Hypercholesterolaemia in anorexia nervosa: Frequency and changes during refeeding

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Abstract

High total cholesterol (TC) is common in patients with anorexia nervosa (AN), but its mechanisms remain unclear.

Patients and methods. – We prospectively studied plasma lipoprotein (LP), haptoglobin, free (f) T3, fT4, TSH, transthyretin and albumin in 120 malnourished adult AN patients (BMI: 13.5 ± 1.5 kg/m²), 116 non-AN malnourished patients and 119 healthy subjects, matched for age and gender.

Results. – In 18% of our AN patients, TC was higher than 270 mg/100 mL (in non-AN: 5%; P < 0.01). TC, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and HDL2 levels were higher in AN patients than in non-AN patients (P < 0.001). Low TC (<150 mg/100 mL) and LP levels were observed in 8% of AN patients, but only when BMI was less than 13 kg/m². Cholesterol ester transfer protein (CETP) activity was higher in AN patients than in healthy subjects. LP was positively correlated with BMI, albumin, fT3 and haptoglobin levels. In AN patients, there was a biphasic LP profile (low values when BMI was very low, normal values in an intermediate state, and high values when BMI was highest and where bulimia was also present).

Conclusion. – In AN, both high and low cholesterol-rich LP levels were observed. Low T3 and low catabolism allow LP to be maintained, while CETP activity increases cholesterol turnover as an adaptation to its low intake. In severely malnourished AN patients, this fails and LP drops. On the other hand, LP values were higher in the bingeing–purging type of AN than in the restrictive type. Recovery from AN results in the normalization of the LP profile.

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Résumé

Lipoprotéines plasmatiques et anorexie mentale : fréquence et évolution des anomalies durant la renutrition.

Une hypercholestérolémie (HCT) est décrite en cas d’anorexie mentale (AM), mais sa fréquence et les facteurs qui l’expliquent sont mal connus.

Patients et méthodes. – Nous avons étudié prospectivement les lipoprotéines plasmatiques (LP), l’haptoglobine, la fT3, la fT4 et la TSH, la transthyrétine et l’albumine chez 120 malades AM dénutris (IMC : 13,5 ± 1,5 kg/m²), 120 malades dénutris « non-AM » et 120 témoins appariés âge et sexe.

Résultats. – Dix-huit pour cent des malades AM avaient un CT supérieur à 270 mg/100 mL (non-Am : 5 % ; P < 0,01). CT, LDL-C, HDL-C et HDL2 étaient plus élevés chez les AM que chez les dénutris non-AM (P < 0,001). Un CT bas (<150 mg/100 mL) et des LP effondrées furent notés chez 8 % des AM, mais seulement si l’IMC était < 13 kg/m². L’activité CETP était plus haute dans l’AM que chez les témoins. Il y avait une corrélation positive entre les LP et l’IMC, l’albumine, la fT3 et l’haptoglobine. En cas d’AM, le profil LP était biphasique : bas en cas d’IMC inférieur à 12 kg/m² et normal, voire haut au-dessus de cette valeur. La forme boulimique s’associait à des LP plus hautes que la forme restrictive de l’AM.

Conclusion. – En cas d’AM, on peut observer des valeurs de CT et de LP très basses ou élevées. Cela est fonction de l’IMC. L’absence de baisse du CT et des LP en cas d’AM, par rapport aux autres dénutritions, pourrait s’expliquer par l’absence de nécessité, dans l’AM, de synthèse des protéines inflammatoires : baisse des LP et de l’albumine en cas de dénutrition. . . . et haptoglobine élevée, non baisse des LP...
et de l’albumine dans l’AM... et haptoglobine très basse. Il est possible aussi que la baisse de la fT3 et la catabolisme des LP bas soit une adaptation aux apports effondrés en lipides, comme la valeur de CETP le suggère. Si la dénutrition est trop sévère (IMC < 12), le CT et les LP s’effondrent. La récupération d’un IMC normal restaure des valeurs de lipoprotéines normales, sauf en cas d’antécédent de dyslipoprotéinémie familiale.

