pressure: a meta-analysis of controlled trials. *Obes Res* 2003; **11**: 1116–1123.

6 Vettor R, Serra R, Fabris R, Pagano C, Federspil G. Effect of sibutramine on weight management and metabolic control in type 2 diabetes: a meta-analysis of clinical studies. *Diabetes Care* 2005; **28**: 942–949.

7 McNulty Steven J, Ur E, Williams G. A randomized trial of sibutramine in the management of obese type 2 diabetic patients treated with metformin. *Diabetes Care* 2003; **26**: 125–131.

8 Filippatos TD, Kiortsis DN, Liberopoulos EN, Mikhailidis DP, Elisaf MS. A review of the metabolic effects of sibutramine. *Curr Med Res Opin* 2005; **21**: 457–468.

9 Cota D, Marsicano G, Tschöp M, Grübler Y, Flachskamm C, Schubert M *et al.* The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *J Clin Invest* 2003; **112**: 423–431.

10 Bensaid M, Gary Bobo M, Esclangon A, Maffrand JP, Le Fur G, Oury-Donat F, Soubrié P. The cannabinoid CB1 receptor antagonist SR141716 increases Acrp30 mRNA expression in adipose tissue of obese fa/fa rats and in cultured adipocyte cells. *Mol Pharmacol* 2003; **63**: 908–914.

11 Liu YL, Connoley IP, Wilson CA, Stock MJ. Effects of the cannabinoid CB1 receptor antagonist SR141716 on oxygen consumption and soleus muscle glucose uptake in Lep(ob)/Lep(ob) mice. *Int J Obes Relat Metab Disord* 2005; **29**: 183–187.

12 Osei Hyiaman D, Depetrillo M, Pacher P, Liu J, Rodaeva S, Bátkai S, *et al.* Endocannabinoid activation at hepatic CB(1) receptors stimulates fatty acid synthesis and contributes to diet-induced obesity. *J Clin Invest* 2005; **115**: 1298–1305.

13 Ravinet Trillou C, Arnone M, Delgorge C, Gonalons N, Keane P, Maffrand JP, Soubrié P. Anti-obesity effect of SR141716, a CB1 receptor antagonist, in diet- induced obese mice. *Am J Physiol Regul Integr Comp Physiol* 2003; **284**: R345–R353.

14 Van Gaal Luc F, Rissanen Aila M, Scheen André J, Ziegler O, Rössner S. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet* 2005; **365**: 1389–1397.

15 Klein Thomas W. Cannabinoid-based drugs as anti-inflammatory therapeutics. *Nat Rev Immunol* 2005; **5**: 400–411.

16 Greeno CG, Wing RR. A double-blind, placebo-controlled trial of the effect of fluoxetine on dietary intake in overweight women with and without binge-eating disorder. *Am J Clin Nutr* 1996; **64**: 267–273.

17 Jain AK, Kaplan RA, Gadde KM, Wadden TA, Allison DB, Brewer ER *et al.* Bupropion SR vs. placebo for weight loss in obese patients with depressive symptoms. *Obes Res* 2002; **10**: 1049–1056.

18 Wilkes Jason J, Nelson E, Osborne M, Demarest Keith T, Olefsky Jerrold M. Topiramate is an insulin-sensitizing compound *in vivo* with direct effects on adipocytes in female ZDF rats. *Am J Physiol Endocrinol Metab* 2005; **288**: E617–E624.

19 Ortmann S, Kampe J, Gossel M, Bickel M, Geisen K, Jähne G *et al.* The novel antiobesic HMR1426 reduces food intake without affecting energy expenditure in rats. *Obes Res* 2004; **12**: 1290–1297.

20 Ahrén B, Schmitz O. GLP-1 receptor agonists and DPP-4 inhibitors in the treatment of type 2 diabetes. *Horm Metab Res* 2004; **36**: 11–12.

Further reading

Norris SL, Zhang X, Avenell A, Gregg E, Schmid CH, Lau J. Pharmacotherapy for weight loss in adults with type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2005; **1**: 1469–493X.

Redmon JB, Raatz Susan K, Reck Kristell P, Swanson JE, Kwong CA, Fan Q *et al.* One-year outcome of a combination of weight loss therapies for subjects with type 2 diabetes: a randomized trial. *Diabetes Care* 2003; **26**: 2505–2511.

