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Impaired glucose tolerance and insulin insensitivity in primary hyperparathyroidism

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Summary

OBJECTIVE A high prevalence of diabetes mellitus has been shown in patients with primary hyperparathyroidism (PHPT). However, it is unclear whether this is related to the metabolic abnormalities in PHPT or to the presence of other risk factors for glucose intolerance in these patients. The aim of our study was to determine whether glucose intolerance and insulin insensitivity occur in subjects with PHPT who do not have other risk factors for diabetes mellitus.

DESIGN Cross-sectional study of glucose metabolism in PHPT patients without other risk factors for diabetes mellitus, compared to age and body mass index (BMI) matched healthy subjects.

SUBJECTS Nineteen non-obese, non-diabetic, normotensive patients with PHPT and 11 age and BMI matched healthy subjects.

MEASUREMENTS The continuous infusion of glucose test was used to assess glucose tolerance. Plasma glucose and insulin were measured during a 1-hour continuous infusion of glucose (5 mg/kg ideal body weight/min); insulin sensitivity and beta-cell function were derived from the glucose and insulin data by mathematical modelling. Fasting serum concentrations of parathyroid hormone, ionized calcium and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) were measured in all subjects.

RESULTS PHPT patients attained higher plasma glucose levels at the end of the glucose infusion (median 9·0 (interquartile range 8·1–9·8) mmol/l) than did controls (7·9 (7·1–8·9) mmol/l, $P < 0·05$), and 8 (42%) PHPT patients had impaired glucose tolerance. Insulin sensitivity was lower in PHPT (60·3% (49·8–85·4)) than in controls (113·7% (89·3–149·2), $P < 0·001$); beta-cell function was not different in PHPT subjects. PHPT subjects with impaired glucose tolerance had reduced beta-cell function compared to PHPT subjects with normal glucose tolerance (89·9% (70·5–106·4) *vs* 120% (98·8–156·6) respectively, $P < 0·05$). No significant correlations were found between insulin sensitivity and PTH ($r_s = -0·21$), $1,25(OH)_2D$ ($r_s = -0·14$), ionized calcium ($r_s = -0·11$) and inorganic phosphate ($r_s = 0·34$). Beta-cell function did not correlate with PTH ($r_s = 0·15$), $1,25(OH)_2D$ ($r_s = 0·04$), ionized calcium ($r_s = 0·23$) or inorganic phosphate ($r_s = -0·35$).

CONCLUSION Insulin insensitivity is present in PHPT even in the absence of hypertension and obesity, and may be the cause of glucose intolerance and diabetes. PHPT subjects with reduced beta-cell function are more likely to develop glucose intolerance.

A high prevalence of diabetes mellitus has been reported in patients with primary hyperparathyroidism (PHPT) (Akgun & Ertel, 1978; Bannon *et al.*, 1988; Ljunghall *et al.*, 1983; Levy *et al.*, 1986; Taylor, 1991). Indeed, recent studies indicate that the prevalence rates may be between 8 and 10%, the highest for diabetes mellitus in any endocrine disorder (Taylor, 1991). The reasons for this are unclear; patients with PHPT have been shown to have peripheral insulin resistance and this is reflected in the high insulin concentrations found in these patients (Kautsky-Willer *et al.*, 1992).

It has proved difficult to elucidate the pathophysiological mechanisms involved because of the complex nature of the metabolic changes in PHPT (Kim *et al.*, 1971; Prager *et al.*, 1983; 1990). PHPT usually results from a parathyroid adenoma causing an excess of circulating PTH which produces hypercalcaemia and hypophosphataemia, all of which can independently affect glucose metabolism (Yasuda *et al.*, 1975; Harter *et al.*, 1976; DeFronzo & Lang, 1980; Akmal *et al.*, 1985; Draznin *et al.*, 1988). Chronic excess of both PTH and hypercalcaemia have been shown to reduce pancreatic beta-cell function (Fadda *et al.*, 1990), whilst hypophosphataemia may contribute to insulin insensitivity (DeFronzo & Lang, 1980). Most cases of primary hyperparathyroidism are diagnosed in middle life and there is a high prevalence of hypertension in such patients so that abnormalities in glucose metabolism are likely to be present and discovered by screening (Ljunghall *et al.*, 1983). It is not clear, therefore, whether the high prevalence of diabetes in PHPT is specifically related to the associated abnormalities

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in calcium metabolism, or to other risk factors for glucose intolerance that are frequently present in these patients.

