Endocrine abnormalities in primary hyperparathyroidism

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Summary

Endocrine abnormalities in 73 patients with primary hyperparathyroidism were studied: 8 patients were diabetic, 3 were thyrotoxic, 2 were hypothyroid, and one had a gastrinoma and carcinoid tumour. In 9 of these patients, carbohydrate metabolism and thyroid function were studied in detail pre- and 3 months postoperatively. In 6 patients following a glucose load, insulin concentrations were markedly elevated pre-operatively when compared with those found postoperatively. Likewise, in 7 patients, serum thyroxine was greater pre- than postoperatively. The aetiology of these changes and their relevance to the management of patients with primary hyperparathyroidism is discussed.

Introduction

The importance of the calcium ion in the regulation and secretion of various hormones is a well established phenomenon, but the effects of the hypercalcaemia in primary hyperparathyroidism on other endocrine glands has received little attention. It may, however, account for the increased incidence of other endocrine abnormalities, in particular those associated with hypersecretion of hormones, a fact which may be of importance in the consideration of surgery in asymptomatic patients with primary hyperparathyroidism. The authors have assessed the endocrine abnormalities in 73 patients with primary hyperparathyroidism.

Patients and methods

The incidence of endocrine abnormalities was sought in 73 patients who presented with primary hyperparathyroidism at the Norfolk and Norwich Hospital over a 10-year period (1969-1979): in 71 patients the diagnosis was confirmed at surgery while in 2 patients surgery was not performed because the patients were deemed medically unfit (the diagnosis was strongly suspect in view of elevated serum calcium, reduced serum phosphate, elevated serum parathyroid hormone, normal protein electrophoresis and in the absence of evidence for other causes of hypercalcaemia).

There were 55 females and 18 males, with an average age of 54 years (range 24-73 years).

In 9 patients (7 female and 2 male, average age 57 years), carbohydrate metabolism and thyroid function were assessed before and 3 months after surgical removal of parathyroid adenomas. Carbohydrate metabolism was assessed by glucose tolerance tests with estimation of glucose and insulin following oral glucose load in 7 patients, and i.v. load in 2 patients. Thyroid function was measured pre- and post-operatively in 9 patients, with estimation of serum thyroxine.

Results

Carbohydrate metabolism

Of the 73 patients with primary hyperparathyroidism, 8 patients were diabetic (11%). In the 9 patients studied prospectively there was little change in serum glucose during glucose tolerance tests between the pre- and postoperative values in patients with primary hyperparathyroidism. However, the major changes which were observed were those of insulin secretion. Insulin concentrations were markedly elevated pre-operatively following a glucose load when compared with those found post-operatively when the serum calcium had returned to normal. Such changes were most marked 30 min after glucose administration, and were independent of whether the glucose was given orally (Fig. 1) or i.v. (Fig. 2). These changes were observed in 6 of the 9 patients studied.

There was a positive correlation between the ratio of insulin pre- and postoperatively and the ratio of glucose pre- and postoperatively ($P, 0.01$).

Thyroid function

Of the 73 patients with primary hyperparathyroidism, 3 (4%) were thyrotoxic, 2 (3%) were hypothyroid and 5 (7%) had goitres.

In 7 of 9 patients studied, serum thyroxine concentrations were higher pre- than postoperatively, although the changes were generally small and not statistically significant (Fig. 3).

Discussion

Halver (1967) did not find any significant changes in glucose metabolism following surgery for primary hyperparathyroidism. Kim *et al.* (1971) reported significantly greater fasting plasma insulin concentrations and insulin levels following glucose administration before surgery for primary hyperparathyroidism than postoperative values. Ginsberg, Olefsky and Reaven (1975) and Yasuda *et al.* (1975) confirmed these findings.

FIG. 1. Oral glucose tolerance test before (—) and after (---) surgery for primary hyperparathyroidism.

