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# Prevalence of diabetes and impaired glucose tolerance in adult hypopituitarism on low dose oral hydrocortisone replacement therapy

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## Summary

**OBJECTIVE The conventional dosage of hydrocortisone, used for many years in the management of hypopituitarism (30 mg per day), has now been shown to be more than is physiologically necessary. On this conventional corticosteroid therapy studies have demonstrated an increased prevalence of diabetes and impaired glucose tolerance, which may contribute to the increased vascular morbidity and mortality reported in the condition. In these studies no information is available on oral glucose tolerance test (OGTT) timing in relation to administration of oral steroid and variable hydrocortisone doses were employed.**

**PATIENTS In order to assess glucose tolerance in patients treated with lower, more physiological doses, we performed a 75-g OGTT at least 1 month after hydrocortisone therapy was adjusted to 15 mg at 0800 h and 5 mg at 1700 h in 45 adult onset hypopituitary patients (30 M, 15 F). Mean (± SD) duration of hypopituitarism was 12 ± 10 years, mean age 52 ± 14 years and BMI 29·3 ± 5·1 kg/m$^2$. All were on hydrocortisone, 43 on thyroxine, 31 on sex steroids, 9 on desmopressin and 33 had documented growth hormone deficiency. Hydrocortisone 15 mg was taken at 0800 and the OGTT commenced at 0900.**

**RESULTS Using standard WHO criteria 36 patients (80%) had normal glucose tolerance, 1 (2%) had newly diagnosed diabetes and 8 (18%) had impaired glucose tolerance. Using the recently announced American Diabetes Association criteria for diagnosis 96% had normal glucose tolerance, 2% had diabetes and 2% impaired fasting glucose.**

**CONCLUSION The markedly reduced prevalence of diabetes and impaired glucose tolerance on lower hydrocortisone replacement doses in our series of patients with hypopituitarism, not previously known to be diabetic, is of great interest. This lower prevalence may eventually result in reduced vascular complication rates.**

Impaired glucose tolerance is established as a risk factor for cardiovascular disease (Fuller *et al*., 1980). Hypopituitary patients on conventional corticosteroid replacement therapy have an increased prevalence of impaired glucose tolerance and diabetes when compared to age- and sex-matched controls (Beshyah *et al*., 1994). Recent epidemiological studies suggest that hypopituitary patients have a reduced life expectancy with a doubling of the expected all-cause mortality (Bates *et al*., 1996). Some have suggested this is due predominantly to both cardio- and cerebrovascular disease (Rosen & Bengtsson, 1990), while others suggested the increase in vascular disease to be predominantly cerebrovascular in origin (Bulow *et al*., 1997). The cause of the increased mortality is obscure and it has been suggested that growth hormone deficiency may be involved. Circumstantial evidence suggests that subtle excess glucocorticoid replacement therapy may also play a part. Excessive endogenous or exogenous glucocorticoids impair carbohydrate metabolism (Pupo *et al*., 1966; Howlett *et al*., 1985). In Cushing's syndrome 80% of patients have abnormal glucose tolerance (Plotz *et al*., 1952) and there is increased mortality from cardiovascular disease. Recently, Esteban *et al*. (1991) demonstrated, using stable isotope dilution thermospray liquid chromatography/mass spectrometry methodology, a daily cortisol production rate substantially lower (5·7 mg/m$^2$/day in adults) than reported previously (12–15 mg/m$^2$/day). The latter values had influenced steroid replacement dose regimens until the work of Esteban *et al*. was accepted. Using cortisol day curves and 24-h urinary free cortisol estimates to guide the total daily hydrocortisone dose required to simulate physiology (Howlett, 1997; Peacey *et al*., 1997), 75% of patients required a reduction in their dose, from a mean of 29·5 mg to 20·8 mg. This has been further substantiated on

