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ORIGINAL ARTICLE

Clinical characterization and detection of subclinical atherosclerosis in subjects with extreme hyperalphalipoproteinemia

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KEYWORDS
Extreme hyperalphalipoproteinemia;
HDL (high-density lipoproteins) cholesterol;
Subclinical atherosclerosis;
Vascular risk

Abstract
Introduction and objectives: The association between HDL cholesterol (HDL-C) levels and death from cardiovascular disease follows a U-shaped pattern, increasing at the extremes. The objective of the study was to characterise a sample of subjects with extreme hyperalphalipoproteinemia (HAE).
Material and methods: 53 cases with HAE were recruited, 24 women (HDL-C > 135 mg/dl) and 29 men (HDL-C > 116 mg/dl). A detailed medical history was taken and questionnaires on adherence to the Mediterranean diet and physical activity were collected. Carotid ultrasounds were performed to detect the presence of suclinical atherosclerosis.
Results: The most prevalent cardiovascular risk factor (CVRF) was dyslipidemia (64%) with no significant differences between men and women, unlike hypertension (21% in women, versus 55% in men, p = 0.01) and others CVRF, for example, diabetes. 7% of the series had previous cardiovascular disease, women had higher LDL cholesterol (p = 0.002) and HDL-C than men (without significant differences). Plaque was detected in 53% of cases, being more prevalent in men. Patients with plaque were older, drank more alcohol and smoked more (p < 0.05).

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Conclusions: Men had a higher prevalence of CVRF than women, except for dyslipidemia. Subclinical atherosclerosis occurred in more than half of the series. Age, alcohol consumption and smoking were independently associated with the presence of plaque, however, our data do not show a significant influence of HDL-C levels.

PALABRAS CLAVE
Hiperalfalipoproteinemia extrema;
Colesterol HDL (lipoproteínas de alta densidad);
Arteriosclerosis subclínica;
Riesgo vascular

Caracterización clínica y detección de arteriosclerosis subclínica en sujetos con hiperalfalipoproteinemia extrema

Resumen
Introducción y objetivos: La asociación entre niveles de colesterol de HDL (C-HDL) y muerte por enfermedad cardiovascular sigue un patrón en forma de U, aumentando en los extremos. El objetivo de nuestro estudio fue caracterizar clínica y analíticamente a un grupo sujetos con hiperalfalipoproteinemia extrema, así como analizar la presencia de arteriosclerosis subclínica.
Material y métodos: Se reclutaron 53 casos con HAE, 24 mujeres (C-HDL>135 mg/dL) y 29 hombres (C-HDL>116 mg/dL). Se realizó una historia clínica detallada y se recogieron cuestionarios de adherencia a dieta mediterránea y actividad física. Se realizaron ecografías carotídeas para detectar la presencia de arteriosclerosis subclínica.
Resultados: El factor de riesgo vascular (FRCV) más prevalente fue la dislipemia (64%) sin diferencias significativas entre hombres y mujeres, al contrario que la hipertensión (21% en mujeres, versus 55% en hombres, $p = 0.01$) y otros FRCV, por ejemplo, la diabetes. El 7% de la serie presentó enfermedad cardiovascular previa, las mujeres tuvieron más elevado que los hombres el colesterol de LDL ($p = 0.002$) y el C-HDL (sin diferencias significativas). Se detectó placa en un 53% de casos, siendo más prevalente en hombres. Los pacientes con placa fueron más mayores, bebían más alcohol y fueron más fumadores ($p < 0.05$).
Conclusiones: Los hombres presentaron mayor prevalencia de FRCV que las mujeres, salvo la dislipemia. Hubo arteriosclerosis subclínica en más de la mitad de la serie. La edad, el consumo de alcohol y el tabaquismo se asociaron independientemente con la presencia de placa, sin embargo, nuestros datos no muestran una influencia significativa de los niveles de C-HDL.

