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LDL physical properties, lipoprotein and Lp(a) levels in acromegalic patients. Effects of octreotide therapy

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Abstract

High vascular morbidity and mortality is associated with acromegaly. The aim of the present study was to assess the effects of octreotide therapy on several known cardiovascular risk factors and to correlate them with octreotide-induced hormonal changes. Lipid levels, LDL particle size distribution as evaluated by single vertical spin density gradient ultracentrifugation, apolipoproteins AI and B, lipoprotein (a) [Lp(a)] concentrations and apo(a) phenotypes were evaluated in 20 non-diabetic acromegalic patients (6 M, 14 F), with normal thyroid, adrenal and gonadal function, aged 29–66 years. Normal subjects (20), matched for age, sex and BMI served as control for lipid variables. Acromegalic patients were characterized by lower HDL cholesterol (and apoA-I) and by higher Lp(a) concentrations in comparison to controls. Treatment with octreotide (100 μg t.i.d. for 3 months) led to: an increase in HDL cholesterol (median: +22%), a decrease in LDL cholesterol (−14%) and a decrease of the Lp(a) levels (all phenotypes) (−28%). The expected decreases of IGF-I levels (median: −48%) and 7-h AUC of GH (−50%), insulin (−40%), and glucagon (−20%) were observed. Only Lp(a) modifications showed a correlation with GH modifications. The study of LDL physical properties showed that acromegalic patients had smaller and/or more dense LDL particles, in comparison with normal controls (relative flotation rate, Rf: 0.40 ± 0.03 versus 0.42 ± 0.02 $P < 0.05$), an alteration that might contribute to the high vascular risk of acromegalic patients. However, the LDL subfraction distribution remained unmodified during octreotide therapy (Rf 0.39 ± 0.03). In conclusion, this study shows that in acromegalic patients octreotide treatment is indeed associated with an amelioration of some lipoprotein parameters, i.e. LDL, HDL, and Lp(a) concentrations. However, this treatment has no effect on the small and/or dense LDL particles present in these patients.

Keywords: Acromegaly; Octreotide; Somatostatin-analogs; Lipoproteins; Small dense low density lipoprotein; Lipoprotein(a); Apo(a)isoform

1. Introduction

Acromegaly is a rare and serious disease associated with an increased cardiovascular mortality [1,2]. For this reason the effects on the cardiovascular risk factors induced by the medical therapy of this disease must be thoroughly evaluated. Octreotide is the most widely investigated and most frequently used somatostatin analogue in the treatment of acromegaly.

Our previous experience, involving a large number of acromegalic patients from all over Italy, seemed to indicate that octreotide, besides decreasing GH and IGF-I concentrations, had also beneficial effects on lipid levels [3]. In fact, a significant decrease of both total and LDL cholesterol was observed after 3 months of octreotide treatment. However, besides LDL cholesterol concentrations, it is now well recognized that the LDL physical characteristics are important, a predominance of small, dense LDL particles being associated

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with increased vascular risk [4,5]. Recent data suggest that GH excess has a direct effect on LDL subfraction distribution [6]; however, no data exist about the possible effects of therapy, and in particular of octreotide, on LDL size and density.

Increased circulating concentrations of lipoprotein(a) [Lp(a)] may represent an independent risk factor for cardiovascular disease in acromegaly. In fact, although the mechanism by which Lp(a) influences cardiovascular morbidity is largely unknown, several epidemiological studies have shown an association between coronary heart disease incidence and Lp(a) levels above a threshold concentration of 20–30 mg/dl [7–9]. Lp(a) shows considerable size variation (from ≈ 300 to $\approx$ 800 KDa) among individuals owing to different numbers of cysteine-rich sequences (homologous to plasminogen kringle 4) in the apolipoprotein(a) [apo(a)], resulting in different apo(a) phenotypes. The serum concentrations of Lp(a) are inversely related to its size, which is genetically determined. Although it is widely accepted that GH has important effects in increasing Lp(a) concentrations [10,11], it is not known if all apo(a) phenotypes are equally sensitive to GH modifications.

The aim of the present study was to assess the effects of octreotide therapy on LDL physical properties, and on lipoprotein and Lp(a) levels (in relation also to the apo(a) phenotype) and to correlate them with hormonal and metabolic changes induced by the therapy. A secondary objective was to verify if acromegaly, non-complicated by diabetes, is associated with modifications of these lipid parameters.