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**Table 1** Clinical characteristics of the hypopituitary patients

| | Male ($n = 30$) | Female ($n = 15$) |
|---|---|---|
| Number | 30 | 15 |
| Age (range) years | 50 (24–80) | 55 (39–77) |
| BMI (kg/m$^2$) | 29·3 ± 5·1 | 29·2 ± 5·4 |
| Duration hypopituitarism (range) years | 11·9(1–44) | 13 (1–37) |
| Diagnosis | | |
| Idiopathic hypopituitarism | 3 | 0 |
| Craniopharyngioma | 2 | 4 |
| Prolactinoma | 9 | 1 |
| Chromophobe adenoma | 11 | 7 |
| Sheehan's syndrome | 0 | 2 |
| Other[a] | 5 | 1 |
| Treatment | | |
| Surgery (TS/TF)[b] | 22 (13/9) | 12 (8/4) |
| Radiotherapy | 10 | 3 |
| Medical | 9 | 1 |
| Replacement therapy | | |
| Hydrocortisone | 30 | 15 |
| Thyroxine | 28 | 15 |
| Sex steroids | 23 | 8 |
| Desmopressin | 7 | 2 |

[a]1 TSH, secreting adenoma,1 optic nerve glioma, 1 arachnoid cyst, 1 germinoma and 1 post-TB meningitis (5 M), 1 parasellar meningioma (1 F). [b]TS, transsphenoidal; TF, transfrontal.

examining markers of bone remodelling and bone mineral density related to dose of steroid replacement therapy (Peacey *et al*., 1997) in adult hypopituitarism.

Because we now know that conventional hydrocortisone therapy induces mild biochemical hypercortisolism in hypopituitary patients and may contribute to the excess impaired glucose tolerance and diabetes recorded in previous studies possibly influencing vascular morbidity and mortality long-term, the present study was designed to estimate the prevalence of impaired glucose tolerance and previously undiagnosed diabetes mellitus in patients reCENving the lower more physiological regime of 15 mg hydrocortisone with breakfast and 5 mg with evening meal.

## Subjects and methods

### *Subjects*

Hypopituitary patients on hydrocortisone replacement therapy for at least 1 year were identified from our database at the Royal Victoria Hospital Endocrine Clinic. Nine patients previously identified as having diabetes were excluded, as were 9 patients who were too frail to attend. This left 115 patients considered well enough to participate and all were offered the opportunity to attend for a glucose tolerance test (OGTT). Fifty-six patients refused despite repeated personal invitation, 14 could not be contacted and 45 accepted. Patients who refused to attend for the OGTT spanned the entire age range. Travelling distances to our regional centre and full-time employment were cited as reasons for non-participation, although some provided no explanation. Hypopituitarism resulted from pituitary or peripituitary tumours treated surgically, medically and/or with radiotherapy (Table 1). ACTH deficiency had previously been confirmed in 32 patients by insulin hypoglycaemia testing (peak cortisol $< 550$ nmol/l), 5 by standard synacthen test (peak cortisol $< 500$ nmol/l) and in 8 by 0800-h serum cortisol level $< 100$ nmol/l. Hydrocortisone was changed to 15 mg at 0800 h and 5 mg at 1700 h at least 1 month prior to GTT testing. Thirty-three patients had documented severe growth hormone deficiency (GHD) on insulin hypoglycaemia testing with a peak GH level of less than 7 mμ/l. Forty-three patients had concomitant thyroxine replacement, 31 sex steroids and 9 desmopressin. Those with concurrent pituitary deficiencies were on stable replacement therapy and no patient had reCENved growth hormone replacement prior to the study. Clinical and endocrine details of the patients are as shown in Table 1. Seven (5 M/2F) had ischaemic heart disease and four (2 M/2F) had hypertension.