Keywords: Anorexia nervosa; Dyslipoproteinaemia; Hypercholesterolaemia; CETP; Malnutrition; Serum albumin

Mots clés : Anorexie mentale ; Dyslipoprotéinémies ; Hypercholestérolémie ; CETP ; Dénutrition ; Albuminémie ; Hormones thyroïdiennes

1. Introduction

High serum total-cholesterol (TC) levels have been reported in anorexia nervosa (AN) patients since 1965 [1–4], and such high TC levels could have important clinical implications: it may lead some physicians to prescribe a low-fat diet to young girls who have AN and in those patients who do not recover by middle age, the high TC may become a risk factor for cardiovascular disease [5–7]. In our cohort of 482 patients, two patients (aged 37 and 41 years) with high TC developed a myocardial infarction. This high TC is paradoxical in AN, as malnutrition is classically associated with low TC, and every AN patient is strictly committed to a low-fat, low-cholesterol diet.

The published frequency of high TC in small groups of AN patients varies from 37 to 76% [1–4,8–17]. The largest reported groups were the 65 patients in the Klinefelter’s study [1], the 74 patients in the Favaro’s et al. study [8] and the 101 patients in the Boland’s et al. study [9]. No comparison was made with non-AN malnourished patients. Moreover, the profile of the high TC remains a subject of debate: Arden et al. [14] observed a high content of high-density lipoprotein cholesterol (HDL-C), and Mordasini et al. [15] a high content of low-density lipoprotein cholesterol (LDL-C). Smorawinska et al. found high TC, LDL-C and HDL-C in 63, 69 and 71% of their 36 AN patients, respectively [16]. For Boland et al. [9], only LDL-C was high. A few authors have reported on the evolution of TC with refeeding and show mixed results [2,3,14–18]. In 14 AN girls, Feillet et al. [17] found that TC and apoprotein (apo) B returned to normal values, while Haluzik et al. [18] observed no change. The mechanism behind these high TC and lipoprotein (LP) levels has been discussed: Misra et al. [19] found that, in their 23 AN girls, free (f) T3 predicted apoB and LDL-C. Recently, Ohwada et al. [20] found that the mean LDL-C, HDL-C, and apoA1 and B values were related to a significantly higher activity of cholesterol ester transfer protein (CETP) than in controls.

These contradictory results suggest that there might be a bimodal repartition of TC and LP in AN. The objective of this study was to clarify this point and to propose a mechanism to explain the high TC levels seen in AN patients. Thus, we prospectively studied plasma LP before, during and after refeeding in a large cohort of adult malnourished AN patients, and compared them with age- and gender-matched non-AN malnourished patients and healthy women.

2. Patients and methods

2.1. Patients

Over a five-year period, 126 AN patients admitted to the hospital nutrition department for renutrition were considered for the study. Six patients were excluded because of infectious diseases. All patients fulfilled the DSM-IV criteria for AN, and were adults (26 ± 9 years old; 96% women) with a long disease duration (median: 7 years; range: 2–25 years) and malnutrition (BMI: 13.5 ± 1.5 kg/m²). All women, but one, complained of amenorrhoea; 83 had the restrictive form of AN (AN-R; 69%) and 37 had the bingeing–purging form (AN-BP; 31%). One patient had a family history of hypercholesterolaemia. On recovery, 59 patients achieved a normal and stable BMI (range: 17.9–19.1 kg/m²) and normal energy intake. The non-AN patients consisted of 120 malnourished patients admitted for renutrition (age: 29.9 ± 9.8 years; women: 95%; BMI: 22.4 ± 1.6 kg/m²). Four were excluded because of known dyslipoproteinaemia. All suffered from digestive diseases (inflammatory: 55%; small bowel malabsorption or resection: 23%; others: 22%), and all had lost at least 10% of their body weight within the last few months. They were matched for gender and age with the AN patients. The normal-weight control group comprised of 120 healthy subjects, matched for gender and age (age: 26.9 ± 7.0 years; women: 95%; BMI: 15.8 ± 1.8 kg/m²), who had consulted during the same time period for dietary counselling and had neither an eating disorder nor a LP disease. One was excluded for technical reasons.