The present study was performed to determine whether abnormalities of glucose metabolism occur in PHPT even in the absence of hypertension, family history of Type 2 diabetes or medication that may adversely affect glucose metabolism, and to relate these changes to parameters of calcium metabolism. In addition, we examined the risk factors for any glucose intolerance in this group of patients.

Methods

Subjects

Nineteen patients with primary hyperparathyroidism diagnosed by the presence of inappropriately high PTH concentrations, high serum ionized calcium and hypercalciuria were included in this study. Eight of these patients subsequently underwent successful parathyroidectomy. Eligibility for this study was restricted to patients without diabetes or hypertension according to the WHO criteria (WHO Expert Committee on Diabetes, 1980), obesity defined as body mass index (BMI) >30 kg/m^2, or family history of diabetes. Patients on medication likely to interfere with glucose metabolism (e.g. beta blockers, thiazide diuretics) were excluded. Eleven healthy subjects matched for age and BMI were also studied. The characteristics of all the subjects studied are shown in Table 1. This study was approved by the Central Manchester Hospitals Trust Ethics Committee and written informed consent which complied with the Declaration of Helsinki was obtained from all subjects studied.

Experimental procedure

All subjects remained on their usual unrestricted diet with at least 50% calories derived from carbohydrate for 3 days before the study. They were then studied recumbent after a minimum fast of 12 hours. A continuous infusion of glucose test (CIGMA) was performed in all subjects (Hosker *et al.*, 1985). One Teflon cannula was inserted in a vein in the dorsum of the hand which was warmed to 50°C using a warm blanket to 'arterialize' blood samples which were drawn from this cannula. Glucose was infused at a low dose (5 mg/kg ideal body weight/min) through a second cannula sited in an antecubital vein. Blood samples were taken at -10, -5, 0 minutes and at 5, 10, 50, 55 and 60 minutes after commencing the glucose infusion. Blood samples were centrifuged and plasma was stored at -20°C until analysis. Glucose, insulin and C-peptide were measured in samples taken before and during the infusion. Ionized calcium, phosphate, creatinine, PTH and 1,25-dihydroxy vitamin D ($1,25(OH)_2D$) were measured only in fasting serum samples.

Analytical methods

Plasma glucose was measured using a glucose oxidase method. Plasma insulin levels were assayed using a sensitive radioimmunoassay modified to use guinea-pig anti-insulin serum (ICN, High Wycombe, UK) with charcoal separation (coefficient of variation 5%). Plasma C-peptide was measured using a kit method (Serono, Windsor, UK) with polyethylene glycol separation (coefficient of variation 4%). A two-site immunoradiometric assay kit (Nichols Allegro, Saffron Walden, UK) was used to measure intact PTH. $1,25(OH)_2D$ was measured by an in house method involving HPLC separation and RIA using a monoclonal antibody (Mawer *et al.*, 1990). Serum ionized calcium was measured using an ionized calcium analyser (Radiometer, Copenhagen, Denmark).

Assessment of glucose tolerance, insulin sensitivity and beta-cell function

An achieved plasma glucose of 9·3 mmol/l or greater at the end of the glucose infusion was considered diagnostic of impaired glucose tolerance (Levy *et al.*,1992). Insulin sensitivity and beta-cell function were derived from the glucose and insulin data by using the CIGMA (continuous infusion of glucose with model assessment) and HOMA (homeostasis model assessment) mathematical models (Hosker *et al.*, 1985; Matthews *et al.*, 1985). These models are based on the assumption that the control of plasma glucose and insulin in the fasting state (HOMA) and after a continuous low-dose glucose infusion (CIGMA) are determined by a self-contained feedback loop involving the pancreatic beta-cells, liver, insulin sensitive and insulin insensitive tissues. Beta-cell function and insulin sensitivity for each subject are expressed as a percentage of those in a reference lean healthy population for whom the model has been calibrated at 100% for insulin sensitivity and beta-cell function.