**Table 2** Clinical characteristics of patients with normal glucose tolerance (NGT) and impaired glucose tolerance (IGT) using WHO criteria. One of the 45 patients had previously undiagnosed diabetes and is not included in this table

| | NGT | IGT |
|---|---|---|
| *N* | 36 | 8 |
| Mean age (years) | 46 ± 12 | 61 ± 9[a] |
| Sex (M/F) | 25/11 | 4/4 |
| Mean BMI (kg/m$^2$) | 29·4 ± 5·2 | 30·1 ± 3·4 |
| Serum IGF-1 (nmol/l) | 8·5 ± 0·7 | 4·3 ± 0·7[a] |
| Fasting plasma glucose (mmol/l) | 4·1 ± 0·1 | 4·8 ± 0·3[b] |
| 2-h plasma glucose (mmol/l) | 5·6 ± 0·2 | 9·0 ± 0·2[c] |
| $HbA_{1c}$ percentage | 4·5 ± 0·1 | 4·8 ± 0·1 |
| Fasting serum insulin (mU/l) | 8·7 ± 1·2 | 10·6 ± 1·9 |
| Fasting c-peptide (mU/l) | 1·9 ± 0·2 | 3·1 ± 0·9[d] |
| Fasting cholesterol (mmol/l) | 5·6 ± 1·2 | 5·5 ± 0·6 |
| LDL-cholesterol (mmol/l) | 3·8 ± 1·0 | 3·6 ± 0·5 |
| HDL-cholesterol (mmol/l) | 1·0 ± 0·2 | 0·8 ± 0·2 |
| Triglycerides (mmol/l) | 1·8 ± 0·8 | 2·5 ± 0·7[a] |

Data are given as mean ± SEM. [a]$P < 0{\cdot}05$; [b]$P < 0{\cdot}005$; [c]$P < 0{\cdot}0001$; [d]$P < 0{\cdot}01$.

Patients with acromegaly and Cushing's disease were excluded because of the known effect of these diseases on glucose tolerance.

### *Study design*

Patients attended the Metabolic Day Ward of the Royal Victoria Hospital after an overnight fast of 10 h. Hydrocortisone, 15 mg, of was taken at 0800 h along with any other scheduled pituitary replacement therapies. A Venflon was inserted and venous blood taken for estimation of plasma glucose, insulin, c-peptide, lipids, and serum cortisol concentration. At 0900 h a 75-g glucose load was ingested over 2–5 minutes. Plasma glucose, insulin and c-peptide were measured every 30 minutes, and serum cortisol levels were measured hourly. During the test subjects remained seated and did not smoke.

Patients were categorized, using two diagnostic criteria, as having normal glucose tolerance (NGT), impaired glucose tolerance (IGT) or diabetes according to the World Health Organization criteria (World Health Organization, 1980) or normal fasting glucose, impaired fasting glucose or diabetes using the American Diabetes Association criteria (The Expert Committee on the Diagnosis & Classification of Diabetes Mellitus, 1997). Using WHO criteria, IGT is defined as fasting venous plasma glucose levels $< 7{\cdot}8$ mmol/l and 2-h venous plasma glucose levels of 7·8–11·1 mmol/l. With the ADA criteria, normal fasting glucose is defined as a fasting venous plasma glucose $< 6{\cdot}1$ mmol/l, impaired fasting glucose as fasting plasma glucose 6·1–7·0 mmol/l or 2-h values in the OGTT of 7·8–11·1 mmol/l, and diabetes as a fasting plasma glucose $> 7{\cdot}0$ mmol/l or 2-h values in the OGTT $> 11{\cdot}1$ mmol/l. All patients had normal renal and liver function tests on routine screening.

Approval for the studies was obtained from the Research Ethical Committee of the Queen's University of Belfast.