Introduction and objectives

The relationship between low levels of HDL cholesterol (HDL-C) and cardiovascular risk has been known for decades and is included in risk equations and clinical practice guidelines.[1,2] Elevated HDL-C levels have been considered protective for cardiovascular disease, but several studies contradict this concept. For example, it has not been possible to demonstrate a reduction effect on cardiovascular events with therapies aimed at raising HDL-C concentration.[3,4] In 2017, a natural population study in Denmark published that very high concentrations of HDL-C (>135 mg/dl for women and >116 mg/dl in men), considered extreme hyperalphalipoproteinaemia (HALP), increased the risk of death from cardiovascular disease with a hazard ratio of 2.53 (95% CI: 1.24–5.18) and 2.89 (95% CI: 1.33–6.24) in men and women, respectively. The association between HDL-C levels and death from cardiovascular disease is therefore U-shaped, increasing considerably at low or high extremes.[5]

Genetic factors are involved in HDL-C concentration. Pathogenic variants in the genes cholesteryl ester transfer protein, scavenger receptor B1, and hepatic lipase cause hyperalphalipoproteinaemia.[6] However, it has been reported that this concentration is not related to the function of HDL particles.[7] These particles are highly complex in their composition, and their function would go beyond reverse cholesterol transport. In fact, it would be this function that would be related to the development of arteriosclerosis.[7]

There is very little literature on the clinical profile of patients with hyperalphalipoproteinaemia,[8,9] and even less on cases of HALP, a condition of which the prevalence is unknown. Moreover, there are no specific recommendations on how to approach these patients clinically, although a review on rare dyslipidaemias in SAD suggests assessing their cardiovascular risk and taking the necessary preventive measures.[10]

On the other hand, subclinical atherosclerosis has been found in populations with elevated HDL-C levels. In women, the menopausal stage has been found to modify the association of HDL-C with coronary artery calcification (CAC). Specifically, higher LDL-C levels and smaller particle size have been associated with an approximately 2-fold increased likelihood of CAC in late menopause, but not in early menopause.[11] Elevated LDL-C values have also been

reported to confer a 56% increased risk of carotid atherosclerotic plaque progression at 5-year follow-up.[12]

The aim of our study was to characterise a group of subjects with HALP clinically and analytically, and to analyse the presence of subclinical atherosclerosis.

Material and methods

Study design

This is a descriptive observational study analysing 53 subjects prospectively included due to HALP between June 2021 and October 2023. They were studied in the Lipid Unit of the Virgen de la Victoria University Hospital in Malaga and the Internal Medicine Department of the Antequera Hospital, from primary care (PC) and hospital care (HC). These cases had to meet the following inclusion criteria: be over 18 years of age, sign the informed consent form, and have had, on some occasion, levels of HDL-C>116 mg/dl in the case of men and above 136 mg/dl in women. The study originated in the context of a grant awarded by the Spanish Arteriosclerosis Foundation (FEA 2020 clinical epidemiological grant).

Recording of clinical data

The following data were collected at the patients' visits: age, sex, family, and personal history of cardiovascular disease (CVD) or cardiovascular risk factors (CVRFs), comorbidities, alcohol and tobacco consumption, oestrogen treatment (contraception or substitution), other treatments received, weight, height, body mass index, waist circumference, and blood pressure levels. Given the influence on HDL-C levels, questionnaires were completed on adherence to the Mediterranean diet[13] and physical activity.[14]

Collection of imaging data

Intima-medial thickness and the presence of atherosclerotic plaque in both carotid arteries were measured with a Philips EPIQ-Elite ultrasound machine, using criteria predefined in the PESA study: luminal protrusion>.5 mm and/or intimal-medial thickness>50% with respect to adjacent area and/or thickness>1.5 mm between the medial adventitia and the intimal lumen.[15]

Obtaining analytical data

In blood samples drawn by cubital venous puncture after 12 h of fasting, the following parameters were analysed: haemoglobin, platelets, neutrophils, renal and hepatic profiles, total cholesterol, LDL-C and HDL-C, triglycerides, lipoprotein (a), and ApoA-I, using the autoanalysers of the patients' hospitals of origin.

