GLUCOSE AND LIPOPROTEIN METABOLISM
IN PRIMARY HYPERPARATHYROIDISM.
EFFECTS OF PARATHYROIDECTOMY

By
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ABSTRACT

Fifteen patients with primary hyperparathyroidism due to parathyroid adenoma were subjected to an investigation on glucose and lipoprotein metabolism before operation and 3 and 12 months later. Hypercalcaemia, hypophosphataemia and an increased urinary excretion of cyclic AMP were normalized after operation. The early insulin response to an iv glucose tolerance test was significantly lower after operation than before, but fasting serum-insulin levels did not differ. This change of the early insulin response was not reflected in any changes of the fasting blood-glucose concentration or the elimination rate of injected glucose. Eleven of 15 subjects had increased levels of very-low-density lipoproteins before operation. The first change in lipoprotein concentrations after operation was a significant increase of high-density lipoproteins, occurring during the first 3 months. Only thereafter did the very-low-density lipoproteins decrease to normal values and concomitant the low density lipoproteins increase. As lipoprotein lipase activity of adipose tissue did not change after the operation it is assumed that the elevation of very-low-density lipoproteins is at least in part due to a change of the lipoprotein lipase concentration in the serum. The decrease of the very-low-density lipoproteins after operation was not fully reflected in the plasma triglyceride concentration. The results suggest a relation between the accumulation of serum lipids and the presence of a parathyroid adenoma.
density lipoproteins before operation was caused by an increased production rate due to an increased lipolysis. This sequence of events, primarily due to a disorder of the metabolism of the very-low-density lipoproteins, was reflected in the whole serum lipids only as an increase of the cholesterol but not the triglyceride concentration.

Calcium is an essential, and well established, requirement to insulin secretion (Malaisse et al. 1970). In experimental animals hypocalcaemia has been associated with low serum insulin concentrations (Littledike et al. 1968) and during hypercalcaemia the insulin responses to various stimuli have been reported to be augmented (Grodsky 1972; Harter et al. 1976).

From the few studies performed on human subjects during various clinical conditions it seems that in man too there are similar associations between the serum calcium and insulin concentrations (Laron & Rosenberg 1970; Kim et al. 1971; Yasuda et al. 1975).

It has also been reported that in primary hyperparathyroidism (HPT) the serum cholesterol and triglyceride levels are decreased and return to normal after parathyroidectomy (Christensson & Einarsson 1977; De Moor et al. 1973). However, a more detailed study on what these changes reflected in terms of lipoprotein metabolism has not been performed. Nor have the effects of HPT on glucose and lipoprotein metabolism been studied in the same subjects. It has become increasingly clear that fundamental changes in lipoprotein metabolism might not be reflected in whole serum lipids and that fractionation studies are necessary for a proper understanding of the basic physiology.

The present study was therefore undertaken to investigate the glucose and lipoprotein metabolism in patients with hypercalcaemia due to primary HPT and to evaluate the effects of parathyroidectomy.

**MATERIAL AND METHODS**

*Subjects and experimental design*

Informed consent for the studies was obtained from 15 patients (10 females, 5 males) with a mean age of 57 years (range 27–70 years). These patients were consecutively admitted for investigation of hypercalcaemia and in all the cases subsequent surgical neck exploration disclosed one parathyroid adenoma. Removal of this normalized the preoperatively raised serum calcium concentrations in all the patients. Also the urinary excretion of cyclic AMP (cAMP) decreased in all instances (Table 1).

All sampling and testing were performed after an over-night fast and smoking was not allowed during the last 12 h before the blood samples were drawn. Studies were carried out immediately prior to parathyroidectomy and 3 months post-operatively. Lipoprotein determinations were also repeated 12 months after surgery.
Table 1.
Serum concentrations of calcium, phosphate and the urinary excretion of cyclic AMP (cAMP) in 15 patients with hyperparathyroidism studied prior to and 3 months after neck surgery. (Mean values ± SD).

<table>
<thead>
<tr>
<th></th>
<th>Serum calcium (mmol/l)</th>
<th>Serum phosphate (mmol/l)</th>
<th>Urinary cAMP (µmol/g creat.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before operation</td>
<td>2.93 ± 0.15</td>
<td>0.79 ± 0.17</td>
<td>6.1 ± 2.2</td>
</tr>
<tr>
<td>After operation</td>
<td>2.36 ± 0.09</td>
<td>0.92 ± 0.11</td>
<td>4.0 ± 1.1</td>
</tr>
</tbody>
</table>