2. Materials and methods

2.1. Design

Open, multicentric prospective study. The study was approved by the local ethics committees and written informed consent was obtained from all patients.

2.2. Subjects

Patients (20) with active acromegaly (as shown by elevated serum IGF-I levels and serum GH not suppressible by glucose load) (14 women, six men), aged 29–66 years (mean $\pm$ SD $= 46 \pm 10$ years), were recruited. Ten patients had been previously submitted to unsuccessful adenomectomy, followed in one case by conventional pituitary radiotherapy and in seven cases by medical therapy with bromocriptine (three patients) and/or somatostatin analogs (seven patients) that was discontinued 1 or more months prior to the start of this study.

Only patients with normal thyroid, adrenal and gonadal functions were admitted to the study, and none of the patients was taking drugs known to influence lipid metabolism, including estrogen-containing drugs or hypoglycaemic agents. Patients with known diabetes mellitus were excluded, and all patients had fasting glucose levels below 110 mg/dl and normal glycated hemoglobin levels. When considering glucose response to OGTT, however, four patients showed an impaired glucose tolerance according to the criteria of the Expert Committee of the American Diabetes Association [12].

A group of 20 subjects, matched for age, sex and BMI (24 ± 2 Kg/m^2) served as control for lipid variables.

2.3. Design of the study

Clinical and biochemical evaluations were performed at baseline and after 3 months of therapy with octreotide (Longastatina®, Italfarmaco S.p.A.), 100 μg t.i.d. sc under controlled dietary conditions. Pre-treatment studies included the following tests: a 4-h OGTT (75 g orally, to confirm active acromegaly) and a 7-h saline infusion, with a light, standardized meal of about 600 kcal given at 4 h, for GH, insulin, glucagon and glucose assay. IGF-I and lipid parameter measurements were done on two basal samples taken on 2 different days. After 3 months of therapy, the same 7-h study giving octreotide 100 μg sc at time 0 and, on a different day, OGTT, giving glucose 2-h after octreotide sc injection, were carried out. Additionally, serum levels of TSH, free T3, free T4, and, in the women, estrogen and progesterone, together with routine laboratory biochemical analysis, were also evaluated.

2.4. Analytical methods

All lipid assays were performed at the lipoprotein laboratory in the Department of Internal Medicine, University of Padova.

Cholesterol [13], HDL cholesterol [14], and triglycerides [15] were measured by standard methods. The coefficient of variation (CV), intra-assay and inter-assay, for total cholesterol were 1.0 and 1.2%, respectively, for triglycerides 1.5% and 2.5%, for HDL cholesterol 1.2% and 1.5%. LDL cholesterol levels were calculated using the equation of Friedewald [16].

LDL distribution and flotation properties were evaluated by single vertical spin density gradient ultracentrifugation (SVS-DGUC) using a modification of the method described by Chung et al. [17,18]. One aliquot of 1 ml of plasma adjusted to a density of 1.080 g/ml (final volume 4 ml), was layered underneath 9 ml of a 1.006 g/ml NaCl solution, producing a discontinuous salt gradient in a Beckman VTi 65.1 vertical rotor (Beckman Instruments, Inc., Palo Alto, CA, USA).

Samples were centrifuged at 65 000 rpm for 70 min (total t2 = 2.36 × 1011) at 5°C; the tubes were then fractionated (Fraction Recovery System by Beckman Instruments, Palo Alto, CA, USA) from the bottom at a flow rate of 1.7 ml/min, and 37 0.35-ml fractions were collected. Total cholesterol was measured in each fraction. The relative flotation rate (Rf), which characterizes LDL peak buoyancy, was obtained by dividing the fraction number containing the LDL-cholesterol peak by the total number of fractions collected. The CV for LDL Rf was 1.1% intra-assay and 1.7% inter- assay.

Apolipoproteins AI and B (apo-AI and apo-B) were measured by radial immunodiffusion using standards and plates from Daiichi Pure Chemicals Company. The CV for apo-AI and apo B were 2.4% and 1.9%, respectively, intra-assay, and 3.8 and 4.3%, respectively, inter-assay.

