Lipid Metabolism in Acromegalic Patients before and after Selective Pituitary Adenectomy

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Abstract

Lipid metabolism was studied in 16 acromegalic patients who all underwent transsphenoidal selective pituitary adenectomy (SPA). Before the operation, their serum lipid levels correlated with none of the basal levels of serum growth hormone (GH), basal levels of plasma somatomedin-C (SM-C), fasting levels of plasma glucose (FPG), peak levels of plasma glucose (PG_p) or basal and peak levels of serum immunoreactive insulin (IRI_b and IRI_p, resp.) in the oral glucose tolerance test (OGTT), and obesity indices. The serum GH levels as well as plasma SM-C levels in the group with decreased serum high density lipoprotein-cholesterol (HDL-C) differed greatly from those of the normal HDL-C group. However, there was no significant difference in either serum GH or plasma SM-C between groups with and without metabolic abnormality of any other lipid examined.

After the operation, the basal levels of serum GH and plasma SM-C decreased significantly. In conjunction with these changes, PG_p, serum IRI_b, serum triglyceride (TG), non-esterified fatty acid (NEFA) and very low density lipoprotein (VLDL) decreased significantly. In contrast, serum HDL-C increased significantly. However, FPG, serum IRI_p, obesity indices, serum total cholesterol (TC) and serum low density lipoprotein (LDL) showed no significant change.

There were no significant differences in the levels of any serum lipid either before or after surgery among the diabetic, borderline and normal types defined by the preoperative OGTT patterns. Atherogenic indices (AIs) decreased significantly and returned to normal postoperatively.

These results suggest that obesity or secondary diabetes is not a direct cause of hyperlipidemia in acromegaly. The prognosis of acromegaly is affected by arteriosclerotic complications. It is intriguing, therefore, that AIs were normalized by transsphenoidal SPA. Being rather a safe procedure, it can be performed without hesitation, aside from a conservative treatment.

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The incidences of arteriosclerotic diseases (ASD) such as coronary arterial and cerebrovascular diseases are high in an acromegalic population, irrespective of age. These diseases are attributed to abnormal carbohydrate metabolism and hypertension which often complicate acromegaly (Wright *et al.*, 1970; Shizume, 1980). Hyperlipidemia is also an important risk factor for ASD and many acromegalic patients have hyperlipemia (Nikkilä and Pelkonen, 1975; Takeda *et al.*, 1982). The mechanism by which lipid metabolism is disordered in this disease has not been fully elucidated, although various theories have been advanced to explain its pathogenesis. For example, excess growth hormone (GH) promotes insulin secretion and accelerates triglyceride (TG) synthesis in the liver (Nikkilä and Pelkonen, 1975); the lipolytic action of GH elevates serum levels of non-esterified fatty acid (NEFA), which enhances the turnover of TG and increases its serum levels (Raben and Hollenberg, 1959; Rabinowitz *et al.*, 1966); GH inhibits lipoprotein lipase (LPL) and hepatic TG lipase (HTGL) activities (Murase *et al.*, 1980; Murase *et al.*, 1981; Takeda *et al.*, 1982; Asayama *et al.*, 1984); and somatomedin, a GH mediator, promotes liposynthesis and inhibits lipolysis (Demura and Demura, 1982). It has been well documented that diabetic complication has some effects on the pathology of acromegaly. Like excess GH, excess prolactin (PRL) was found in 20–60% of acromegalics (Kameyama *et al.*, 1980; Camanni *et al.*, 1982; Kanie *et al.*, 1983; Tsuchiya *et al.*, 1985). Excess PRL may also affect lipid metabolism in acromegaly (Garrison and Scow, 1975; Aisaka, 1982; Botta *et al.*, 1982; Demura and Demura, 1982).

Transsphenoidal selective pituitary adenectomy (SPA) combined with bromocriptine administration is nowadays performed on acromegalic patients rather frequently. However, there are few reports detailing

lipid metabolism before and after the operation. In this study we investigated pre- and postoperative lipid metabolism in acromegalic subjects.

Materials and Methods

Subjects

Sixteen acromegalic patients aged 21–60 years (mean $\pm$ SD, 45.0 ± 11.9 years) participated in this study. They consisted of 7 males (46.9 ± 10.4 years) and 9 females (43.6 ± 13.4 years). None of them had a hereditary background of hyperlipemia. SPA was performed on all patients via a transsphenoidal route. Basal levels of serum GH, plasma somatomedin-C (SM-C) and serum lipids were determined before and after SPA.

