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Lipid profile and cardiovascular risk in anorexia nervosa; the effect of nutritional treatment

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Abstract

Objective: The aim of this study was to explore the lipid profile in patients with anorexia nervosa (AN), and the changes with refeeding.

Methods: The sample comprised 102 AN outpatients (mean age 22.32 ± 3.17). Blood tests, after 12-hour overnight fast, were performed before refeeding (M0) and after weight restoration (M1). Total cholesterol (TC), high-density lipoproteins (HDL), low-density lipoproteins (LDL) and triglycerides (TRG) were determined and the following cardiovascular risk markers were calculated: LDL/HDL and TC/HDL ratios. These cut-off points were considered: TC < 200 mg/dl; HDL > 40 mg/dl; LDL < 100 mg/dl and TRG < 150 mg/dl.

Results: The time leading to weight restoration was 8.16 ± 7.35 months. Considering patients with scores higher and lower than the corresponding cut-off points, χ2-test revealed a significant difference (M0-M1) in case of TC (p < 0.05) as well as between LDL/HDL0 and LDL/HDL1 (p < 0.05) and between TC/HDL0 and TC/HDL1 (p < 0.01). Significant differences were found between HDL0 and HDL1 (p < 0.01) and between TRG0 and TRG1 (p < 0.05). Significant and negative associations between BMI0 and TC0 (r = -0.331; p < 0.05) and between TRG0 and HDL0 (r = -0.387; p < 0.05) were found. The association between TRG1 and LDL1 was significant and positive.

Discussion: Weight restoration tends to decrease the TC/HDL and LDL/HDL ratios despite a considerable percentage of patients maintain scores on the different variables of the lipid profile usually considered at risk.

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Key words: Anorexia nervosa. Lipid profile. Cardiovascular risk. Refeeding.

Resumen

Objetivo: El objetivo de este estudio fue explorar el perfil lipídico en pacientes con anorexia nervosa (AN) y los cambios con la realimentación.

Métodos: Se estudiaron 102 pacientes ambulatorios con AN (edad media de 22.32 ± 3.17). Se determinaron en sangre, tras de 12 horas en ayunas, antes de la realimentación (M0) y después de la recuperación del peso (M1), colesterol total (CT), lipoproteínas de alta densidad (HDL), lipoproteínas de baja densidad (LDL) y triglicéridos (TRG) y se calcularon los siguientes marcadores de riesgo cardiovascular: LDL/HDL y CT/HDL ratios. Se consideraron los siguientes puntos de corte: CT < 200 mg/dl; HDL > 40 mg/dl; LDL < 100 mg/dl y TRG < 150 mg/dl.

Resultados: El tiempo para la recuperación del peso fue de 8.16 ± 7.35 meses. Teniendo en cuenta los pacientes con puntuaciones superiores e inferiores a los correspondientes puntos de corte, el test de χ2 reveló una diferencia significativa (M0-M1) en el caso de CT (p < 0.05), así como entre LDL/HDL0 y LDL/HDL1 (p < 0.05) y entre TC/HDL0 y TC/HDL1 (p < 0.01). Se encontraron diferencias significativas entre el HDL0 y HDL1 (p < 0.01) y entre TRG0 y TRG1 (p < 0.05). Se obtuvieron asociaciones significativamente negativas entre BMI y CT (r = -0.331, p < 0.05) y entre TRG y HDL (r = -0.387, p < 0.05) y entre TRG y HDL (r = -0.387, p < 0.05) se encontraron. La asociación entre TRG1 y LDL fue significativa y positiva.

Debate: La recuperación del peso tiende a disminuir los índices TC/HDL y LDL/HDL a pesar de que un considerable porcentaje de pacientes mantiene puntuaciones en las distintas variables del perfil lipídico generalmente consideradas de riesgo.