Lp(a), was measured by non competitive sandwich-ELISA method (Immuno AG, Vienna Austria). Lp(a) glicoprotein phenotype was determined by gel electrophoresis according to Utermann et al. [19] (Immuno AG, Vienna, Austria). The CV, intra-assay and inter-assay, was 2.9 and 4.1%, respectively.

Hormone measurements were also centralized. Serum GH assay was carried out by IFMA (Delfia, Pharmacia®) at the University of Milano. Plasma IGF-I was measured by RIA after acid-ethanol extraction at the University of Genova [20]. The upper limit of normal IGF-I levels (mean ± 3SD) was 366 μg/l for age-matched adults. Insulin and glucagon levels were measured by commercial RIA kits (provided by Medgenix Diagnostics, Belgium and DPC, USA, respectively) at the University 'La Sapienza' of Rome. Intra-assay and inter-assay CV were below 5 and 8%, respectively, for all hormone measurements.

Table 1
Effects of 3 months of octreotide therapy (100 μg t.i.d., sc) on hormonal and metabolic parameters (mean ± SD and AUC ± SD)

Parameters	Before therapy	Octreotide	P
IGF-I (ng/ml)	665.5 ± 155	354.3 ± 206	<0.01
GH (μg/l)[a]	14.3 ± 31	7.5 ± 22	<0.01
GH, 7-h AUC (μg∗min/l)	6021 ± 13283	3002 ± 9089	<0.01
Insulin (μU/ml)[a]	47.2 ± 26	29.9 ± 21	<0.01
Insulin, 7-h AUC (μU∗min/ml)	19 718 ± 11137	11 904 ± 8086	<0.01
Glucagon (pgml)[a]	72.2 ± 24	59.6 ± 25	<0.05
Glucagon, 7-h AUC (pg∗min/ml)	30 018 ± 10494	24 120 ± 10370	<0.05
Glucose (mg/dl)[a]	100.4 ± 10	112.0 ± 16	<0.01
Glucose, 7-h AUC (mg∗min/dl)	42 184 ± 4480	47 003 ± 6686	<0.01

[a] Mean of eight samples taken hourly during 7-h saline infusion.

2.5. Statistical analysis

Data with multiple observations for each time (GH, insulin) were quantified by measuring the area under the curves (AUC) using the trapezoidal method. Areas and the mean hormonal and lipid levels were compared using non-parametric statistics (Wilcoxon's signed rank test or Mann–Whitney *U*, as appropriate). Correlation between continuous variables was investigated by regression analysis. All results are expressed as mean ± SD, unless otherwise stated. Significance is taken as $P < 0.05$.

3. Results

3.1. Hormonal and metabolic changes induced by octreotide

Basal serum GH and IGF-I were elevated in all patients. During octreotide therapy, serum GH levels (mean of eight samples taken hourly during 7-h saline infusion) decreased from 14.3 ± 31 to 7.5 ± 22 μg/l (median: −60%) ($P < 0.01$). GH AUC (7-h) was halved ($P < 0.01$). Plasma IGF-I levels (mean of two samples) decreased from 665 ± 155 to 354 ± 206 ng/ml (median: −48%); ($P < 0.01$). Nine patients showed a decrease of mean serum GH levels to below 2 μg/l and normalized IGF-I levels, while one patient normalized IGF-I levels even if mean serum GH concentration was 5.5 μg/l.

During octreotide therapy mean insulin and glucagon concentrations significantly decreased, while glucose levels (both pre-prandial and post-prandial), significantly increased (Table 1). Expressed as 7-h AUC, a mean insulin decrease of about 40%, a mean glucagon decrease of about 20% and a mean glucose increase of 11% were observed.

As far as the response to a glucose load is concerned, during treatment the blood glucose peak at 2 h (4 h after octreotide administration) was increased in comparison with the baseline test (glucose peak: 194.1 ± 50 versus 162.4 ± 42 mg/dl, $P < 0.01$). Insulin release after glucose load was significantly reduced during octreotide therapy with respect to baseline (129 ± 89 versus 155 ± 243 μU/ml, $P < 0.01$).

3.2. Lipids

Before treatment, fasting total cholesterol was 207 ± 47 mg/dl, ranging from 128 to 291 mg/dl, and being higher than 200 mg/dl in ten patients. After treatment, it slightly decreased to 196 ± 47 (range from 137 to 305 mg/dl, median: −5.%), being higher than 200 mg/dl (5.2 mol/l) in seven patients.