Tolerance tests and stimulation tests

Oral glucose tolerance tests (OGTT), thyrotropin releasing hormone (TRH) tests and luteinizing hormone releasing hormone (LHRH) tests were done before and 2–5 weeks after surgery. These three kinds of tests were conducted on separate days, each starting at 0600 h after an overnight fast, except that the patient was allowed to take water ad libitum. During each test the patient was allowed to rest comfortably, but was not allowed to take food or sleep. An indwelling needle was put in an arm vein, and then 75 g glucose (Trelan-G; Shimizu Pharmaceutical Co. or Takeda Chemical Industries, Osaka, Japan) was administered orally for the OGTT, and 0.5 mg TRH (Protirelin; Tanabe Seiyaku Co., Osaka, Japan) and 0.1 mg LHRH (Gonadorelin Diacetate; Tanabe Seiyaku Co.) were injected into the contralateral arm vein simultaneously for the TRH test or the LHRH test. Blood samples were obtained via the indwelling needle immediately before (0 min), and 30, 60, 90, 120, 150 and 180 min after glucose ingestion for glucose and immunoreactive insulin (IRI) measurement; 0, 15, 30, 60, 90, 120 and 180 min after the injection of TRH for GH measurement; and 0, 30, 60, 90 and 120 min after the injection of LHRH for GH measurement. Sodium fluoride-treated plasma samples for glucose measurement and serum samples for IRI and GH measurement were separated promptly and were stored at -20°C until assay.

Assays

Plasma glucose was measured by a glucose-oxidase method on a Beckman II Glucose Analyzer (Beckman Instruments, Fullerton, Calif., U. S. A.). The normal range of fasting plasma glucose (FPG) as determined by this method was 70–110 mg/dl.

Serum GH was measured by double antibody radioimmunoassay (RIA) with the HGH-RIA KIT (Dainabot Radioisotope Laboratories, Tokyo, Japan). The lower limit of detection was 1.0 ng/ml. The intra- and interassay coefficients of variation (CV) were 3.0% at 13.3 ng/ml and 4.8% at 7.9 ng/ml, respectively. The overall recovery was $107.5 \pm 11.6\%$ (mean $\pm$ SD). The normal range of overnight fasting, resting levels of GH was 0–5.0 ng/ml.

SM-C was measured in EDTA Na₂-treated plasma by double antibody RIA with the SM-C RIA Kit (Nichols Institute Diagnostics, San Juan Capistrano, Calif., U. S. A.). The lower detection limit was 5.0 mIU/ml. The intra- and

interassay CV were 7.2% at 2.1 IU/ml and 13.3% at 1.6 IU/ml, respectively. The overall recovery was $99.2 \pm 9.2\%$. The antiserum for SM-C showed virtually no cross-reactivity with human GH (hGH), human PRL (hPRL), human thyroid stimulating hormone (hTSH), porcine proinsulin, porcine insulin or porcine glucagon. The normal range determined in 22 healthy adults was 0.3–2.5 IU/ml (Tsuchiya *et al.*, 1985).

Serum IRI was measured by solid phase RIA with the PHADEBAS INSULIN TEST (Pharmacia Diagnostics, Uppsala, Sweden). The sensitivity of the assay was 3.0 μ U/ml. The intra- and interassay CV were 3.7% at 15.1 μ U/ml and 7.3% at 6.5 μ U/ml, respectively. The overall recovery was $98.4 \pm 11.6\%$. The normal range of overnight fasting, resting levels of serum IRI was 0–20.0 μ U/ml.

Serum total cholesterol (TC), TG, NEFA, low density lipoprotein (LDL) and very low density lipoprotein (VLDL) were measured by an enzymatic method (Allain *et al.*, 1974;

Table 1. Levels of serum lipids, serum GH and plasma SM-C and incidences of metabolic abnormalities of lipids in 16 acromegalic patients