2.2. Methods

The patients had blood samples drawn before refeeding, after fluid correction and then every month during refeeding for LP, determined from 20 mL of blood drawn after a 12-hour overnight fast. Agarose gel electrophoresis was performed (for chylomicrons). Total serum and very-low-density lipoprotein cholesterol (VLDL-C), LDL-C and HDL-C and triglycerides (TG) were assayed twice (Biotrol, Paris, France). VLDL was prepared by ultracentrifugation: 2 mL of serum were mixed with 1 mL solution containing 0.9% NaCl and centrifuged (3 h at 45,000 rpm); LDL in infranatant was precipitated by MgCl2 and the supernatant was considered HDL. Reliability was checked by reference standards supplied by the French institution ARCOL [21]. Serum apoA1 and B
were determined in duplicate by double-antibody immunosor- 

bent assay (ELISA), using monoclonal antibodies for apo A1 and 

a polyclonal antibody for apo B (interassay coefficient of varia-

tion: 2.8–5.6%). The HDL2 and HDL3 fractions were assayed 

discontinuous-gradient gel electrophoresis as described else-

where [22], with an interassay variation <6%. In 52 AN patients 

and 49 matching healthy subjects, CETP mass and activity were 

measured [23].

Fat mass, determined by skinfold thickness (four sites), serum 

albumin, thyroxin-binding prealbumin (transthyretin), transferrin, 
haptoglobin by laser-nephelometry, and fT3, fT4 and TSH by 
immunossay.

Three-day dietary recall, where the same dietitian (V.R.) 
calculated nutrient intake—specifically, fat, cholesterol, and 
saturated and unsaturated fatty acids—using a computerized 

programme (Bilnut 1999, Tours, France).

3. Statistical analyses

Results are expressed as means ± standard deviations (S.D.). The patients were divided into five classes by BMI (kg/m²): 

>18; 16–18; 14–16; 12–14; <12. The significance of differences 
between groups and BMI classes was determined by a 
two-way analysis of variance (ANOVA), using the disease as 
the variate and the BMI as covariate. Percentages of patients 
in each LP or disease groups were compared using the chi² 
test. Factors associated with LP levels were tested in a multiple-

regression analysis, with BMI, binges, amenorrhoea, total body 
fat, albumin, fT3, fT4 and TSH as independent variables. The 
changes with refeeding were analyzed by Student’s paired t

test. Correlations between LP and nutritional variables were per-

formed by linear-regression analysis, and detailed by ANOVA 
(three variables and their interactions). All analyses were per-

formed using the MGLH module of Systat (Systat Inc., IL, 
U.S.A).

4. Results

4.1. Before refeeding

4.1.1. Total cholesterol

Using ANOVA, the TC level was related to disease (AN, 

non-AN, healthy: F = 16.2; P < 0.001). Integrating the BMI into 
the model did not change the results. Twenty-two AN patients 
(18%) had TC values higher than 270 mg/100 mL versus none 
of the non-AN malnourished patients and only 7% of the healthy 
controls (Fig. 1; chi²: α = 5.4; P < 0.02). In contrast, 42 AN 
patients (35%) had TC levels less than 180 mg/100 mL versus 
only 11% of the healthy controls. For each BMI class, TC lev-

els were higher in AN than in non-AN patients (Fig. 2; chi²: 