Table 2
Fasting lipid, lipoprotein levels and the relative flotation rate, an index of LDL peak buoyancy, in 20 acromegalic patients before and after 3 months of octreotide therapy (100 μg t.i.d., sc) in respect to 20 normal controls[a]

Parameters	Controls	Acromegalics	
		Before therapy	Octreotide
Total cholesterol (mg/dl)	207 ± 42	207 ± 47	196 ± 47
Total triglycerides (mg/dl)	84 ± 30	98 ± 94	99 ± 38
LDL cholesterol (mg/dl)	125 ± 40	146 ± 43**	125 ± 40
HDL cholesterol (mg/dl)	65 ± 13	42 ± 10*,**	51 ± 15*
Apo-AI (mg/dl)	175 ± 25	131 ± 17*	140 ± 18*
Apo-B (mg/dl)	89 ± 15	84 ± 27	79 ± 26
Lp(a) (mg/dl)	13 ± 13	19 ± 19**	14 ± 13
Relative flotation rate (Rf)	0.42 ± 0.02	0.40 ± 0.03*	0.39 ± 0.03*

[a] Data are given as mean ± SD.
* $P < 0.05$ versus controls.
** $P < 0.05$ versus octreotide.

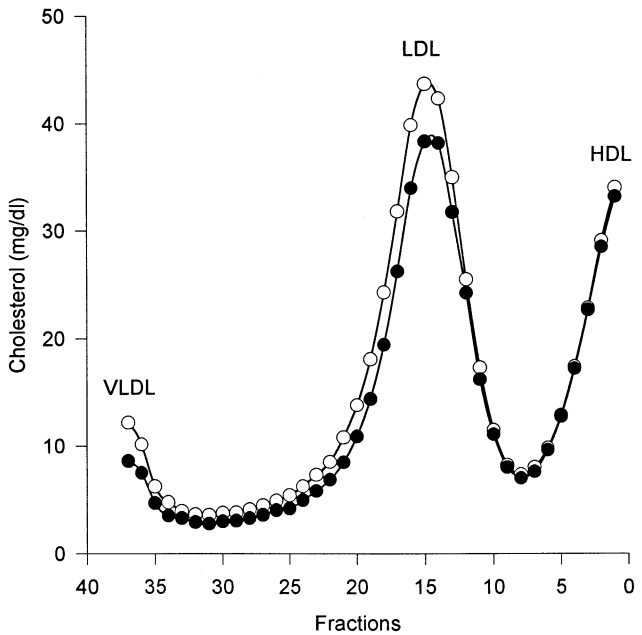

Fig. 1. Vertical spin density gradient ultracentrifugation of plasma lipoproteins in acromegalic patients before (open circles) and during (closed circles) octreotide therapy.

Octreotide therapy induced a significant decrease of LDL cholesterol from 142 ± 41.1 to 125 ± 40 mg/dl (median: − 14%, $P < 0.05$) and a significant increase of HDL cholesterol from 41.7 ± 9.7 to 50.6 ± 15.2 mg/dl (median: + 22%, $P < 0.05$). The number of patients with HDL-cholesterol above 50 mg/dl increased from 4 to 9 and the number of patients with LDL-cholesterol below 130 mg/dl increased from 8 to 13. Triglyceride levels were not modified by octreotide administration. Slight hypertriglyceridemia was present in two patients only, and in both triglyceride levels decreased (from 228 to 206 mg/dl, and from 161 to 115 mg/dl).

In respect to normal subjects, there was no significant difference in the pre-treatment or post-treatment levels of total cholesterol and triglycerides. HDL cholesterol levels of untreated acromegalic patients were significantly lower than HDL cholesterol levels of normal subjects (Table 2). The statistical significance was still present when considering post-treatment HDL values.

Single vertical spin-LDL ultracentrifugation showed that the physical characteristics of LDL before and during therapy remained unmodified (Fig. 1). In fact the relative flotation rate, Rf, was 0.40 ± 0.03 before octreotide treatment and 0.39 ± 0.03 after therapy. In comparison with controls, the LDL particles (both before and during therapy) in acromegalic patients appeared different, with a significantly lower Rf (Table 2).

