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Evaluation of Insulin Resistance in Patients with Primary Hyperparathyroidism (38665)

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(Introduced by D. A. Rytand)

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Increased plasma insulin levels, both in the fasting state and in response to glucose loads have been reported in patients with primary hyperparathyroidism (1). In this study surgical correction of the hyperparathyroidism was associated with a decrease in plasma insulin levels. However, since glucose tolerance in these patients was similar before and after surgery, it appears that a state of insulin resistance coexisted with the hyperparathyroidism. Documentation of these findings would add hyperparathyroidism to the list of pathologic states associated with antagonism to the action of insulin (2). Furthermore, since hyperinsulinemia and insulin resistance are often associated with hypertriglyceridemia (3), patients with primary hyperparathyroidism might have an increased incidence of elevated plasma triglyceride levels. In order to evaluate these possibilities, we have measured plasma levels of glucose, insulin, triglyceride, and cholesterol, and directly estimated insulin resistance in a group of patients before and after surgical correction of primary hyperparathyroidism.

Methods. Seven subjects with suspected primary hyperparathyroidism were admitted to the Stanford Clinical Research Center. The group included six females and one male, and had a mean age of 43 yr. All patients consumed a weight maintenance liquid formula diet which included 10 mg/kg/day of calcium. Various studies of calcium metabolism were undertaken after 3 days of dietary stabilization; including serum calcium, phosphorus and parathyroid hormone level determinations, 24-hr urinary calcium and phosphorus measurements, and hand, skull, and chest X-rays. Other possible causes of hypercalcemia were excluded by appropriate investigation.

On the fifth and sixth days of hospitalization, blood was drawn after an overnight fast for measurement of plasma triglyceride and cholesterol levels. On the fifth hospital day, each patient received an oral glucose load of 40 g/m^2, and samples for plasma glucose and insulin determination were drawn during the following three hours. On the sixth hospital day, five patients received a constant infusion of glucose (6 mg/kg/min), insulin (80 munits/min), epinephrine (6 μg/min), and propranolol (0.08 mg/min). As previously reported (4), endogenous insulin secretion and hepatic glucose production are both inhibited during the infusion. Steady state plasma glucose and insulin levels are reached 90 min after the start of the infusion, and blood is then taken for measurement of plasma glucose and insulin levels every 10 min for the next 60 min. Since similar steady plasma insulin levels are achieved in all subjects, and since each patient receives glucose at the same infusion rate, the mean of these seven steady state plasma glucose measurements provides a direct estimate of the efficiency of each patient's insulin mediated glucose uptake, i.e., his insulin resistance.

All patients returned for reevaluation one to 4 mo following surgical correction of their hyperparathyroidism. The protocol was identical to that followed during the preoperative investigation. No patient had a change in weight of more than 1.8% between the two study periods.

Plasma glucose was determined by the method of Hoffman (5) and plasma insulin by a double antibody system (6). All insulin

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measurements for a subject were done in triplicate, in a single assay after completion of the postoperative studies. Plasma triglyceride, cholesterol and serum calcium were measured on a Technicon AutoAnalyzer (7). Serum parathyroid hormone levels were measured by Dr. C. D. Hawker of the Upjohn Laboratory, with a normal range 163–347 pg/ml (8). Statistical analysis was performed by the use of the paired two-tailed Student's t test.

Results. The diagnosis of primary hyperparathyroidism was confirmed at surgery in all seven patients. Mean (±SE) serum calcium, which was 12 ± 0.3 mg/100 ml preoperatively, fell to 9.5 ± 0.3 mg/100 ml after surgery ($P < .001$). Parathyroid hormone levels decreased in all patients, and fell from a mean preoperative level of 312 ± 20 pg/ml to 231 ± 13 pg/ml postoperatively ($P < 0.01$). (Although the preoperative parathyroid hormone levels were within the normal range, it must be pointed out that these preoperative levels were associated with hypercalcemia.)

Mean plasma glucose and insulin responses to an oral glucose load before and after surgery are presented in Fig. 1. Although the glucose levels appear comparable during the two tests, the fasting and three hour glucose levels are significantly lower following surgical correction of hyperparathyroidism. The plasma insulin levels are also similar, with the exception of the mean insulin level at 30 min which is significantly greater when the patients are hyperparathyroid.

Figure 2 depicts the pre- and postoperative steady state levels of plasma glucose and insulin during the infusion of glucose, insulin, epinephrine and propranolol. It can be seen that similar levels of plasma insulin existed in both studies. There was no significant difference in mean steady state plasma glucose levels, and examination of the individual steady state glucose levels during the two infusion studies indicates that three of the five patients studied had modest decreases in their postoperative glucose levels, while two did not change. Furthermore, there was no significant degree of correlation between the mean steady state plasma glucose level and the preoperative serum levels of either parathyroid hormone or calcium.