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**Introduction**

High total cholesterol (TC) levels have been reported among patients with anorexia nervosa, with a frequency, which varies between 37 to 76%.1 In addition, a high content of high-density lipoprotein cholesterol (HDL), and a high content of low-density lipoprotein cholesterol (LDL) have been found.2-3 In one of these studies, high TC, HDL and LDL were found in 63, 69 and 71% of the patients with anorexia nervosa.4 The high TC may become a serious risk of cardiovascular disease among those patients who do not recover appropriately when they reach middle age. Nevertheless the reports of lipoprotein levels in anorexia nervosa are inconsistent, demonstrating normal or elevated mean LDL and HDL levels.1

The possible causes of the above-mentioned altered profile have been largely discussed. Thus, Misra et al.,5 have found that free T3 predicts apoproteine B and LDL. Ohwada et al.,6 have found that the mean LDL, HDL and apoproteine A1 and B values are related to a significantly higher activity of cholesterol ester transfer protein than in controls. The higher lipoprotein levels in patients with anorexia nervosa could be explained by a higher rate of synthesis of cholesterol-rich lipoprotein in these patients. Nevertheless, this higher synthesis is surprising taking into account the usual low protein, cholesterol and saturated fat intakes of these patients. Another explanation for these findings may be the existence of a low catabolism of cholesterol-rich lipoprotein.1

Taking into account these results, it has been suggested that there might be a bimodal repartition of TC and lipoproteins in anorexia nervosa. This means that there could be patients in the highest and in the lowest values of lipoprotein levels, with a non-Gaussian distribution. This possibility is relevant considering that other malnourished patients (without anorexia nervosa) as well as healthy population have a Gaussian distribution of their levels of TC, HDL and LDL.1

With respect to the influence of refeeding on the serum lipid profile it must be noted that the high TC in these patients is paradoxical because malnutrition is usually associated with low TC. In addition, patients with anorexia nervosa normally follow low fat and low cholesterol diets. The influence of refeeding in this field of study is controversial. While some authors (e.g., Feillet et al.7) have reported that TC returns to normal levels, others (e.g., Haluzik et al.8) have observed no changes.

The aim of this study was to explore the lipid profile in a sample of patients with anorexia nervosa, and the evolution of this profile with refeeding in order to add some data to this controversial field of study.

**Method**

**Participants**

The sample comprised 102 patients with anorexia nervosa (DSM IV-TR)9 who were receiving treatment in an eating disorders unit as outpatients. All of them were women, with a mean age of 22.32 ± 3.17 years old. With respect to the lipid profile, no cases with familial hyperlipidaemia were detected.

**Procedure**

The patients had blood samples drawn before refeeding, during refeeding and, finally, once a normal weight had been reached. For the proposal of this work the study comprised the blood test before refeeding (Moment 0) and the latter test, when a normal weight was obtained (Moment 1). In all cases, determinations were performed after 12-hour overnight fast. As a result, TC, HDL, LDL, and triglycerides (TRG) were assayed twice. Having obtained these parameters, the following risk markers of cardiovascular and coronary diseases were calculated: LDL/HDL ratio and TC/HDL ratio. The following cut-off points were considered: TC < 200 mg/dl; HDL > 40 mg/dl; LDL < 100 mg/dl and TRG < 150 mg/dl.

The ratios LDL/HDL and TC/HDL permit the study of lipid-based cardiovascular risk with only one value. Each ratio includes a variable, which is positively associated with that risk and another one, which is negatively associated with the cardiovascular risk. The predictive power of these ratios increases if the triglyceridaemia is taken into account. A TC/HDL > 4.5 and a LDL/HDL > 3 in women are considered the cut-off points for primary prevention. The risk is two times higher when TRG > 200 mg/dl.9-11

The weight and height of the participants were assessed and the body mass index (BMI) was calculated (kg/m²) both before refeeding and once the BMI was normalised (> 18.5 kg/m²). The period of time to recover the normal weight was considered. The patients were not taking neither dietetic supplements nor special diets. The diet was adjusted taking into account the age and the requirements of each patient and maintaining a normal proportion of macronutrients (carbohydrates: 50-60%; fats ≤ 30%; proteins: 12-15%).

Written informed consent was obtained from all subjects.

**Statistical analysis**

Descriptives are expressed as means (M) and standard deviations (SD), and percentages are presented in case of proportions. The differences among proportions were obtained by means of the χ²-test. The Kolmogorov-Smirnov test was used to determine whether the data fitted a normal distribution. In case of normal distribution the pairwise t-test was applied. In other cases, non-parametric tests for related samples were performed. Correlations were calculated by means of the Pearson’s correlation coefficient. All the
analyses were performed by means of SPSS, v. 18.0., and the level of significance was set at the 0.05.

Results

Table I shows data referring to BMI, TC, HDL, LDL, TRG, LDL/HDL and TC/HDL both at the beginning of treatment and after weight restoration. The period of time leading to weight restoration was 8.16 ± 7.35 months.