α = 6.7; P < 0.01). All AN patients with TC levels less than 
150 mg/100 mL had a BMI less than 14 kg/m², whereas none of 
the AN patients with a BMI higher than 14 kg/m² had TC 
levels less than 150 mg/100 mL; TC values increased with BMI 
(F = 7.3; P < 0.01; Table 1). The bingeing–purging AN patients 
had higher TC levels than the restrictive ones (P < 0.01 with 
ANOVA using BMI as covariate; data not shown).
Data are expressed as means ± S.D.; for AN and non-AN malnourished patients, the above profile was prior to refeeding; cholesterol (C) and triglyceride (TG) values are expressed as mg/100 mL; –: not done; HDL2 and HDL3 are expressed as percentages of total particle numbers. *: \( P < 0.05 \) versus AN patients; **: \( P < 0.01 \) versus AN patients; ***: \( P < 0.001 \) versus AN patients (ANOVA, then Student’s \( t \) test).
HDLC, and apo B and A1 on one hand, and BMI (r > +0.38; P < 0.001), serum albumin (r > +0.55; P < 0.02), transthyretin (prealbumin, r > +0.25; P < 0.05) and haptoglobin (r > +0.32; P < 0.02) on the other. Increasing the BMI in AN patients (ANOVA) increased TC, LDL-C, apo B, HDL-C and apo A1 levels (Table 2; P < 0.001), while VLDL-C and VLDL-TG were decreased (P < 0.001). In AN patients, the positive correlation between TC, LDL-C and HDL-C on one hand, and albumin or transthyretin on other, was stronger in the <12 and 12–14 kg/m² BMI classes (r > +0.45 for transthyretin; r > +0.40 for albumin; n = 51; P < 0.02) than in the higher BMI groups.

4.2.2. Inflammatory markers and thyroid hormones

In AN patients (with multiple-regression analysis using haptoglobin as covariate), TC, LDL-C and apo B, HDL-C and apo A1 levels were explained by haptoglobin (P < 0.002): the lower the haptoglobin, the lower the TC. This relationship persisted even when BMI or albumin was included in the model (P < 0.01). In contrast, in non-AN patients, the correlation between haptoglobin and TC, LDL-C or HDL-C was negative (r > −0.40; P < 0.001). In AN patients, fT3 was negatively correlated with TC, LDL-C and HDL-C (r > −0.34; P < 0.01).

4.3. During refeeding

At this time, the mean TC levels remained unchanged (from 190 ± 51 to 197 ± 29 mg/100 mL at week 12), although there was a shift in both the lowest and the highest quintiles of TC to normal values. In the 22 AN patients with TC higher than 270 mg/100 mL, levels of TC, LDL-C, apo B and VLDL-C progressively decreased (P < 0.02) during the six weeks of refeeding: TC from 297 ± 32 to 187 ± 21 mg/100 mL; LDL-C from 189 ± 15 to 111 ± 11 mg/100 mL; and HDL-C from 76 ± 9 to 64 ± 7 mg/100 mL. These values all reached normal in 17 patients (77%), but only several weeks before recovery. Indeed, in these 22 patients, while LP levels decreased, energy and fat intake increased. At week 12, energy intake had increased from 865 ± 357 to 2252 ± 405 kcal per day, fat intake from 29 ± 18 to 74 ± 9 g per day, cholesterol intake from 138 ± 46 to 453 ± 59 mg per day and saturated FA from 9.3 ± 1.2 to 25.9 ± 1.4 g per day.

4.4. After recovery

In 56 (95%) of the 59 AN patients who achieved a normal BMI (>18.5 kg/m²), all LP levels were within the normal range for age and gender. However, LDL-C remained higher than 150 mg/100 mL in one patient who had a family history of high TC and in two others who had bulimia nervosa.

5. Discussion

In our AN patients, TC, LDL-C, HDL-C, apo B and apo A1 levels were all markedly higher than those observed in non-AN malnourished patients. The percentage of high TC and LDL-C values was higher in AN: 18% of our young AN women had TC higher than 270 mg/100 mL plus LDL-C higher than 150 mg/100 mL compared with 8% of our age- and gender-matched healthy controls.