### *Analytical methods*

Plasma samples obtained during the oral glucose tolerance test were analysed for plasma glucose, insulin concentrations and c-peptide at 0, 30, 60, 90 and 120 minutes. Plasma glucose was measured by the dye chemistry method, originally developed by Kodak, using reagents supplied by Johnson & Johnson Clinical Diagnostics, Inc., Rochester, New York, USA. The intra-assay coefficient of variation (CV) was 1·2% at a mean value of 4·9 mmol/l; 1·5% at a mean value of 13·3 mmol/l and 1·2% at a mean value of 17·1 mmol/l. Serum insulin concentration was measured by radioimmunoassay with insulin antibody precipitate (Hales & Randle, 1963), using reagents supplied by Abbott Laboratories (Maidenhead, Berkshire, UK) on an IMX analyser. The interassay CV was 5·2% at a mean value of 7·3 mU/l; 3·8% at a mean value of 16·7 mU/l and 4·1% at a mean value of 58·4 mU/l. Serum c-peptide was measured using reagents supplied by Diagnostic Products Corporation (Los Angeles, USA), using an Immulite analyser. The interassay CV was 6·2% at a mean value of 2·7 μg/l and 3·8% at a mean value of 6·4 μg/l. Serum cortisol was determined by radioimmunoassay, using reagents supplied by Diagnostic Products Corporation (Los Angeles, USA). The interassay CV was 3·5% at a mean value of 234 nmol/l, 3·8% at a mean value of 432 nmol/l and 3·6% at a mean value of 981 nmol/l.

Cholesterol and triglycerides were measured by standard enzymatic techniques on a Kodak Ektuchen analyser. All samples were assayed in a single batch in each case, with an intrassay coefficient of variation of $< 5\%$.

### *Statistical analysis*

The values given in the text are means ± SEM. Comparisons between NGT and IGT patients were calculated using the Mann–Whitney *U*-test for unpaired non-parametric data. Area under the curve during the GTT for glucose, insulin and c-peptide were calculated from the trapezoidal rule for both normoglycaemics and those with impaired glucose tolerance.

## Results

Table 2 indicates the mean age, sex ratio and mean body mass

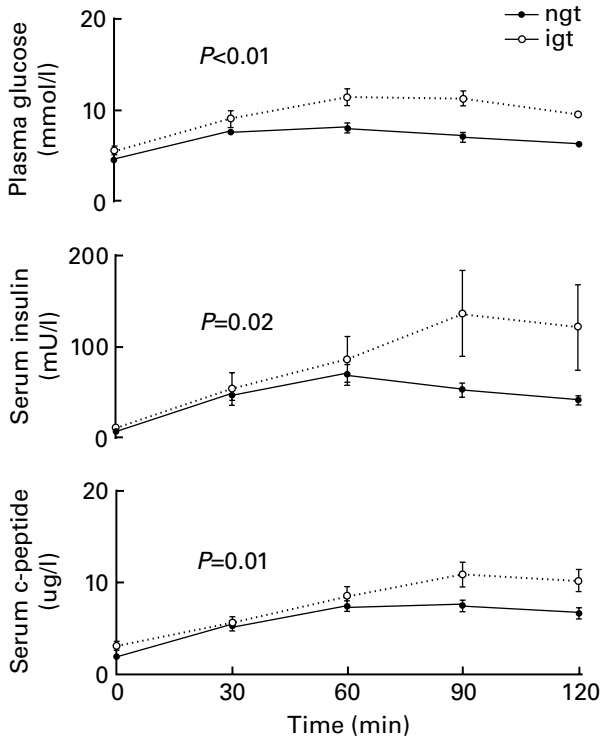


**Fig. 1** Plasma glucose, serum insulin and c-peptide levels during oral glucose tolerance test for hypopituitary patients with normal glucose tolerance (NGT) and impaired glucose tolerance (IGT). *P*-value refers to comparison of areas under dose–response curves.