Methods

The serum lipoprotein density fractions were isolated by preparative ultracentrifugation (Havel et al. 1955) and precipitation with a heparin-manganese chloride solution (Burnstein & Samaille 1960), as described previously (Hedstrand & Vessby 1976). Triglyceride and cholesterol concentrations of whole serum and of the lipoprotein classes were determined in a Technicon Auto Analyzer II (Rush et al. 1971). The method was standardized against control samples from the Centre for Disease Control, Atlanta, Georgia, USA. Agarose gel electrophoresis analyses (Noble 1968) were carried out on whole serum and on the top and bottom fractions after ultracentrifugation at density 1.006. The WHO recommendations for classification of hyperlipoproteinemia were followed (Beaumont et al. 1970). Cut-off points for very low density lipoprotein triglyceride was >1.4 mmol/l for males and >1.0 mmol/l for females and for low density lipoprotein cholesterol >5.2 mmol/l for males and >5.7 mmol/l for females. These cut-off points corresponded to the upper 85th percentile in a local control material (Carlson & Ericsson 1975).

An injection of glucose, 0.5 g/kg body weight, was given during 2½ min. Blood samples were taken before the injection and 4 and 6 min after the injection started for determination of serum insulin concentrations. Blood glucose concentrations were determined in samples taken 20, 30, 40, 50 and 60 min after the injection. Blood glucose concentrations were analyzed by a glucose oxidase method (Hjelm & de Verdier 1963) (normal range 3.4–5.7 mmol/l) and the elimination rate constant (K-value) for blood glucose during the intravenous glucose tolerance test (IVGTT) was calculated by the least squares method (Ikkos & Luft 1957). K-values ≥ 1.1 were regarded as normal and values 0.9–1.1 as “border line” values. Insulin was determined with the Phadebas Insulin Test (Pharmacia Diagnostics AB, Uppsala, Sweden) based upon the radioimmunosorbent technique described by Wide et al. (1967). The serum sample (0.1 ml) was pre-incubated with the Sephadex-coupled antibodies for 3 h before the labelled insulin was added. The incubation was then continued at room temperature for about 24 h. The standard was dissolved in sera with low insulin concentration. The sensitivity was 0.7 mU/l and the inter-plus intra-assay variation expressed as coefficient of variation was 10% at 11 mU/l, 7% at 34 mU/l and 6% at 150 mU/l (n = 75). The mean value of the serum insulin concentration at 4 and 6 min was calculated. The ratio between this value and the fasting serum insulin concentration was called the “insulin index” (Wide & Ohlsson 1974).
Table 2.
Fasting blood glucose and K-values, fasting and peak serum insulin concentrations and insulin index (peak/fasting) during an iv glucose tolerance test, fat cell weight and lipoprotein lipase activity (LPLA) in adipose tissue in 15 patients with primary hyperparathyroidism investigated before and 3 months after parathyroidectomy. Paired t-test with 2-tailed significance limits was used, n. s. = not significant. Mean values ± so are given.

<table>
<thead>
<tr>
<th></th>
<th>Blood glucose mmol/l</th>
<th>K-value</th>
<th>Serum insulin</th>
<th>Fat cell weight μg (n = 10)</th>
<th>Adipose tissue LPLA mU/g (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before operation</td>
<td>5.0 ± 0.7</td>
<td>1.31 ± 0.28</td>
<td>9.8 ± 5.3</td>
<td>82 ± 42</td>
<td>7.5 ± 4.8</td>
</tr>
<tr>
<td>After operation</td>
<td>4.8 ± 0.7</td>
<td>1.22 ± 0.44</td>
<td>11.1 ± 5.2</td>
<td>61 ± 34</td>
<td>6.0 ± 3.2</td>
</tr>
<tr>
<td>Significance of difference</td>
<td>n. s.</td>
<td>n. s.</td>
<td>n. s.</td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.01</td>
</tr>
</tbody>
</table>
Adipose tissue cell size was determined according to Sjöström et al. (1971). Adipose tissue lipoprotein lipase activity was determined as the release of labelled fatty acids when the adipose tissue specimens were incubated in a reaction medium containing trace amounts of tritium-trioleate in Intralipid emulsion (Vitrum AB, Stockholm, Sweden). A release of 1 \( \mu \text{mol} \) fatty acid per min was taken as one enzyme unit (U). It was expressed per gram of adipose tissue. All details about this method are given elsewhere (Lithell & Boberg 1977).

The urinary excretion of cyclic AMP (cAMP) was determined by a radioimmunoassay technique using a commercial kit (Schwartz & Mann, Orangeburg, New York). With this method the reference range obtained from healthy subjects is 0.6–5.4 \( \mu \text{mol/g} \) creatinine (Wälinder et al. 1978).

**RESULTS**

**Glucose and insulin metabolism**

After parathyroidectomy there was a decrease in both the peak insulin response to iv glucose and of the insulin index, whereas the fasting serum insulin concentration was not significantly affected (Table 2). All 15 patients had blood glucose values within the normal range both before and after the operation. Pre-operatively, one woman had a low K-value, which also persisted post-operatively. Borderline K-values were found in 2 patients before and in 3 patients after neck surgery.