A number of theories have been propounded to explain the changes in insulin secretion in patients with primary hyperparathyroidism. Calcium plays a key role in hormonal secretion (Rubin, 1970). Curry, Bennet and Grodsky (1968) found that *in vitro* there was a very low level of spontaneous

FIG. 2. Intravenous glucose tolerance test before (—) and after (---) surgery for primary hyperparathyroidism.

release of insulin when a pancreas was perfused with a calcium-free solution containing excess glucose. The release of insulin was rapidly augmented by the addition of calcium to the perfusate. The amount of insulin released by glucose was proportional to the calcium concentration in the perfusate over the range of 0.25–2.00 mmol/l. The ionized calcium concentration in plasma is about 50–60% of the total. Since the average calcium was 3.04 mmol/l in the present patients, the average ionized calcium is approximately 1.67 mmol/l.

Moreover, basal insulin concentrations are low in hypocalcaemic patients, and glucose-stimulated insulin release is markedly reduced in them (Gedik and Zileli, 1977). On correction of the hypocalcaemia, insulin levels return to normal.

Kim *et al.* (1971) suggest that chronic hypercalcaemia of hyperparathyroidism maintains a form of

endogenous insulin resistance that necessitates augmented insulin secretion to maintain plasma glucose homeostasis. Subjects with hyperparathyroidism should, therefore, be added to the list of those in whom antagonism to the action of insulin is found, such as those with acromegaly, uraemia, and Cushing's syndrome and those receiving oestrogen therapy.

FIG. 3. Pre- and postoperative thyroid function in 9 patients with primary hyperparathyroidism.

The rare but well documented association between hyperparathyroidism and pancreatitis suggests another way in which hyperparathyroidism might be linked with diabetes, but it does not explain the hyperinsulinism found pre-operatively in patients with hyperparathyroidism. Moreover, in none of the present patients was there any history of pancreatitis.

A relationship between parathyroid hormone (PTH) and glucagon secretion has been suggested. Paloyan *et al.* (1967) showed elevated concentrations of circulating glucagon in 7 of 8 patients with hyperparathyroidism. Postoperatively, in 6 of the 7 tested, glucagon concentrations returned to normal. Hyperparathyroidism may result in elevated glucagon which then causes impaired glucose tolerance and increased insulin secretion to compensate. Pancreatic islet hyperplasia, which is observed in acquired forms of endogenous insulin resistance and diabetogenic stress such as obesity or pregnancy, has also been found at post-mortem examination of patients with primary hyperparathyroidism (Cushard *et al.*, 1971).

An alternative theory to account for the relationship between these 2 hormones, suggests that the primary event is hyperglucagonaemia, secondary to diabetes, which results in parathyroid hyperplasia. Glucagon infusions have been shown to increase

PTH concentrations in normal subjects (Cushard *et al.*, 1971).

Elevated concentrations of PTH rather than hypercalcaemia may be responsible for the changes in carbohydrate metabolism which have been observed in patients with primary hyperparathyroidism. Plasma insulin concentrations following glucose administration are significantly higher in those patients with chronic renal failure with severe secondary hyperparathyroidism than those without severe secondary hyperparathyroidism (Lindall *et al.*, 1971). Indeed, the insulin response in the former group is comparable to the response of those patients with primary hyperparathyroidism. These observations strongly support a close relationship between PTH and insulin secretion. The specific action of PTH is to stimulate adenyl cyclase at the cellular level in the kidney and bone (Chase and Aurbach, 1967; Wells and Lloyd, 1969). Since cyclic AMP may have an important role in regulating the release of insulin from the pancreatic islets, it is possible that a relationship exists at a cellular level involving these 2 endocrine glands.