Statistical analysis

IBM SPSS 26.0 software was used. Statistical power was calculated for the achieved sample size using OpenEpi (open-source epidemiological statistics for public health. Available at: https://www.openepi.com/Menu/OE_Menu.htm). Quantitative variables are shown as mean ± standard deviation or as median (interquartile range) when they do not follow normality after testing their distribution with the Kolmogorov-Smirnov test. Qualitative variables are shown as n (%). To determine whether there were significant differences between sexes or between patients with and without plaque, quantitative variables were compared by Student's t-test, or Mann–Whitney *U* test and χ^2 test, or Fisher's test for qualitative variables. A Wald forward stepwise binary logistic regression model was developed for the association of variables that showed significant differences in the univariate analysis with the presence or absence of plaque, in addition to other variables with known impact on subclinical atherosclerosis. Statistical significance was considered a p-value <.05.

Ethical aspects

The study was approved by the Malaga Provincial Research and Ethics Committee (code 1895-N-20; resolution of 24/09/2020). The recommendations of the Declaration of Helsinki and the regulations on confidentiality and personal data protection, as well as the standards of good clinical practice, were followed. All subjects included in the study signed the informed consent form

Results

General characteristics

Fifty-three subjects were recruited (24 women and 29 men) with a mean age of 57 ± 9.6 years, 19 cases were from PC and 22 from HC. The clinical and anthropometric characteristics are shown in Table 1. The subjects had abdominal girth and body mass index values within the normal range, and higher in the men than in the women. Among the cardiovascular risk factors, 40% of the subjects were found to have hypertension, more prevalent in the men who had significantly higher blood pressure than the women. Diabetes was only observed in the males (21%). More than half of the subjects studied had dyslipidaemia (mainly hypercholesterolaemia: 45%), more frequent in the women than the men, although without statistically significant differences. Most of the patients with dyslipidaemia were on lipid-lowering treatment (mainly statins: 55%), less frequently in the women, although without significant differences. Family and personal history of CVD was observed in 7% of cases and, even without significant differences, 25% of the women had previous CVD compared to only one male patient. The presence of at least one comorbidity was observed in 74% (9 cases with liver diseases, 6 with autoimmune diseases, 5 with thyroid diseases, 5 with nephropathies, 4 with pneumopathies, and 3 with neoplasms).

Almost half of the patients consumed alcohol moderately (more frequently the men; 67%) and 34% smoked. Adherence to the Mediterranean diet was very low (19%), especially in the men, although without statistically significant differences with respect to the women. Finally, most subjects were moderately or highly physically active, with no significant differences between the men and the women.

Table 1 Clinical and anthropometric characteristics of the study subjects.

Variable	Total	Women (n = 24)	Men (n = 29)	p
Age (year)[a]	57.0 ± 9.6	55.8 ± 9.3	58.0 ± 9.9	NS
AG (cm)[a]	88.3 ± 16.1	80.1 ± 12.5	94.8 ± 15.7	<.001
BMI (kg/m²)[a]	23.2 ± 4.3	22.1 ± 3.3	24.1 ± 4.9	.05
SBP (mmHg)[b]	131 (119—148)	120 (109—137)	132 (124—160)	.03
DBP (mmHg)[b]	79 (70—88)	74 (67—83)	85 (74—94)	.02
HTN[c]	21 (40%)	5 (21%)	16 (55%)	.01
DM[c]	6 (11%)	0 (0%)	6 (21%)	.03
Dyslipidaemia[c]	34 (64%)	18 (75%)	16 (55%)	NS
Lipid-lowering treatment[c]	20 (38%)	8 (33%)	12 (41%)	NS
Early CVD in family members[c]	7 (13%)	2 (8%)	5 (17%)	NS
CVD patients[c]	7 (13%)	6 (25%)	1 (4%)	NS
Comorbidities[c]	39 (74%)	17 (71%)	22 (76%)	NS
Alcohol consumption[c]	25 (49%)	7 (29%)	18 (67%)	.01
SUA/day[b]	0 (0—2)	0 (0—1)	2 (0—3)	.003
Tobacco consumption[c]	18 (34%)	7 (29%)	11 (38%)	NS
Nº. cigarettes/day[b]	.0 (.0—10)	0 (0—9)	.0 (.0—10)	NS
Years of consumption[b]	.0 (.0—20)	.0 (.0—20)	.0 (.0—25)	NS
Adherence to diet[c]	10 (18.9%)	6 (25%)	4 (13.8%)	NS
Level of physical activity[c]				NS
Low	13 (22%)	5 (22%)	8 (31%)	
Moderate	20 (41%)	10 (43%)	10 (38%)	
High	16 (33%)	8 (35%)	8 (31%)	