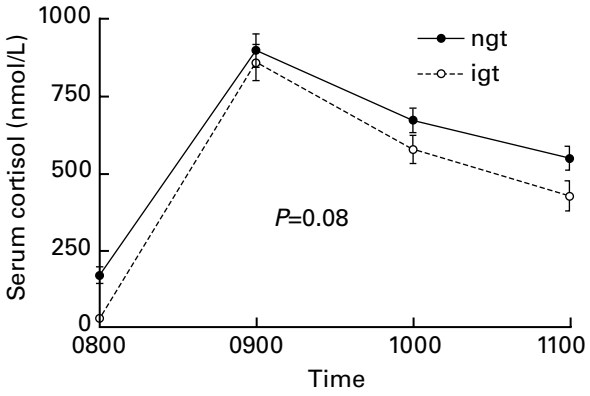


**Fig. 2** Serum cortisol levels during oral glucose tolerance test for hypopituitary patients with normal glucose tolerance (NGT) and impaired glucose tolerance (IGT). *P*-value refers to comparison of areas under dose–response curves.

index together with fasting plasma glucose and plasma glucose concentrations 2 h after the oral glucose tolerance test in 45 subjects. According to the WHO classification, 36 patients (80%) were normoglycaemic, having a 2-h plasma glucose concentration below 7·8 mmol/l, 8 patients (18%) had impaired glucose tolerance, with a 2-h plasma glucose concentration of 7·8–11·0 mmol/l and 1 patient (2%) had previously undiagnosed type 2 diabetes, with a 2-h plasma glucose concentration greater than 11·1 mmol/l. The patient found to have a diabetic OGTT was excluded from further analysis. Using the ADA criteria for fasting glucose, 43 patients (96%) had normal fasting glucose, 1 patient (2%) had impaired fasting glucose and 1 patient (2%) had diabetes. The WHO criteria have been used for further analysis and comparisons.

The subjects with glucose intolerance were older (61 ± 9 *vs.* 46 ± 12 years, $P = 0{\cdot}03$) but had similar BMI and duration of disease as the patients with normal glucose tolerance. Fasting triglycerides were significantly increased in subjects with IGT (2·5 ± 0·7 *vs.* 1·8 ± 0·8 mmol/l, $P = 0{\cdot}02$) and HDL-cholesterol was significantly reduced (0·8 ± 0·2 *vs.* 1·0 ± 0·2 mmol/l, $P = 0{\cdot}02$). Fasting glucose was significantly increased in patients with IGT (4·8 ± 0·3 *vs.* 4·1 ± 0·1 mmol/l, $P < 0{\cdot}005$), and similarly the AUC for glucose was increased during the OGTT (Fig. 1); however, there was no significant difference in haemoglobin $A_{1c}$ (4·8 ± 0·1 *vs.* 4·5 ± 0·1%, $P = 0{\cdot}2$). There was no significant difference in fasting serum insulin (10·6 ± 1·9 *vs.* 8·7 ± 1·2 mU/l) but there was a significant increase in the area under the insulin curve (AUC) during the OGTT (294·3 ± 108·8 *vs.* 136·5 ± 15·0, $P = 0{\cdot}02$) (Fig. 1). Glucose-intolerant patients had a significantly higher fasting c-peptide (3·1 ± 0·3 *vs.* 1·9 ± 0·2 μg/l, $P < 0{\cdot}01$) and a correspondingly greater AUC (Fig. 1) during the OGTT (25·7 ± 3·0 *vs.* 18·5 ± 1·1, $P < 0{\cdot}05$). There was no significant difference between IGT and NGT in the AUC (Fig. 2) for serum cortisol concentrations during the OGTT (1100·5 ± 56·5 *vs.* 1429·8 ± 68·3 nmol/l, $P = 0{\cdot}08$).