The changes in carbohydrate metabolism have been described as of relatively minor biological significance (Ginsberg *et al.*, 1975). However, they may explain the increased incidence of diabetes mellitus in patients with primary hyperparathyroidism. Dent (1962) reported the coexistence of diabetes mellitus and primary hyperparathyroidism in only 1% of his patients, Werner, Hjern and Sjöberg (1974) found 8%, while Irvin *et al.* (1972) found that 54% of their patients with primary hyperparathyroidism were diabetic pre-operatively. S. Birge, in an unpublished observation (Kipnis, 1969) found that 80% of patients with primary hyperparathyroidism had an abnormal glucose tolerance test, the majority of which were corrected by surgery. In the present series, 11% of the patients were diabetic.

In several patients with diabetes and primary hyperparathyroidism the latter condition has resulted in a worsening of the diabetes. Furthermore, insulin-dependent diabetic patients with primary hyperparathyroidism may suffer hypoglycaemic reactions if their usual insulin dosages are continued following removal of parathyroid tumours. Insulin requirements postoperatively may need to be reduced by more than 50% (Akgun and Ertel, 1978).

Calcium has been shown as being of importance in the release of thyroxine (Rubin, 1970) as it is in the secretion of insulin. An increase in the serum thyroxine before surgery, in patients with primary hyperparathyroidism, may not result in thyrotoxicosis, although in some cases this may indeed occur. Thyrotoxicosis coincident with primary hyperparathyroidism was found by Werner *et al.* (1974) to be present in 5% of their patients. In the present series,

4% were found to be thyrotoxic. Of these 3 patients, 2 were diabetic, an association not previously reported although Walsh, Soler and Malins (1975) reported for the first time the association of hypothyroidism, diabetes and primary hyperparathyroidism.

The secretion of a number of hormones has been shown to be calcium-dependent (Rubin, 1970; Worley, Rich and Pryor, 1978). The authors postulate that in hyperparathyroidism their secretion is increased, thereby accounting for a number of epiphenomena which occur in patients with primary hyperparathyroidism. The elevated secretion of renin may account for the increased incidence of hypertension in primary hyperparathyroidism; over 70% of patients with chronic primary hyperparathyroidism, and up to 35% of those with hypercalcaemia of whatever cause are hypertensive (Britton *et al.*, 1971; Purnell *et al.*, 1971; Rosenthal and Roy, 1972). In some patients, the hypertension disappears after successful treatment of the hypercalcaemia. In the present series, 31 patients (42%) were hypertensive. Initially it was believed that the reversibility of the hypertension might be due to an improvement of the hypercalcaemia and functional renal alterations. Brinton, Jubiz and Lagerquist (1975), however, demonstrated reversible elevated plasma renin activity and reversible hypertension in patients with primary hyperparathyroidism and hypertension. In a recent paper, the disappearance of 'primary hyperaldosteronism' on correction of the primary hyperparathyroidism is described (Barkan *et al.*, 1980).

Gastrin secretion has also been shown to be calcium-dependent (Reeder *et al.*, 1970). Elevated gastrin levels in primary hyperparathyroidism might account for the increased incidence of peptic ulcers in this condition.

Hyperparathyroidism has been reported in association with various other endocrine disturbances including Cushing's syndrome (Raker, Henneman and Graf, 1962), acromegaly (Dent, 1962), and carcinoid tumour (Samaan *et al.*, 1975). In addition, it is the principle endocrine disorder in the polyglandular syndrome (Ballard, Frame and Hartsock, 1964). It is of relevance that a recent report has shown that the development of the Zollinger-Ellison syndrome in multiple endocrine adenomatosis Type 1 depends on the presence of chronic hyperparathyroidism (Betts, O'Malley and Rosenthal, 1980).

Other endocrine pathology, in particular diabetes mellitus, should be sought in patients presenting with primary hyperparathyroidism. Since primary hyperparathyroidism may be associated with an increased secretion of other hormones (which may return to normal following surgery), there may be some justification for advising surgery in asymptomatic

patients with primary hyperparathyroidism, to prevent the development of associated endocrine abnormalities.

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