Dyslipidaemia: concentration of LDL cholesterol>116 mg/dl and/or triglycerides>150 mg/dl and/or previous lipid-lowering treatment. AG: abdominal girth; BMI: body mass index; CVD: cardiovascular disease; DBP: diastolic blood pressure; DM: diabetes mellitus; HTN: hypertension; NS: non-significant differences with a p-value >.100; SBP: systolic blood pressure; SUA: standard unit of alcohol. Early cardiovascular disease was defined as occurring in men before the age of 55 years and in women before the age of 65 years.

[a] Mean ± standard deviation.

[b] Median (interquartile range).

[c] Number of patients (percentage with respect to total, women, or men respectively).

Analytical characteristics

As shown in Table 2, glucose concentrations, HbA1C values, and triglyceride levels were not elevated. Blood glucose was higher in the men, where there were 6 diabetic subjects (Table 1), than in the women. As expected for subjects with HALP, total cholesterol and HDL-C were elevated and higher in the women than in the men, with significant differences between the sexes in the case of total cholesterol. Consistent with the higher prevalence of dyslipidaemia in the women (Table 1), the women had higher apolipoprotein B LDL-cholesterol than the men. The maximum HDL-C values were in accordance with the cut-off point for the definition of HALP and without significant differences between the men and the women, nor for the minimum HDL-C recorded in the subjects' medical history (pre-recruitment analyses).

Ultrasound characteristics

As shown in Table 3, IMT values were within the normal range[15] and were similar in the women and the men. Importantly, there was a statistical trend for a higher prevalence of plaques in the left carotid artery in the men than in the women. These differences reached statistical significance when analysing the presence of plaques in the 2 territories, being twice as frequent in the men than in the women.

Table 4 shows the variables for which significant differences were found between the patients with and without plaque. As noted above, there was a higher percentage of males than females in the cases with plaque. Age was significantly higher in the men, as well as the frequency of alcohol consumption and the volume and years of tobacco consumption, the amount, and years of consumption, they had higher systolic blood pressure, lower peak HDL, and greater intima-media thickness. Multivariate analysis showed a significant association with the presence of subclinical atherosclerosis of patients' age, alcohol consumption, and tobacco use (Table 5).

Discussion

This study describes the clinical, analytical, and radiological characteristics of a group of patients with HALP. Taking into account the current scant knowledge of the clinical profile of patients with HALP, this study provides relevant information on the prevalence of cardiovascular risk factors, cardiovascular events, and subclinical atherosclerosis in these patients.

The U-shaped relationship between cardiovascular disease and HDL-C levels is well documented. The first observation of an inverse relationship between HDL-C lev-

Table 2 Analytical data (mg/dl).