Statistical analysis

The data were analysed using SPSS-PC software package (SPSS Inc., Chicago, USA). Data which were not normally distributed are presented as the median and interquartile range; the Mann–Whitney *U*-test was used to make comparisons between such groups. Normally distributed unpaired data were compared using Student's *t*-test and are shown as mean $\pm$ SD. Spearman's rank correlations were used to examine associations between parameters of calcium metabolism and insulin sensitivity. *P*-values are two-tailed and a value $<0·05$ was considered significant.

Table 1 Characteristics of the subjects recruited into the study and the results of the continuous infusion of glucose test, shown as median (interquartile ranges) or mean ± SD

	Primary hyperparathyroidism ($n=19$)	Normal subjects ($n=11$)	Significance (P)
Age (years)	54 (41–59)	54 (42–61)	NS
Sex (M/F)	7/12	1/10	<0·05
Body mass index (kg/m^2)	22·3 (21·2–24·1)	22·9 (22·1–25·3)	NS
Mean arterial blood pressure (mmHg)	97 (93–105)	94 (83–100)	NS
Serum ionized calcium (mmol/l)	1·54 ± 0·14	1·2 ± 0·04	<0·001
Serum intact PTH (ng/l)	66 (52–85)	20·5 (16·5–25·5)	<0·001
Serum 1,25(OH)$_2$D (ng/l)	46 (41·5–60·5)	35·9 (30·2–54·3)	<0·05
Plasma glucose (mmol/l)			
Fasting	5·3 (5·0–5·8)	5·2 (4·5–5·4)	NS
Achieved	9·0 (8·1–9·8)	7·9 (7·1–8·9)	<0·01
Plasma insulin (mU/l)			
Fasting	6·6 (3·5–7·5)	5·0 (3·7–5·6)	NS
Achieved	22·0 (18·0–28·0)	15·0 (11·0–19)	<0·01
Plasma C-peptide (pmol/l)			
Fasting	0·55 (0·34–0·78)	0·4 (0·28–0·51)	<0·05
Achieved	1·28 (1·1–1·57)	0·86 (0·76–1·03)	<0·01
Beta-cell function (%)	110·9 (86·2–120·0)	95·8 (73·8–107·2)	NS
Insulin sensitivity	60·3 (49·8–85·4)	113·7 (89·3–149·2)	<0·001
Impaired glucose tolerance	8	0	<0·001

Results

The characteristics of the subjects recruited into the study are shown in Table 1. As expected from the recruitment criteria, there were no differences between the groups for age or BMI. PHPT patients had significantly higher PTH and ionized calcium concentrations ($P<0·001$).

Glucose, insulin and C-peptide concentrations in the fasting state (mean of three fasting samples at −10, −5 and 0 minutes) and 'achieved' glucose at the end of the glucose infusion (mean of three samples at 50, 55 and 60 minutes) for the patients and control subjects are shown in Table 1; their profiles during the glucose infusion test are shown in Fig. 1. None of the control subjects studied had diabetes, but 8 (42%) patients with PHPT had impaired glucose tolerance compared to none amongst the normal subjects ($P<0·001$).

Although plasma fasting glucose and insulin were similar in the two groups, achieved glucose and insulin levels after the glucose infusion were significantly higher in patients with PHPT (Table 1). Insulin sensitivity derived from fasting plasma glucose and insulin levels (HOMA model) was not significantly different in the two groups (PHPT 66·6% (54·6–112·4) *vs* control 89·8 (60·4–106), $P=$ NS). However, insulin sensitivity derived from the achieved plasma glucose and insulin data (CIGMA model) revealed reduced insulin sensitivity in the patients with PHPT (Table 1).