Group	Serum lipid (mg/dl or μ Eq/l) ^c	Normal range	Serum GH (ng/ml)	Plasma SM-C (IU/ml)	N= ^a	Incid ^b (%)
Hyperchol ^d	258.6 $\pm$ 19.7	160.0–210.0	32.9 $\pm$ 8.8	6.2 $\pm$ 1.3	5	31.3
Normochol ^d	169.6 $\pm$ 4.2		91.6 $\pm$ 25.1	6.2 $\pm$ 1.0	11	
Hypertrigly ^a	259.4 $\pm$ 36.1	42.0–169.0 ^f (35.0–136.0)	37.5 $\pm$ 9.4	7.0 $\pm$ 1.4	6	37.5
Normotrigly ^a	114.5 $\pm$ 7.8		94.8 $\pm$ 27.5	5.7 $\pm$ 0.9	10	
High NEFA	698.1 $\pm$ 47.3	100.0–540.0	112.1 $\pm$ 32.5	5.7 $\pm$ 1.6	4	25.0
Normal NEFA	373.9 $\pm$ 36.8		60.4 $\pm$ 21.7	6.4 $\pm$ 0.9	12	
High LDL	869.0 $\pm$ 117.0	250.0–600.0	35.5 $\pm$ 12.8	6.0 $\pm$ 2.3	3	20.0
Normal LDL	466.5 $\pm$ 19.7		87.8 $\pm$ 23.3	6.1 $\pm$ 0.9	12	
High VLDL	203.0 $\pm$ 52.0	0–150.0	46.1 $\pm$ 24.4	5.1 $\pm$ 2.3	2	13.3
Normal VLDL	78.4 $\pm$ 7.1		82.1 $\pm$ 22.0	6.2 $\pm$ 0.9	13	
Low HDL-C	29.6 $\pm$ 1.6	35.0– 58.0 ^f (38.0– 65.0)	105.6 $\pm$ 27.2*	7.6 $\pm$ 0.9**	8	53.3
Normal HDL-C	39.4 $\pm$ 0.7		45.0 $\pm$ 23.8*	4.4 $\pm$ 1.1**	7	

Each value represents the mean $\pm$ SE.

a: No. of patients. b: Incidences of metabolic abnormalities of lipids. c: Units for all parameters except NEFA are mg/dl. d: Hyper- or normocholesterolemic group. e: Hyper- or normotriglyceridemic group. f: Normal ranges in males followed by those in females in parentheses.

*: Significantly different ($p < 0.005$). **: Significantly different ($p < 0.05$).

Hayashi and Ogawa, 1976), a lipoprotein lipase-glycerol kinase-pyruvate kinase-lactate dehydrogenase method (Bucolo *et al.*, 1975), an acyl CoA synthetase-acyl CoA oxidase-peroxidase method (Takahashi *et al.*, 1975), heparin-calcium nephelometry (Koide, 1975) and heparin-calcium nephelometry (Koide *et al.*, 1975), respectively, on a TBA-80S Auto Analyzer (Toshiba Instruments, Tokyo, Japan). Serum high density lipoprotein-cholesterol (HDL-C) was measured by a precipitation method with a heparin- CaCl_2 series reagent (Liedke *et al.*, 1978; Ash and Hentschel, 1978; Fujita *et al.*, 1980) on an Auto Analyzer II (Technicon Instruments, New York, U. S. A.). The normal ranges of these lipids are shown in Table 1.

In order to reduce interassay variations, all samples from each individual subject were analyzed at the same time in each assay.

Calculations and statistical analyses

Each value is expressed as the mean $\pm$ SD or mean $\pm$ SE. The standard weight (W_s) was calculated by Broca's innovated method [$W_s = (\text{height in cm} - 100) \times 0.9 \text{ kg}$]. The obesity index was calculated by the formula, obesity index (%) = $(\text{weight}/W_s) \times 100$. The normal range of this index was 90–110%. Student's two-tailed, paired t-test was used to compare pre- and postoperative data in the individual cases and Student's two-tailed, unpaired t-test to compare determinations between groups. Wilcoxon's test was employed to assess the significance of differences in the serum GH concentration between groups with and without an abnormality of any serum lipid. An α probability less than 0.025 was accepted as an indication of a significant difference.

Results

The incidences of lipid metabolic disorders in the present series are shown in Table 1. None of the 7 males had hypercholesterolemia, while its incidence was 55.6% (5/9) in the female group. The incidence of hypertriglyceridemia was 14.3% (1/7) in the male group and 55.6% (5/9) in the female group. A study of phenotypes as assessed merely from TC/TG ratios

according to the WHO classification of hyperlipemia (Beaumont *et al.*, 1970) revealed one case of type II_a and another of type II_b, but the phenotypes of the remaining cases could not be identified.

None of the basal levels of serum GH and plasma SM-C, FPG levels, peak plasma glucose (PG_p) levels in the OGTT, basal and peak serum IRI (serum IRI_b and IRI_p, resp.) levels in the OGTT, and obesity indices were correlated with any serum lipid. Serum GH and plasma SM-C were significantly different only between the low and normal HDL-C groups and not between a pair of groups, one with and the other without metabolic disorder of any other lipid examined (Table 1).