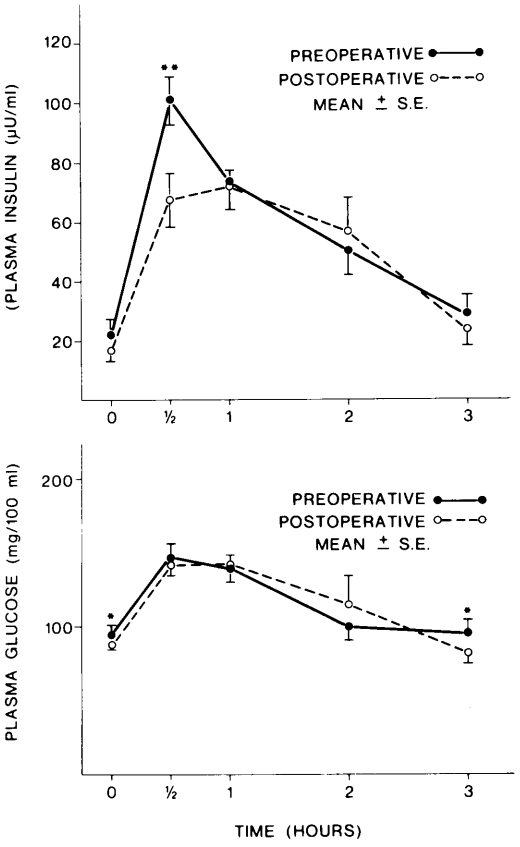

FIG. 1. The 3-hr glucose and insulin levels (mean ± SE) of the seven subjects after an oral glucose load of 40 g/m² during the preoperative (pre) and postoperative (post) study period. * $P < 0.05$; ** $P < 0.01$.

Mean levels of plasma triglyceride and cholesterol were unchanged after surgery compared to the preoperative period (Table I). Three patients had increases in their levels of plasma triglyceride after surgery, three patients had decreased levels postoperatively, and one patient showed no change. Plasma cholesterol levels did not change in any of the patients.

Discussion. On one hand, the results of the current study seem to corroborate the observations of Kim and associates (1) that insulin resistance and plasma insulin levels fall following surgical correction of primary hyperparathyroidism. Thus, plasma glucose levels were modestly increased in

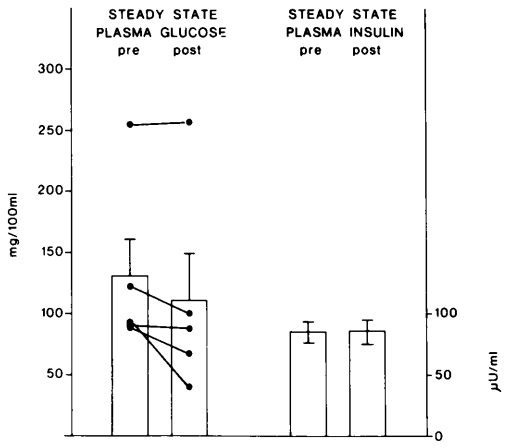

FIG. 2. The steady state plasma glucose and insulin levels (mean ± SE) and the individual preoperative (pre) and postoperative (post) steady state plasma glucose levels in the five subjects studied.

TABLE I. EFFECTS OF PARATHYROIDECTOMY ON PLASMA LIPIDS.

	(Mean < SE)	
	Before	After
Plasma triglycerides (mg/100 ml)	170 ± 28	167 ± 24
Plasma cholesterol (mg/100 ml)	221 ± 24	211 ± 14

patients with hyperparathyroidism in the fasting state and 3 hr after oral glucose. Furthermore, plasma insulin levels were significantly higher at the 30-min time interval during the oral glucose tolerance tests in hyperparathyroid patients. These changes are certainly consistent with the hypothesis that increased levels of circulating parathyroid may modify glucose and insulin metabolism.

On the other hand, our results also indicate that the effects of primary hyperparathyroidism on glucose and insulin metabolism are quantitatively modest. For example, the only patient with an abnormal oral glucose tolerance test by the revised criteria of Fajans and Conn (9) before surgical repair of this hyperparathyroidism, still had an abnormal test postoperatively. Similarly, an effect of hyperparathyroidism on insulin response was only seen at the 30 min time interval. Furthermore, although three subjects showed a modest postoperative decrease in their level of insulin resistance, as measured by our infusion technique, all three had quite normal steady state plasma glucose levels during the preoperative study (4). Only the patient with abnormal glucose tolerance had an abnormally high steady state glucose level, and he showed no change postoperatively. It is interesting to note that this individual had the second lowest preoperative serum parathyroid hormone levels. Furthermore, in this regard, preoperative levels of parathyroid hormone and calcium did not correlate with the degree of insulin resistance. Finally, although the mean plasma triglyceride level was somewhat elevated preoperatively, the range of individual values varied widely and only one of the seven subjects had a plasma triglyceride level outside of the 95% confidence limits (corrected for sex and age) found in a recent survey of a normal population (10). Furthermore, correction of the hyperparathyroidism had no consistent effect on plasma triglyceride levels.

Taken together, these results indicate that while increased levels of parathyroid hormone may result in insulin resistance, the effect on plasma glucose, insulin, and lipid levels in patients with primary hyperparathyroidism is a modest one. This conclusion is consistent with the fact that previous clinical surveys have failed to note carbohydrate intolerance in patients with hyperparathyroidism (11, 12). In addition, Halver (13) could not document any change in the plasma glucose response when intravenous glucose tolerance tests were performed pre- and postoperatively in hyperparathyroid patients. Indeed, many of the differences in insulin response of hyperparathyroid patients before and after surgery described by Kim, *et al.* (1) were relatively minor in magnitude. Thus, although there appear to be statistically significant effects of parathyroid hormone on plasma glucose and insulin levels, the changes in carbohydrate and lipid metabolism that occur in patients with primary hyperparathyroidism seem to be of relatively minor biological significance.

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