**Lipoprotein metabolism**

Pre-operatively 11 of the 15 patients (77 \%) displayed increased very low density lipoproteins, compared to 15 \% of age-matched subjects in the local control material. This predominance of type IV hyperlipoproteinaemia was most evident in the female group (9 out of 10) and also persisted 3 months after surgery. At re-evaluation one year post-operatively, however, only 3 patients (20 \%) still had increased levels of very low density lipoprotein triglycerides.

One woman, aged 70 years, had on all occasions a pronounced elevation of the very low density lipoproteins (triglyceride concentrations of 4, 3 and 6 mmol/l, respectively). All the other patients exhibited a common pattern with a decrease of the triglyceride and cholesterol concentrations of the very low density lipoproteins. This decrease was less evident during the first 3 months post-operatively than during the following 9 months (Table 3). The low density lipoproteins were unchanged 3 months after the operation but thereafter increased significantly. In contrast to this the high density lipoproteins increased already during the first 3 months but not any further during the following observation period.

The whole serum triglyceride concentration was unchanged during the first 12 months following parathyroidectomy as the decrease of the very low density
Table 3.
The mean value (± sn) of the triglyceride and cholesterol concentrations of very low, low and high density lipoproteins, respectively, and in whole serum before and 3 and 12 months after parathyroidectomy are shown. Paired t-test was used to calculate the significance of difference between 0–3, 3–12 and 0–12 months. Two-tailed significance limits were used.

<table>
<thead>
<tr>
<th></th>
<th>Very low density lipoproteins</th>
<th>Low density lipoproteins</th>
<th>High density lipoproteins</th>
<th>Whole serum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>Significance 0–3</td>
<td>3</td>
<td>Significance 3–12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>t</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Triglyceride mmol/l</td>
<td>1.19 ± 0.31</td>
<td>1.15</td>
<td>n. s.</td>
<td>1.10 ± 0.39</td>
</tr>
<tr>
<td>Cholesterol mmol/l</td>
<td>0.54 ± 0.18</td>
<td>0.72</td>
<td>n. s.</td>
<td>0.51 ± 0.23</td>
</tr>
<tr>
<td>Triglyceride mmol/l</td>
<td>0.50 ± 0.17</td>
<td>-1.12</td>
<td>n. s.</td>
<td>0.54 ± 0.16</td>
</tr>
<tr>
<td>Cholesterol mmol/l</td>
<td>3.49 ± 0.96</td>
<td>-1.41</td>
<td>n. s.</td>
<td>3.69 ± 0.90</td>
</tr>
<tr>
<td>Triglyceride mmol/l</td>
<td>0.26 ± 0.06</td>
<td>-2.24</td>
<td>*</td>
<td>0.32 ± 0.10</td>
</tr>
<tr>
<td>Cholesterol mmol/l</td>
<td>1.30 ± 0.30</td>
<td>-2.40</td>
<td>**</td>
<td>1.46 ± 0.26</td>
</tr>
<tr>
<td>Triglyceride mmol/l</td>
<td>2.04 ± 0.35</td>
<td>0.17</td>
<td>n. s.</td>
<td>2.02 ± 0.53</td>
</tr>
<tr>
<td>Cholesterol mmol/l</td>
<td>5.39 ± 0.89</td>
<td>-2.03</td>
<td>n. s.</td>
<td>5.81 ± 1.02</td>
</tr>
</tbody>
</table>

n. s.: not significant.  * < 0.05  ** < 0.01  *** < 0.001
lipoprotein fraction was associated with a concomitant increase of both the low density lipoprotein and high density lipoprotein triglycerides. On the other hand, serum cholesterol concentrations increased during the first post-operative year due to increases of both the low density lipoprotein and high density lipoprotein fractions. The adipose tissue lipoprotein lipase activity was not affected by the operation (Table 2). In most patients the first period following surgery was characterized by a gain in body weight. This increase in body weight, however, was small and did not cause any significant changes in the fat cell weight (Table 2).