## Discussion

It is important to determine glucose tolerance in hypopituitary patients for the following reasons. Studies of groups of individuals with IGT have shown an increased prevalence of atherosclerotic disease (Burchfiel *et al*., 1990) and association with other known cardiovascular risk factors including hypertension, dyslipidaemia and central obesity. The British Heart Study demonstrated a doubling of mortality in subjects with asymptomatic hyperglycaemia (Perry *et al*., 1994). In a Japanese prospective study using WHO criteria, subjects with impaired glucose tolerance had an increased coronary heart disease (CHD) relative risk of 1·9 compared to subjects with normal glucose tolerance (Fujishima *et al*., 1996). Although

few data exist on the association of impaired glucose tolerance and direct measures of atherosclerosis, such as coronary angiography or B-mode ultrasound of the carotid arteries, one Japanese study demonstrated that impaired glucose tolerance was significantly associated with intimal carotid wall thickness (Yamasaki *et al*., 1995). Impaired glucose tolerance may therefore have important prognostic implications.

It was thought originally that patients with growth hormone deficiency were sensitive to insulin with a greater tendency towards hypoglycaemia (Landon *et al*., 1966; Taylor, 1991). Laron (1993), however, demonstrated that long-standing IGF-1 deficiency or GH deficiency leads to a decrease in insulin sensitivity which, in adult GHD patients, may lead to glucose intolerance (Merimee *et al*., 1972). Impaired glucose tolerance (IGT) is associated with the insulin resistance syndrome sometimes known as syndrome X or metabolic syndrome, comprising insulin resistance, compensatory hyperinsulinaemia to maintain glucose homeostasis, obesity (especially abdominal or visceral), dyslipidaemia and hypertension (Reaven, 1988). The present study was designed to examine the prevalence of previously unidentified diabetes and impaired glucose tolerance in adult hypopituitary patients on lower, more physiological hydrocortisone replacement therapy (20 mg daily) compared to previous data derived in groups of patients on higher dose therapy (Beshyah *et al*., 1994).

The percentage of previously undiagnosed diabetes (WHO criteria) (2%) and impaired glucose tolerance (18%) is much lower than that reported previously (11%, 33%, respectively) (Beshyah *et al*., 1994). The latter specifically examined 63 GHD patients rather than ACTH deficient patients. Of this group, only 49 patients were on cortisol replacement. In our study when patients with combined ACTH and growth hormone deficiency ($n = 33$) were examined, according to WHO criteria, 29 patients had normal glucose tolerance (88%), 1 patient had diabetes (3%) and 3 patients had IGT (9%), still considerably lower figures than those of the London study. The prevalence of previously undiagnosed diabetes in Northern Ireland has been reported as 1·4% (Stewart D., 1996), and is probably an underestimation. There is no information available on the prevalence of impaired glucose tolerance in Northern Ireland. We excluded 9 patients from the analysis in whom diabetes was diagnosed previously. Similarly, Beshyah and colleagues (Beshyah *et al*., 1994) also excluded patients known to have diabetes from their analysis, although no comment was made on the number known to have diabetes or the total number of hypopituitary patients from which the original group were selected. The difference in prevalence may be explainable by the fact that more of our patients were noted to have diabetes during routine outpatient appointments, but this seems unlikely. We also imposed strict timing for the replacement therapy to be taken as well as a specific time for the OGTT to begin. In comparison, patients in the previous study (Beshyah *et al*., 1994) took replacement therapy between 0700 and 0800 h with metabolic tests starting between 0830 and 0930 h.

Further evidence that the dose of glucocorticoids is important in hypopituitarism comes from a study by Al-Shoumer *et al*. (1995). They examined glucose tolerance twice in 8 hypopituitary patients separated in time by 1 week, witholding glucocorticoids on one occasion and giving them 1 h before the OGTT on the other. Despite normal fasting glucose, 3 of these 8 patients had impaired glucose tolerance on the glucocorticoid day, only one of whom continued to have this on the non-glucocorticoid day. Post-prandial glucose was significantly higher on the glucocorticoid day as was post-glucose insulinaemia. In contrast, Dunne and colleagues found no significant difference in fasting glucose or HbA1c following a reduction in hydrocortisone from 30 mg to 15 mg over a 3-month period (Dunne *et al*., 1995).