The basal levels of serum GH and plasma SM-C, which had been markedly elevated to $73.3 \pm 18.6 \text{ ng/ml}$ (mean $\pm$ SE) and $6.2 \pm 0.8 \text{ IU/ml}$, respectively, before surgery, decreased significantly to $3.3 \pm 0.7 \text{ ng/ml}$ and $1.2 \pm 0.3 \text{ IU/ml}$, respectively ($p < 0.001$). Postoperative decreases in serum GH and plasma SM-C were seen in all individuals. In 13 patients, they returned to normal ($< 5.0 \text{ ng/ml}$ and $< 2.5 \text{ IU/ml}$, resp.). Furthermore, the GH responses to the postoperative TRH and LHRH tests were normal, even in those in whom GH had responded abnormally to these tests before surgery. The peak levels of GH in response to TRH decreased significantly from the preoperative levels of 298.1 ± 91.7 to $11.9 \pm 2.9 \text{ ng/ml}$ postoperatively ($p < 0.006$) and those in response to LHRH from 149.9 ± 60.8 to $6.6 \pm 3.0 \text{ ng/ml}$ ($p < 0.03$) (Fig. 1).

According to the 75 g OGTT criteria established by the Japan Diabetes Society (Kosaka *et al.*, 1982), 4 cases were classified as the diabetic type, 9 as the borderline type and the remaining 3 as the normal type before surgery. Out of the 4 diabetic type cases, 2 still gave a diabetic pattern of response to the postoperative OGTT, but one case changed into the borderline type and the last one into the

Fig. 1. Responses of GH to intravenous TRH (upper panels, $n=16$) and LHRH injection (lower panels, $n=15$) in acromegalic patients before and after surgery.

normal type after surgery. All but one borderline type case had a normal pattern after surgery. The exceptional case could not be examined postoperatively. Of the 3 normal type cases, one responded normally to the postoperative test as well, but another changed into the borderline type after

surgery. The last case could not be examined postoperatively. The postoperative FPG levels (93.4 ± 5.8 mg/dl, mean $\pm$ SE) were not significantly different from the preoperative levels (144.9 ± 26.7 mg/dl) in 14 patients, although they showed a tendency to decrease after surgery. PG_p de-

creased significantly after surgery (168.9 ± 20.8 vs 254.2 ± 35.1 mg/dl, $p < 0.02$) in the 14 patients (Fig. 2, upper panels). Serum IRI_b decreased significantly after surgery (6.1 ± 1.1 vs 11.2 ± 1.7 μ U/ml, $p < 0.003$). Serum IRI_p tended to decrease after surgery

Fig. 2. Responses of glucose (upper panels, $n=14$) and IRI (lower panels, $n=14$) to oral glucose administration in acromegalic patients before and after surgery.

Fig. 3. Obesity indices (n=15) and serum TC (n=13), TG (n=13), NEFA (n=13), LDL (n=13), VLDL (n=13) and HDL-C (n=13) levels in acromegalic patients before and after surgery. $\bar{x} \pm SE$ represents the mean $\pm$ SE. Shaded areas indicate the normal ranges, provided that those in males are shown as for serum TG and HDL-C. S: statistically significant, NS: statistically not significant.

(from 52.5 ± 11.7 to 83.8 ± 23.5 $\mu\text{U/ml}$), but no significant difference was present between the two determinations (Fig. 2, lower panels).

The obesity indices, serum TC and serum LDL were apt to decrease postoperatively, though the changes were not significant. Serum TG, NEFA and VLDL levels decreased significantly in 13 patients (from 153.6 ± 22.1 to 75.6 ± 7.9 mg/dl, $p < 0.004$; from 474.0 ± 54.5 to 174.8 ± 34.5 $\mu\text{Eq/l}$, $p < 0.0003$; and from 94.2 ± 15.9 to 39.4 ± 6.8 mg/dl, $p < 0.003$, resp.). In contrast, serum HDL-C increased significantly from 33.5 ± 1.8 to 42.7 ± 2.0 mg/dl ($n = 13$, $p < 0.0002$) (Fig. 3).