No significant correlation was found between insulin sensitivity and PTH ($r_s=-0·21$), 1,25(OH)$_2$D ($r_s=-0·14$), ionized calcium ($r_s=-0·11$) and inorganic phosphate ($r_s=0·34$) (all $P=$ NS). Beta-cell function did not correlate with PTH ($r_s=0·15$), 1,25(OH$_2$)D ($r_s=0·04$), ionized calcium ($r_s=0·23$) or inorganic phosphate ($r_s=-0·35$) (all $P=$ NS).

In patients with PHPT, there was no significant difference between those with impaired glucose tolerance and those with normal glucose tolerance with respect to age, fasting plasma glucose and insulin, BMI and modelled insulin sensitivity (Table 2). Beta-cell function was reduced in HPT subjects with IGT (89·9 (70·4–106·4)) compared to those with normal glucose tolerance (120·0 (98·8–156·6), $P<0·05$). No difference was observed between these groups with respect to their serum concentrations of PTH, 1,25(OH)$_2$D and ionized calcium (Table 2).

Discussion

A reduction in peripheral insulin sensitivity has been shown in patients with PHPT (Prager *et al.*, 1983; 1984; Kautzky-

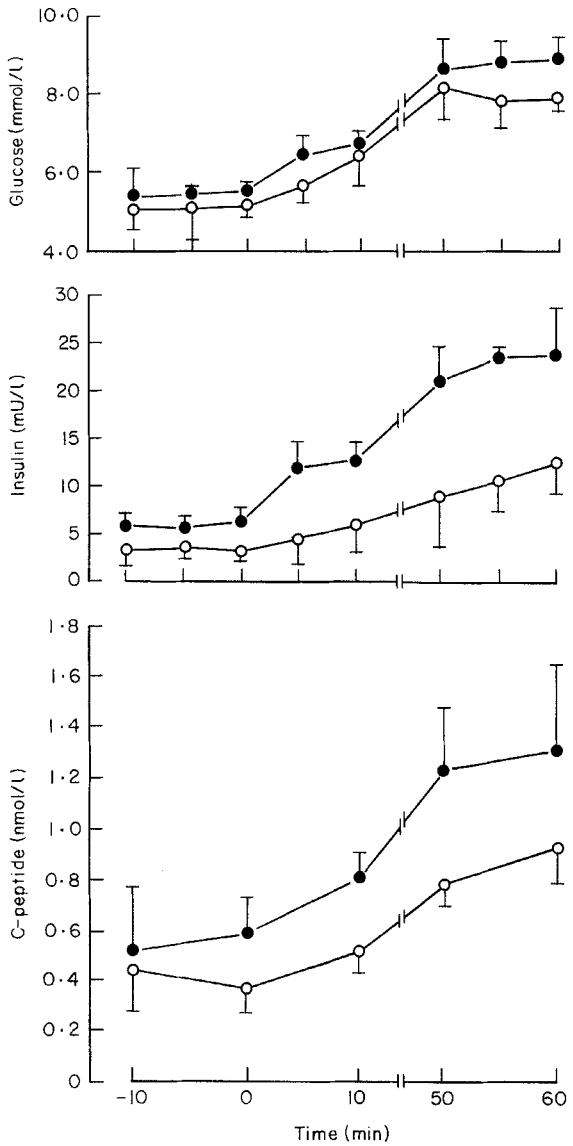

Fig. 1 Glucose, insulin and C-peptide profiles during the continuous infusion of glucose test is shown for ●, patients with primary hyperparathyroidism and ○, control subjects.