During therapy apo-AI increased and apo-B decreased in parallel with HDL and LDL changes (Table 2), but the differences failed to reach statistical significance. Just like HDL, apo-AI were significantly lower in acromegalic patients (both before and after therapy) in comparison to normal subjects.

No significant correlations were found between these lipid modifications and GH, IGF-I, insulin, and glucagon changes. Indeed, a greater decrease of LDL was observed in patients who did not normalize GH and IGF-I concentrations in comparison with patients who did (− 19 ± 13 versus 1 ± 28%, $P < 0.05$).

Lp(a) levels were significantly reduced from 19 ± 19 to 14 ± 13 mg/dl (median: − 28%) (Table 2). Apo(a) phenotype distribution in these acromegalic patients is reported in Table 3. All phenotypes were affected by octreotide. Both pre-treatment and post-treatment Lp(a) concentrations were significantly correlated with pre-treatment ($r = 0.6$, $P < 0.01$) and post-treatment ($r = 0.5$, $P < 0.05$) GH concentrations respectively, but not with IGF-I or insulin levels. Lp(a) percent decrease observed during therapy, was significantly correlated with GH percent decrease, (Fig. 2). However, this correlation was not statistically significant when one patient who had major modifications of both GH and Lp(a) is excluded.

3.3. Other findings

Thyroid function tests remained within the normal range during the entire study period in all patients. Serum TSH, free T3 and freeT4 were unchanged (TSH: 1.1 ± 0.7 versus 1.0 ± 0.8 μU/ml; free T4: 8.4 ± 5 versus 8.4 ± 6; free T3 3.5 ± 1.5 versus 3.4 ± 1.4). In 12 women, mean 17 β-estradiol levels were 38.9 ± 68 on the day of pre-treatment saline infusion, and 40.7 ± 57

Table 3
Phenotypes of Lp(a): distribution and levels before and after octreotide (mean ± SD) in acromegalic patients

Phenotype of Apo(a)	No of patients (% of total)	Before therapy mg/dl	Octreotide mg/dl
S2	2 (10)	36.1 ± 28	22.1 ± 17
S3	7 (35)	32.8 ± 20	25.4 ± 11
S4	8 (40)	2.9 ± 1	2.3 ± 1
S2/S3	2 (10)	16.2 ± 10	11.2 ± 10
S2/S4	1 (5)	30.5	25.0

the day of control in therapy (P: NS), progesterone levels non-significantly changed from 3.1 ± 8.9 to 0.3 ± 0.3.

4. Discussion

Acromegalic patients were characterized by lower HDL cholesterol levels (and apo-AI) in comparison to controls. Treatment with octreotide led to remarkable changes of the plasma lipoprotein parameters with beneficial effects on several known cardiovascular risk factors: an increase in HDL cholesterol (+22%), a decrease in LDL cholesterol (−14%) and a decrease of the Lp(a) levels (all phenotypes) being observed. The study of LDL particles confirmed that acromegalic patients had smaller and/or more dense LDL particles in comparison with normal controls. However, the LDL subfraction distribution remained unmodified during octreotide therapy, as we have shown for the first time.

The results on the effects of octreotide on total, LDL, and HDL cholesterol and on triglyceride concentrations are in agreement with the observations previously made in another multicenter Italian study [3]. In fact in that study we found a significant decrease of both total (−9%) and LDL cholesterol (−18%), and a slight, but not significant increase of HDL (+4%) cholesterol. In both studies triglyceride levels decreased only in patients with pre-treatment hypertriglyceridemia (only two cases in the present series).

Only a few other studies report on serum lipid changes in acromegalic patients treated with octreotide [10,21–25]. A decrease of triglyceride levels has been reported [21–24], mostly in patients who had hypertriglyceridemia [22]. The different results with our study may be explained by the facts that in all the mentioned series, about one third of patients had diabetes mellitus (that we have excluded) and also that about 50% of their patients had moderate hypertriglyceridemia before treatment. No or minor modifications of triglycerides, a significant increase of HDL cholesterol, and a significant decrease of Lp(a) were observed by Lam et al. [10] and by Wildbrett et al. [25], in agreement with us, after 6 months of octreotide therapy. No significant change in LDL cholesterol levels has been previously reported. As in our study, Lp(a) apart, no correlations between lipid, and hormonal changes have been reported.