**DISCUSSION**

In the present study of patients with primary HPT the peak serum insulin response to an iv glucose load and the insulin index were reduced after removal of a parathyroid adenoma. These findings agree with those previously reported by Kim et al. (1971) and Yasuda et al. (1975). Irrespective of the common pattern of hypersecretion of insulin in response to glucose and other stimuli, none of the studies, including ours, showed any disturbances of the glucose tolerance. Primary HPT may be associated with a complex variety of metabolic disturbances including elevated levels of parathyroid hormone (PTH), hypercalcaemia, hypophosphataemia and hyperchloraeic acidosis (Malette et al. 1974). In previous studies it appeared as if PTH, itself, did not affect the insulin release in response to glucose in human subjects nor had PTH any effect on insulin release when added to isolated rat pancreatic cells incubated in vitro (Kim et al. 1971). In dogs dietary induced hypophosphataemia was associated with a mild glucose intolerance and with an augmented glucose-stimulated insulin release independent of acute changes in plasma ionized calcium levels (Harter et al. 1976). Furthermore, in healthy subjects there seems to be a similar association between a low serum phosphate concentration and an exaggerated glucose-mediated insulin release (Lindgärde & Trell 1978). Thus, although calcium is required for insulin secretion and despite the fact that chronic hypercalcaemia has been held responsible for the hypersecretion of insulin in HPT (Kim et al. 1971; Yasuda et al. 1975) it is possible that other factors may also be involved. The present study was not primarily designed to elucidate which of these possible mechanisms was of major importance. However, it seems unlikely that the small post-operative increase of the serum phosphate concentrations was large enough to exert more than minor effects on the insulin secretion.

Among all the patients, particularly the females, there was an increased frequency of type IV hyperlipoproteinaemia. This was evident although several of the patients had an impaired general condition before parathyroidectomy. Generally otherwise a change from a well-nourished to a catabolic state is associated with a decrease in the very low density lipoproteins (Streja et al.
An increased lipolysis might be a possible explanation for the findings of elevated very low density lipoproteins in our patients with HPT. Thus, it has been reported that PTH produces lipolysis in human adipose tissue in vitro (Sinha et al. 1976; Forster et al. 1974) and also when exogenous PTH is administered in vivo (Sinha et al. 1976). As the production of very low density lipoproteins from the liver is directly related to the level of free fatty acids in plasma (Steinberg et al. 1974) it is reasonable to suggest that an increased lipolysis caused the elevated very low density lipoprotein concentrations in the present study. This hypothesis is in accordance with the fact that several hormones stimulate lipolysis in the adipose tissue via cAMP (Butcher 1970). In our patients it seems likely that the pre-operatively raised excretion of cAMP reflects a generally increased peripheral stimulation of PTH (i.e. including adipose tissue).

The lipoprotein lipase activity in adipose tissue did not differ when measured before and 3 months after operation. So, it does not seem as if a depressed lipoprotein lipase activity in adipose tissue is responsible for the increased very low density lipoproteins in the hyperparathyroid state. However, a greater part of the removal of serum triglycerides takes place in the skeletal muscle tissue than the adipose tissue in the fasting state (Rössner 1974) and an inhibiting effect of the parathyroid hormone on lipoprotein lipase activity in skeletal muscle cannot be ruled out as being partly responsible for the increase of the very low density lipoproteins pre-operatively.

The fact that the very low density lipoproteins remained increased at the first post-operative investigation was probably due to the concomitant weight gain (Goldrick et al. 1972). When thereafter the body weight did not increase further the very low density lipoproteins decreased, and reciprocally with this an increase of the low density lipoproteins was observed as previously observed in other conditions (Wilson & Lees 1972). In spite of the fact that these lipoprotein fractions were virtually unaffected immediately following the operation the high density lipoproteins increased during the first post-operative period. The high density lipoproteins are in general low when very low density lipoproteins are elevated (Fredrickson & Levy 1972). The changes in very low density lipoproteins are generally fast compared to those of high density lipoproteins following specific therapeutic regimes. In the present study it is believed that the increased very low density lipoproteins before operation were mainly due to an increase of lipolysis but 3 months after mainly to a state of weight gain. In contrast to the common pattern of subnormal levels of high density lipoproteins together with increased levels of very low density lipoproteins (Fredrickson & Levy 1972), normal values of high density lipoproteins are sometimes seen together with elevated very low density lipoproteins e.g. following excessive alcohol intake (Johansson & Medhus 1974). The assumed different causes to the increased very low density lipoproteins pre- and 3 months
post-operatively in the present study may thus explain the different concentrations of the high density lipoproteins on these occasions. The present study suggests that following parathyroidectomy the raised very low density lipoproteins decrease as a result of a normalization of lipolysis. This reduction is accompanied by an increase of both high density and low density lipoproteins. Previous studies of whole serum lipids have indicated that the post-operative increase of the cholesterol concentration might be a primary event (De Moor et al. 1973; Christensson & Einarsson 1977). The study by Christensson & Einarsson (1977), in contrast to our own, also displayed a significant increase, from depressed levels, in serum triglycerides following parathyroidectomy. The reasons for this difference are not clear but as serum lipoproteins have not been analyzed in their study the changes of the very low density lipoproteins can not be assessed. Our data suggest that the primary disorder of lipid metabolism in patients with HPT is connected with the metabolism of the triglyceride-rich very low density lipoproteins.

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