Willer *et al.*, 1992). However, in their studies the inclusion of subjects with hypertension (often taking medication that could potentially affect glucose metabolism) makes it difficult to attribute the observed disturbances in glucose metabolism solely to altered calcium homeostasis. Our finding of impaired glucose tolerance and peripheral insulin insensitivity in normotensive, non-obese, non-diabetic patients with PHPT suggests that the basis for these defects in glucose metabolism is related to abnormalities in calcium homeostasis. Thus, glucose intolerance and insulin insensitivity are additional metabolic abnormalities in PHPT that coexist in this condition independently of hypertension or other risk factors for glucose intolerance.

The continuous infusion of glucose test has been used to assess glucose tolerance, beta-cell function and insulin sensitivity in this study, as repeatable measures of all these three parameters can be obtained with this single test (Hosker *et al.*, 1985). The use of the continuous infusion of glucose test in the diagnosis of impaired glucose tolerance (IGT) and diabetes has been validated against repeated OGTTs and an achieved plasma glucose value of >9·3 mmol/l has been found to be equivalent to the threshold value of 7·8 mmol/l for IGT using OGTT (Levy *et al.*, 1992). Glucose tolerance assessed in this way is more reproducible (coefficient of variation 5%) than the oral glucose tolerance test for which the coefficient of variation may be as high as 40% (Levy *et al.*, 1992). Using mathematical modelling, measures of insulin sensitivity and beta-cell function may be obtained that correlate highly with results obtained with the euglycaemic and hyperglycaemic glucose clamps (Hosker *et al.*, 1985).

Although fasting glucose was similar in the patients and controls (partially explained by the exclusion of patients with diabetes in both groups) the achieved glucose at the end of the glucose infusion was higher in the patients with PHPT and 42% had impaired glucose tolerance. Beta-cell function was inadequate in some patients with PHPT and resulted in IGT because the insulin secretory capacity was clearly inadequate to maintain normoglycaemia. Such patients are relatively insulin deficient and experimental studies suggest that this may be due to direct effects of both PTH and calcium on beta-cells reducing insulin secretory capacity (Fadda *et al.*, 1990; Akmal *et al.*, 1985). Therefore, despite peripheral insulin insensitivity, patients with PHPT are able to remain normoglycaemic if they sustain an appropriate insulin secretory response. Patients with PHPT who do not have adequate beta-cell function may develop overt diabetes. Thus, there are apparent similarities in the pathogenesis of some subsets of type 2 diabetes in the general population (O'Rahilly *et al.*, 1988) and of diabetes in PHPT. Although insulin insensitivity is a common metabolic abnormality, beta-cell dysfunction is a prerequisite for the development of diabetes in PHPT.

Another finding in this study is the apparently normal hepatic insulin sensitivity in subjects with PHPT which is reflected in the insulin sensitivity measured using the HOMA model which is derived from fasting glucose and insulin data, both of which are dependent mainly on hepatic sensitivity to insulin. Thus, the metabolic abnormalities in PHPT would appear principally to affect peripheral glucose disposal in muscle whilst hepatic sensitivity to insulin appears to be less affected. Lack of an effect of PTH on hepatic glucose

Table 2 Comparison of HPT patients with and without glucose intolerance, shown as median (interquartile range)

	HPT with normal glucose tolerance ($n=11$)	HPT with IGT ($n=8$)	Significance (P)
Age (years)	54 (41–59)	53·5 (40·8–64·5)	NS
BMI (kg/m^2)	22·0 (21·2–23·6)	25·8 (20·7–28·8)	NS
Serum intact PTH (ng/l)	70 (60·0–80·0)	59 (46·8–131·5)	NS
Serum ionized calcium (mmol/l)	1·58 (1·51–1·6)	1·47 (1·41–1·49)	NS
Serum 1,25(OH)$_2$D (ng/l)	46 (39–60·5)	53·4 (42–61)	NS
Plasma glucose (mmol/l)			
Fasting	5·2 (5·0–5·3)	5·7 (5·2–6·4)	NS
Achieved	8·1 (7·9–8·8)	9·9 (9·5–10·5)	<0·001
Plasma insulin (mU/l)			
Fasting	6·5 (3·5–7·0)	7·0 (3·5–8·5)	NS
Achieved	22·0 (18·0–28·0)	23 (16·0–28·0)	NS
Plasma C-peptide (pmol/l)			
Fasting	0·55 (0·33–0·57)	0·71 (0·33–0·71)	NS
Achieved	1·23 (1·06–1·68)	1·28 (1·02–1·85)	NS
Beta-cell function (%)	120·0 (98·8–156·6)	89·9 (70·4–106·4)	<0·05
Insulin sensitivity (%)	71·5 (54·5–89·3)	51·8 (45·7–74·7)	NS