It has been shown that GH is able to increase hepatic LDL receptor expression, resulting in an accelerated elimination rate of the LDL particles and subsequent lowering of LDL cholesterol [26]. The lack of a correlation between hormonal parameters and LDL reduction, suggests that this modification is not due to the GH metabolic effects. Other factors, including octreotide, might be responsible for the LDL reduction here observed.

The data regarding LDL physical characteristics are of interest. In fact, the LDL physical properties have recently attracted a great deal of attention because of an increased risk of vascular complications associated to the presence of small and/or dense LDL particles in both diabetic and non diabetic patients [4,5].

To our knowledge, only a previous paper by Tan et al. [6] dealt with LDL subfractions distribution in acromegaly, obtaining similar results. According to this author, an increased activity of plasma cholesteryl ester transfer protein (CETP) could contribute to the enhanced formation of small dense LDL particles. Other factors might be involved in modifying the LDL physical properties in acromegalic patients. Both hyperinsulinism and reduced post-heparin lipase activity might be involved in the development of hyperlipidemia in acromegaly [6,27–29]. Hyperinsulinism and insulin resistance are associated with the presence of small and/or dense LDL particles in diabetic patients [30].

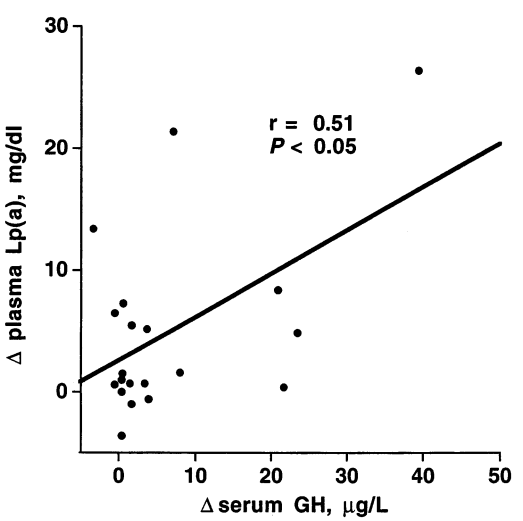

Fig. 2. Correlation between GH and Lp(a) decreases observed during octreotide therapy.

LDL physical characteristics might also be affected by the hepatic lipase activity. In fact it has been demonstrated that LDL size is inversely related to the hepatic lipase activity [31]. Hepatic lipase is low in acromegalic patients [6,27]. Therefore, the presence of small and/or dense LDL particles in acromegalic patients must be determined by factors other than hepatic lipase. Tan et al. [6] indicated that in acromegalic patients GH and HDL are the main determinants of the LDL subclass distribution. The effects of octreotide on CETP and lipases are not known. However, during octreotide treatment we did observe a reduction of GH and an increase of HDL, without any significant effect on LDL physical properties. Octreotide seems to improve insulin sensitivity [21,32,33]. A reduced insulin sensitivity is associated with the presence of small and/or dense LDL particles [30]. The lack of modifications of the LDL physical properties during octreotide therapy is therefore probably due to the balanced results of the modifications in the CETP and hepatic lipase activities, GH levels, HDL levels and insulin sensitivity.

Lp(a) appears to be clearly modulated by GH. The Lp(a) concentrations in acromegalic patients are usually increased [10] and octreotide treatment resulted in a significant reduction of these concentrations, apparently without any regard to the apo(a) phenotype. We have found, in agreement with Lam [10], a good correlation between Lp(a) and GH, but not IGF-I, modifications. This lack of a correlation between Lp(a) and IGF-I levels is consistent with the hypothesis that GH and IGF-I have different, probably opposing effects on Lp(a) levels [34], but also suggests a most important role for GH in the physiological regulation of Lp(a) expression in respect to IGF-I.

In conclusion, Lp(a) concentrations are high and directly correlated with GH levels in acromegalic patients. Octreotide therapy decreases Lp(a) levels by decreasing GH concentrations. Low HDL cholesterol levels and a predominance of small and/or dense LDL particles are also present in acromegalic patients and could contribute to the high vascular risk of these patients. Treatment with octreotide is associated with an increase of HDL levels and a decrease of total concentrations of LDL. However, this treatment has no effect on the LDL physical properties.

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