Redmon JB, Reck Kristell P, Raatz Susan K, Swanson JE, Kwong CA, Ji H *et al.* Two-year outcome of a combination of weight loss therapies for type 2 diabetes. *Diabetes Care* 2005; **28**: 1311–1315.

Halpern A, Mancini Marcio C. Diabesity: are weight loss medications effective? *Treat Endocrinol* 2005; **4**: 65–74.

Porter Julie A, Raebel Marsha A, Conner Douglas A, Lanty FA, Vogel EA, Gay EC, Merenich JA. The Long-term Outcomes of Sibutramine Effectiveness on Weight (LOSE Weight) study: evaluating the role of drug therapy within a weight management program in a group-model health maintenance organization. *Am J Manag Care* 2004; **10**: 369–376.

General description and methods

Aims and editorial philosophy

This section of *Diabetic Medicine* aims to promote good care of people with diabetes by meeting the educational needs of trainee and trained professionals. Its goals are to:

- Respect adult learning principles.
- Report and comment on important changes in the evidence base of diabetes care.
- Explore problems and controversies in care and offer expert solutions when the evidence base is weak.

• Explain scientific concepts and developments that impact on diabetes care.
• Support the readers' development of study skills.
• Promote and report interaction with the readership.
• Be concise.

It aims to be rigorous, always clinically relevant, and to draw on the discipline of evidence-based medicine.

Editorial panel

The contents of the Section are contributed or commissioned by a panel whose members are:
Dr Carol Amery, Leeds; Dr Mark Freeman, Dewsbury; Dr Steve Jackson, Leicester; Dr Marie-France Kong, Leicester; Dr Ian Lawrence, Leicester (Coordinating Editor); Dr Michael Mansfield, Leeds; Dr Eleanor Scott, Leeds.

Publication details

Continuing Education is published three times per annum. Full-text and PDF versions are available to *Diabetic Medicine* subscribers on the *Blackwell Synergy* website (http://www.blackwell-synergy.com). The electronic version of the section provides an electronic link to MedLine and, whenever available, to the full electronic text of any original article cited. An electronic discussion forum will be linked to the website to promote communication between readers (http://www.mediabetes.com).

Contents

Each issue contains some or all of the following types of article:

Editorial. A brief commentary on the contents of the issue and other matters relevant to continuing education and clinical practice in diabetes.

Learning and teaching skills. These commissioned articles on topics related to professional development aim to help readers develop their learning skills.

Clinical practice question. The Editorial Panel commissions an expert to write a short commentary around a difficult situation arising in clinical practice. The article begins with self-assessment questions, and then answers them as far as existing evidence and the experience of the commentator permit. The Editorial Panel invites readers to submit questions and nominate commentators. The electronic discussion forum will, with time, act as a source of topics.

Today's evidence. Members of the Editorial Panel screen the following journals for original articles which, in their opinion, have the potential to change clinical practice:

General journals: *British Medical Journal; Journal of the American Medical Association; The Lancet; New England Journal of Medicine; British Journal of General Practice; Annals of Internal Medicine.*

Specialist journals: *Diabetes; Diabetic Medicine; Diabetes Care; Diabetologia; Journal of Clinical Endocrinology and Metabolism; Circulation; Kidney International; American Journal of Obstetrics and Gynaecology.*

Having identified a paper, the screener scores it for its potential to change practice, originality, importance and strength of evidence. At present, the journals are not second-screened. Six months before an issue is due to be published, all articles identified in the preceding 4 months are ranked. A structured abstract of the highest-ranking article is prepared, prefaced by self-assessment questions, and an expert in the field is commissioned to write a short commentary discussing the article and putting it in the context of the current medical literature, and clinical practice generally. Other articles are cited with a short comment.

Horizons. These articles aim to give a succinct discussion of a new or evolving aspect of basic science that impacts on clinical practice. They are commissioned in response to important biomedical developments.

Correspondence. A resume of any important correspondence, electronic and on paper, may be published.

Citation

For citation purposes, each issue will be regarded as a single article; citations should be in the following format: Continuing Education. *Diabetic Med* 1999; **17**: 000–000.

Communication with the readership

The Editorial Panel hopes to develop two-way interaction with its readership, through;
• The website, electronic discussion forum and use of e-mail.
• Publication of correspondence on previously published material.

Correspondence from readers is welcomed, both electronically on our bulletin board and on paper. Letters should be addressed to: Continuing Education, c/o Diabetic Medicine, 9600 Garsington Road, Oxford OX4 2DQ, UK.
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