metabolism has been noted in dogs (Bevilacqua *et al.*, 1981) and our findings would suggest this to be the case in humans too.

The presence of hypercalcaemia with hypophosphataemia and high PTH (each of which could potentially affect glucose metabolism) makes it difficult to determine which of these metabolic abnormalities is the main contributor to reduced glucose disposal in PHPT. Chronic hypercalcaemia may enhance insulin secretion but can also reduce insulin sensitivity (Yasuda *et al.*, 1975; Kautzky-Willer *et al.*, 1992). Hypophosphataemia has been shown to affect insulin-mediated glucose disposal and is thought to contribute to insulin insensitivity (DeFronzo & Lang, 1980) and 1,25(OH)$_2$D can increase insulin secretion in man (Gedik & Akalin, 1986). PTH can suppress pancreatic beta-cell secretion, probably by increasing cytosolic calcium concentrations (Fadda *et al.*, 1990; Perna *et al.*, 1990). The possibility of an antagonistic effect of PTH on insulin action has been suggested in studies of patients with secondary hyperparathyroidism due to renal failure (Amend *et al.*, 1975; Mondon *et al.*, 1978), and also in patients with PHPT (Prager *et al.*, 1984), but no such defect could be detected by others (Akmal *et al.*, 1985; DeFronzo *et al.*, 1973). The failure to demonstrate any correlation between peripheral insulin sensitivity in patients with PHPT and PTH, ionized calcium or 1,25(OH)$_2$D makes it unlikely that serum concentrations of PTH, calcium, ionized calcium or inorganic phosphate directly influence glucose disposal. However, the majority of the patients studied had only mild hyperparathyroidism, and patients with other risk factors for glucose intolerance were excluded which may have masked any relationships with parameters of calcium metabolism. Further studies of patients with a wider range of hyperparathyroidism are needed to detect any subtle influence that parameters of calcium metabolism may have on insulin sensitivity. Nevertheless, it is more likely that alterations in intracellular calcium concentrations in PHPT cause post-receptor defects in insulin action. Increased intracellular cytosolic calcium has been found in type 2 diabetes and in essential hypertension, and it has been suggested that this may be the underlying metabolic disorder linking insulin resistance, glucose intolerance and hypertension (Draznin, 1991; Levy *et al.*, 1986). Thus, it is conceivable that abnormalities in intracellular calcium homeostasis may be the underlying metabolic defect predisposing to hypertension, insulin insensitivity and glucose intolerance in PHPT.

An increased risk for cardiovascular mortality has been described in subjects with PHPT (Palmer *et al.*, 1987). Peripheral insulin insensitivity together with hypertension may contribute to the increased risk of cardiovascular disease in these patients. Although it may be argued that even mild PHPT should be treated surgically, patients who have been cured of PHPT continue to have hypertension and there are no convincing data to show that curing PHPT reduces the risk of premature death (Lind *et al.*, 1991). Long-term follow-up studies on the effect of parathyroidectomy on

peripheral insulin sensitivity are needed to see if insulin insensitivity can be ameliorated in the long term and if this has any effect on cardiovascular disease.

In conclusion, our findings of impaired glucose tolerance and insulin insensitivity in subjects with PHPT, even in the absence of hypertension or other risk factors for diabetes, indicate that hyperparathyroidism and/or the associated abnormalities in calcium metabolism are responsible for defects in glucose metabolism in this condition. Reduced beta-cell function is important for the development of glucose intolerance in this group of patients.

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