With respect to the patients with scores higher and lower than the corresponding cut-off points, these are shown in table II. The $\chi^2$-test revealed a significant difference in case of TC ($p < 0.05$). With respect to the LDL, the difference was not significant ($p = 0.06$). In case of HDL and TRG all patients in moment 1 were within normal rank.

The ratios LDL/HDL and TC/HDL did not fit a normal distribution, so the Wilcoxon signed rank test for paired samples was applied. As a result a significant difference was found between LDL/HDL$_0$ and LDL/HDL$_1$ ($p < 0.05$) as well as between TC/HDL$_0$ and TC/HDL$_1$ ($p < 0.01$). The rest of parameters were compared by means of the $t$-test for paired samples. Significant differences were found between HDL$_0$ and HDL$_1$ ($t = -2.88; p < 0.01$) and between TRG$_0$ and TRG$_1$ ($t = 2.89; p < 0.01$).

The analyses of the correlations showed a significant and negative association between BMI$_0$ and TC$_0$ ($r = -0.331; p < 0.05$) and a significant and negative association between TRG$_0$ and HDL$_0$ ($r = -0.387; p < 0.05$). In addition, the association between TRG$_1$ and LDL$_1$ was significant and positive.

Considering the scatterplots of these associations it must be noted that the fit line is different when BMI and TC are taken in moments 0 and 1 with respect to the total association between BMI and TC during the follow-up. These fit lines represent a lineal association at moment 0 and 1 but a quadratic-like one considering the changes during refering (figs. 1, 2 and 3). In addition, figure 4 shows the tendency of TRG to decrease along the treatment in relation with weight restoration.

Discussion

Despite the controversial results in the literature with respect to the lipid profile in patients with anorexia nervosa and the great range with regards to the TC level in these patients,$^1-3$ the current study shows that a significant percentage of patients with anorexia nervosa presented a significant improvement of their lipid profile during weight restoration.

Table I

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<th>Descriptives and differences between Moment$_0$ and Moment$_1$</th>
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<td>BMI (kg/m$^2$)</td>
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$^a$t-test for paired samples.

Table II

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<th>Patients with scores higher and lower than cut-off points N (%)</th>
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<tr>
<td>TC &gt; 200 mg/dl</td>
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<td>HDL &lt; 40 mg/dl</td>
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<td>LDL &gt; 100 mg/dl</td>
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<td>TRG &gt; 150 mg/dl</td>
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$^a$Wilcoxon signed rank test for paired samples.

Fig. 1.—Moment$_0$. Correlation between total cholesterol and body mass index.

Fig. 2.—Moment$_1$. Correlation between total cholesterol and body mass index.
patients with anorexia nervosa, contrary to others, Rigaud et al. (2009) reported 79% and 75% of high HDL and LDL levels respectively considering those with high TC levels. In the current study the percentage of patients with high LDL was significantly lower (42.84% at M0 and 44.12% at M1).

The effect of the treatment, specifically weight restoration, may be the main topic with regards to the lipid profile in anorexia nervosa. Thus, it has been found that TC and LDL were high on admission and after treatment there was a tendency for most of the abnormal markers to normalise. However, HDL levels decreased leaving patients with an undesirable lipid profile. In a 1-year follow-up of serum biochemical parameters in a homogeneous group of patients with anorexia nervosa, hypercholesterolemia was found at all time points, the authors concluding that hypercholesterolemia seems to need longer periods of treatment with further weight gain to fully normalize. Other evidence had shown that, to some extent, when patients are treated by refeeding, the serum cholesterol levels tend to fall 16 and the lipid profile tend to normalise too.

Contrary to those who have not found changes in TC during refeeding, the current study shows a clear tendency to decrease the proportion of patients with TC > 200 mg/dl after weight restoration. Nevertheless, after an average time to recovery of eight months, 20% of the patients remain with high TC. This finding seems to confirm the results reported by Nova et al. (2008). The distribution of TC taking into account the changes in BMI during the treatment seems not to be a Gaussian one, but a quadratic-like distribution. It seems to have a border with respect to the BMI and once this border is crossed the TC tends to increase again.