The prevalence of impaired glucose tolerance varies widely between different populations in the same country and between countries. Strong predictors of IGT include age, BMI and race. Our patients were on average older ($52 \pm 14$ *vs.* $48 \pm 13$ years) and more overweight (BMI $29{\cdot}3 \pm 5{\cdot}1$ kg/m$^2$ *vs.* $27{\cdot}8 \pm 4{\cdot}7$ kg/m$^2$) compared to those studied by Beshyah *et al*. This therefore does not explain our results, as increasing age is associated with a higher prevalence of abnormal glucose tolerance (Harris *et al*., 1987; Harris, 1989; Stolk *et al*., 1997) as is increasing Pomi (Modan *et al*., 1986), respectively. Non-parametric tests confirmed that in the present study patients with impaired glucose tolerance were older ($61 \pm 9$ years) than those with normal glucose tolerance ($46 \pm 12$ years), as would have been expected. A control group of subjects matched for age, sex, and body mass index to ascertain the baseline prevalence of diabetes and impaired glucose tolerance in Northern Ireland would have been helpful but was beyond the scope of this pilot study.

Previous studies have yielded conflicting prevalences of IGT in the UK. In one recent study, white people from the UK aged 35–64 years had a prevalence of IGT of 10·7% in males and 9·7% in females (Unwin *et al*., 1997). Earlier Brown *et al*. (1991) had reported a higher level of 21·1% for white males and females from the UK. Our incidence of impaired glucose tolerance by WHO criteria in hypopituitary patients treated with the newer lower conventional doses of hydrocortisone is within the ranges above at 18%. In contrast to the results of Beshyah and colleagues (Beshyah *et al*., 1994), Fisher's exact probability test showed no increase in IGT in females compared with males ($P = 0{\cdot}41$). However, the number of females was small (15 of 44).

Fasting insulin concentrations have been used as a measure of insulin resistance (Reaven, 1983; Matthews *et al*., 1985). In

our study, however, there was no significant difference in fasting serum insulin concentrations between male and female patients with normal glucose tolerance or IGT. There was, however, a significant increase in the AUC for serum insulin during the OGTT in IGT patients. There was also a significant increase in fasting c-peptide and the AUC for c-peptide. Insulin responses to oral glucose reflect pancreatic beta cell function (Saad *et al*., 1988) and the IGT patients would therefore appear to be more insulin-resistant.

Serum cortisol peak at 0900 h, 1 h after 15 mg oral hydrocortisone, is much higher than levels reported in normal control subjects (Weitzman *et al*., 1970; Brandenberger *et al*., 1984) and we cannot exclude that this may still contribute to the development of abnormal glucose tolerance.

When our results are re-analysed using the new ADA criteria, 96% have normal fasting glucose, 2% are diabetic and only 2% have impaired fasting glucose compared to the previous 18% who had IGT by WHO criteria. This would have classified 16% of those who had IGT by WHO criteria as having normal glucose tolerance. It may therefore have prevented us from educating these patients with regard to diet and life-style in an attempt to further reduce cardiovascular mortality.

It would appear in hypopituitary patients that hydrocortisone replacement therapy may have a substantial role to play in the development of diabetes and IGT. In our series the prevalence of diabetes and IGT is clearly less than that seen in previous studies using higher doses. There have been no comparative studies of different steroid regimes in the same group of patients to provide definitive proof, but the present study is clearly suggestive of a trend towards a lower prevalence when lower doses are used. The prevalence of abnormal glucose tolerance on the previous conventional steroid regimen prior to a reduction would have been helpful in providing the necessary proof and this should be tested directly in further experiments. Since hypopituitary patients have a doubling of all cause mortality (Bates *et al*., 1996; Rosen & Bengtsson, 1990; Bulow *et al*., 1997) any factors which may influence this should be addressed. We recommend the routine monitoring of glucose tolerance in patients with hypopituitarism, as it remains a significant problem.

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