However, the surgery-induced decrement in serum GH, PG_p or serum IRI_b ($-\Delta\text{GH}$, $-\Delta\text{PG}_p$ or $-\Delta\text{IRI}_b$, resp.) had no significant correlation with the surgery-induced de-

crement in serum TG, NEFA or VLDL ($-\Delta\text{TG}$, $-\Delta\text{NEFA}$ or $-\Delta\text{VLDL}$, resp.), or with the increment in serum HDL-C ($\Delta\text{HDL-C}$). Furthermore, no significant differences were recognized in the level of any serum lipid before or after surgery among the three types (diabetic, borderline, normal) defined on the basis of the preoperative OGTT patterns (Fig. 4).

Eleven patients could be examined for the atherogenic index [$\text{AI} = (\text{TC} - \text{HDL-C}) / \text{HDL-C}$, normal range < 4.0] (Gordon *et al.*, 1977; Yamamoto *et al.*, 1982; Mizuno *et al.*, 1984) both before and after surgery. Their AIs, which were increased to 4.8 ± 1.5 (mean $\pm$ SD) preoperatively, decreased significantly and returned to normal (3.7 ± 0.9 , $p < 0.009$) after surgery.

Fig. 4. Pre- and postoperative levels of serum lipids in the diabetic (●, $n = 4$), borderline (⊗, $n = 9$) and normal (○, $n = 3$) types (defined according to the preoperative OGTT profiles) of acromegaly. Each ⊗, ⊗ and ⊗ represents the mean $\pm$ SE. Shaded areas indicate the normal ranges, provided that those in males are shown for serum TG and HDL-C.

Discussion

Nikkilä and Pelkonen (1975) detected hypercholesterolemia in 11% of acromegalic patients and hypertriglyceridemia in 32% and 19% of male and female patients, respectively. Takeda *et al.* (1982) found one or another form of hyperlipemia in 62.5% of acromegalic patients. The incidence of hyperlipemia, which was defined as an increase in the concentration of any lipid in serum, was as high as 75.0% (12/16) in the present series. According to the WHO phenotype classification of hyperlipemia, type II_a was recognized in only one of our 16 patients with acromegaly and type II_b in another. Nikkilä and Pelkonen (1975) found type IV at a much higher frequency than the generally expected frequency (19.6% vs 7.3%) in acromegaly.

In our acromegalic subjects the level of no lipid in serum correlated with serum GH, plasma SM-C, FPG, PG_p, serum IRI_b, IRI_p or obesity indices. These observations were in good accord with an earlier report (Nikkilä and Pelkonen, 1975). Takeda *et al.* (1982) stated that serum GH levels were significantly higher in acromegalic patients with hypercholesterolemia than in those without it. However, the present study demonstrated a significant difference in serum GH concentration only between the low and normal HDL-C groups and never between a group with a metabolic disorder of any other lipid and its counterpart.

The normalization of the basal level of serum GH and its response to TRH and LHRH suggested that pituitary adenomas could be almost completely extirpated in all of our patients (Hoyte and Martin, 1975; Faglia *et al.*, 1978). Obesity or diabetes is said to not contribute to the occurrence of hyperlipemia in acromegaly (Nikkilä and Pelkonen, 1975; Takeda *et al.*, 1982). Our findings were compatible: Although serum lipid levels were changed significantly by

surgery, obesity indices were not. Therefore, obesity is unlikely to be a direct cause of hyperlipemia. On the other hand, transsphenoidal SPA improved plasma glucose response to the OGTT and caused significant decreases in PG_p and serum IRI_b in the OGTT as well as significant changes in serum lipid levels. These raised the possibility of diabetes having some relation to hyperlipemia. However, no significant differences were found in any serum lipid before or after surgery among the three types defined according to the preoperative OGTT profiles. Therefore, the direct etiologic role of diabetes in hyperlipemia seems to be denied.

GH has been reported to inhibit both LPL and HTGL not only *in vivo* (Murasé *et al.*, 1980; Takeda *et al.*, 1982; Asayama *et al.*, 1984) but also *in vitro* (Murasé *et al.*, 1981). Probably for this reason, many acromegalic patients have hyperlipemia. In this study SPA induced significant changes in serum lipid levels and significant decreases in serum GH and plasma SM-C levels. A reasonable inference from this fact is that GH and/or SM-C might play an etiologic role in the derangement of lipid metabolism in acromegaly.

In our acromegalic patients AIs decreased significantly and returned to normal after surgery. It is generally accepted that increased mortality from acromegaly is largely due to frequent arteriosclerotic complications. In this connection, it was reported that mortality was significantly lower in a group treated for ASD than in an untreated group (Wright *et al.*, 1970). Since transsphenoidal SPA and bromocriptine administration can be conducted relatively safely, we think that they should be tried positively in the management of acromegalic patients.

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