The lipid alterations in anorexia nervosa are not clearly explained. Different studies find that cholesterol ester transfer protein (CETP) activity is higher in patients with anorexia nervosa than in controls and this activity decreases after weight gain, suggesting that CETP is accelerated in these patients. Considering the LDL, the total body fat, free thyroxine, BMI, free triiodothyronine and non-esterified glycerol seem to predict LDL in patients with anorexia nervosa. In this regard it has been suggested that elevated cholesterol concentrations in patients with anorexia nervosa are generally due to an increase in LDL, which is mostly determined by the severe loss of body fat and the resulting changes in thyroid hormones, increased lipolysis and decreased endogenous cholesterol synthesis with resulting decrease in LDL removal. In addition, it has been proposed that changes of plasma lipids and lipoproteins in anorexia nervosa result from complex mechanisms including increased synthesis of triglyceride-rich lipoproteins along with unchanged cholesterol synthesis rate. Hypercholesterolemia in anorexia nervosa may also result from increased resorption of exogenous cholesterol. Despite normal levels of

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Cardiovascular risk in anorexia nervosa


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triglycerides, hepatic triglyceride lipase and lipoprotein lipase activities in post-heparin plasma have been found to be low.\(^{3}\)

A relative hypocatabolism of cholesterol-rich lipoproteins in anorexia nervosa is supported by the fact that, when high, lipoprotein levels decrease with refeeding while protein catabolism increases. Different factors could be involved in the lipid profile alterations in anorexia nervosa. Thus, malnutrition and low nitrogen and low amino-acids intakes lead to lowered protein synthesis which, in turn, is the reason for a decrease in protein catabolism.\(^{3}\) As it was mentioned above, the increase in CETP activity when low fat and cholesterol intakes in anorexia nervosa might also allow the increased transfer of cholesterols esters leading to save endogenous cholesterol.\(^{37,38}\)

The current study has been focused on patients with anorexia nervosa. Alterations in lipid profile have also been studied on patients with other eating disorders and/or with different subtypes of anorexia nervosa. Thus, the study of Rigaud et al.\(^1\) included both patients with anorexia nervosa restrictive type and bingeing-purgating type. In this study, bingeing-purgating anorexia nervosa patients had higher TC and LDL levels than restrictive patients. Authors did not give an explanation for this finding. Hypercholesterolemia seems to occur most commonly in anorexia nervosa patients comparing with bulimia nervosa.\(^1,24\)

With respect to the TC/HDL and LDL/HDL it must be noted that they are considered as good markers to estimate the cardiovascular and coronary risk.\(^{27,29}\) These indexes have different variables, which are positively and negatively associated with the cardiovascular risk. In the current study the level of HDL is higher with respect to the mean HDL reported in previous studies among women.\(^{26,30}\) Weight restoration tends to decrease the mean TC level as well as to increase the HDL level. As a result both TC/HDL and LDL/HDL tend to decrease. Despite the fact that BMI is usually associated with TC/HDL (significant and positively) it seems not to be the case among women with anorexia nervosa. Weight restoration tends to decrease the TC/HDL and LDL/HDL ratios despite a considerable percentage of patients maintain scores on the different variables of the lipid profile usually considered at risk.

The fact that both high and low levels of lipoproteins appear among patients with anorexia nervosa has been related with an alteration of catabolism of cholesterol-rich lipoprotein as well as with a decreased thyroxin activity and increased cholesterol turnover due to the increased CETP activity. In addition it has been suggested that cholesterol released from cells could be incorporated during the turnover cycles by CETP in order to maintain cholesterol in the body when cholesterol from food is lacking. Finally it has been noted that in cases of severe and too long-lasting malnutrition the above-mentioned adaptive changes cannot be maintained, and so lipoprotein synthesis drops.\(^{1,37}\)

Besides the blood parameters considered in this study others like CETP, free T\(_1\), free T\(_3\), TSH or some inflammatory markers were not taken into account, which could be a limitation. In addition, the comparisons between subtypes of anorexia nervosa were not performed, considering that the main point was the relationship between BMI, refeeding and the lipid profile. The former literature has pointed out that weight restoration is the key to normalise the lipid profile regardless of the different types of eating disorders. In fact when some differences between subtypes have been found no explanation has been given in this regard.

The lipid profile in anorexia nervosa should be assessed periodically during nutritional treatment. The concept of nutritional status improvement with regards to weight restoration and the recovery of fat mass\(^{34}\) should be extended to the control of the lipid profile in order to avoid possible cardiovascular risk factors in the future. With regards to the diet, it has been shown that a tendency exists among anorectic patients to maintain some characteristic eating patterns and modify others. This is not so much in terms of therapeutic objectives but rather, as a way of following the usual eating patterns of their social environment.\(^3\) Strict supervision of these patterns is necessary with respect to the changes in the lipid profile of these patients.

References