Contrary to Arden et al. [14] and Mordasini et al. [15], we found high LDL-C in 75% and high HDL-C in 79% of the AN patients with high TC levels. The mean high LDL-C and HDL-C levels in our AN patients are surprising, considering their malnutrition [24,25]: lower-than-normal values would be expected in AN patients, who had lower BMIs than the non-AN patients. These higher LP levels in AN patients could be explained by a higher rate of synthesis of cholesterol-rich LP in such patients. Indeed, other levels of circulating proteins (albumin and transthyretin) were also higher in our AN than non-AN patients. In addition, in severely malnourished AN patients (BMI <14 kg/m²2), the levels of LP, albumin and transthyretin were all lower. Furthermore, a positive correlation was found in both groups between TC or LDL-C and albumin or transthyretin. Nevertheless, the higher rate of synthesis in AN patients compared with non-AN patients is surprising, as the

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<td>Nutritional markers and serum lipoprotein values for AN and non-AN patients in relation to BMI.</td>
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In AN patients with BMI <13 kg/m²: **: P < 0.01 and ***: P < 0.001 versus AN patients (Student’s t test); apo B from 13–18 BMI AN subgroup was higher than that of non-AN malnourished controls (P < 0.05); normal values for fT3, fT4 and TSH are 4.0–7.5, 8.5–18 and 0.25–3.5, respectively.
AN patients had very low protein, cholesterol and saturated FA intakes.

The low catabolism of cholesterol-rich LP could theoretically explain the absence of low levels in 92% of our AN patients. Such a low catabolism was also described in hypothyroidism [26]. One argument for a relative hypocatabolism in AN patients is that, when high, LP levels decrease with refeeding while protein catabolism increases. Also, we observed lower haptoglobin levels (an acute-phase inflammatory protein) in AN patients versus non-AN patients, which suggests lower catabolism related to the absence of an inflammatory process. In non-AN patients with an inflammatory process, the higher their haptoglobin levels, the lower their TC, LDL-C and HDL-C levels. Others [25,27,28] have also described such a relationship. Moreover, an infectious disease developed in five AN patients (data not shown): in four, TC, LDL-C and HDL-C decreased within two weeks. Thus, it may be concluded that, in AN patients, malnutrition, and low nitrogen and low amino-acid intakes lead to lowered protein synthesis which, in turn, is responsible for a decrease in protein catabolism. This ‘near-to-zero balance’ between low synthesis and the subsequent low catabolism allows normal serum levels of albumin, transthyretin and LP to be maintained [25,28]. A possible mechanism for these unexpectedly normal LP levels in AN could be hypothyroidism [12,16,26]. In the present study, high TC and LDL-C levels were associated with high HDL-C, as seen in hypothyroidism [14,26].

In our cohort, we also observed inhibition of TG-rich LP catabolism in the 20% of AN patients with high TC levels: in these cases, high TC was associated with high VLDL-C and VLDL-TG levels, and all LP levels reverted to normal with refeeding. This suggests a transfer of cholesterol from VLDL to LDL by CETP, which is known to increase cholesterol turnover and, thus, TC and LDL-C levels. The reason for this could be to scavenge cholesterol from dead cells. The increase in CETP activity in the face of the low fat and cholesterol intakes in AN patients might also allow the increased transfer of cholesterol esters, thereby saving endogenous cholesterol [15,17].

One piece of unexplained data from the present study was the higher TC and LDL-C levels in the binging–purgers. AN patients compared with the restrictive ones. Although high TC levels have been described in bulimia nervosa by Monteleone et al. [29], Weinbrenner et al. made no such observation [10]. Could these mixed results be related to differences in alimentary fat, in body fat mass and levels of physical activity in binging patients? Further studies are needed to find any answers.

The high VLDL-TG that we noted in 14% of our patients could be related to the low catabolism of TG because of the low fat mass: TG could not be picked up by adipose tissue. Another explanation is that the liver is relatively deficient in lipoprotein lipase activity and, thus, TC and LDL-C levels. This could also be related to the decreased thyroxin activity and increased cholesterol turnover due to the increased CETP activity. In addition, it is possible that cholesterol released from cells is incorporated during the turnover cycles by CETP to maintain cholesterol in the body when cholesterol from food is lacking. However, when malnutrition is too severe and too long-lasting, the above adaptive changes cannot be maintained, and so LP synthesis drops [27]. Future studies using stable isotopes for determination of apo B synthesis and catabolism as well as cholesterol synthesis will confirm (or not) these hypotheses.

**Conflicts of Interest**

Authors declare no conflict of interest in this subject.

**References**