Variable	Total	Women	Men	p-Value
Glucose[a]	93.0 (84.0—104)	90.0 (80.0—98.3)	96.5 (84.3—112)	.047
Triglycerides[a]	73 (55—99)	78.0 (62.3—107.3)	68.0 (53.5—95.5)	NS
Total cholesterol[a]	232 ± 55.3	269 ± 43.3	227 ± 37.3	<.001
LDL[a]	109 ± 41.8	127 ± 47.3	93.2 ± 29.3	.002
Non-HDL cholesterol[b]	124 ± 45.0	145 ± 44	107 ± 37	NS
HDL-C[a]	116 (91.0—135)	121 (75.0—138)	109 (75.0—128)	NS
Minimum HDL-C[c]	96.0 (57.0—116)	97 (70—119)	95 (46—113)	NS
Maximum HDL-C[c]	138 (126—149)	146 (139—156)	127 (122—133)	NS
Apolipoprotein A1[a]	270 ± 64.0	280 ± 62.3	262 ± 65.1	NS
Apolipoprotein B[a]	94 ± 29	106 ± 30.0	83.4 ± 22.7	.002
Lipoprotein(a)[a]	35.6 ± 40.3	35.1 ± 41.0	36.0 ± 40.4	NS

HDL: high-density lipoproteins; LDL: low-density lipoproteins; NS: non-significant differences at a p-value >.100.
[a] Values obtained from routine analyses of the hospitals of origin at recruitment.
[b] Calculated value.
[c] Data collected retrospectively from the patients' medical records.

Table 3 Radiological data.

Variable	Total	Women (n = 24)	Men (n = 27)[a]	p
RCA IMT (mm)	.70 (.56—.80)	.70 (.55—.70)	.75 (.56–.80)	NS
LCA IMT (mm)	.65 (.60—.80)	.65 (.52—.70)	.79 (.60–.85)	NS
RCA plaque[b]	23 (45%)	8 (33%)	15 (56%)	NS
LCA plaque[b]	22 (43%)	7 (29%)	15 (56%)	.058
Plaque[b,c]	27 (53%)	9 (38%)	18 (67%)	.037

LCA IMT: left carotid artery intima-media thickness; NS: non-significant differences at a p-value <.05; RCA IMT: right carotid artery intima-media thickness.
[a] Two patients without radiological tests.
[b] The variables RCA plaque, LCA plaque and plaque are expressed as number of subjects and percentage in brackets.
[c] Presence of plaque in one or both carotid arteries.

Table 4 Variables with significant differences between patients with and without plaques.

Variable	Without plaque (n = 24)	With plaque (n = 27)[a]	p-Value
Sex[b]			.037
Women	15 (62.5%)	9 (33.3%)	
Men	9 (37.5%)	18 (66.7%)	
Age	51.7 ± 8.89	61.3 ± 8.17	.0001
SBP	121 (109—135)	135 (124—161)	.010
Alcohol consumption	4 (25.0%)	18 (72%)	.001
SUA/day	0 (0—0)	2.0 (.0—3,5)	.001
Tobacco consumption[b]	5 (28.8%)	12 (44.4%)	.026
Nº. cigarettes/day	0 (0—0)	3.0 (0—10)	.012
Years of consumption	0 (0—0)	.0 (.0—40)	.025
Maximum HDL-C	143 (136—153)	132 (122—141)	.013
RCA IMT (mm)	.60 (.51—.60)	.73 (.65—.80)	.011
LCA IMT (mm)	.60 (.51—.70)	.80 (.60—.86)	.024

LCA IMT: left carotid artery intima-media thickness; RCA IMT: right carotid artery intima-media thickness.
[a] Two patients without radiological tests.
[b] The variables sex and tobacco consumption are expressed as number of subjects and percentage in brackets.

els and coronary heart disease dates back to the 1950s.[16] In the 1970s, numerous studies later confirmed this.[7] The incidence of cardiovascular disease in subjects with hyperalphalipoproteinaemia has been documented in several cohort studies.[17] In our sample it is striking that 25% of the women had previous CVD (6/24, Table 1) while only one man had such a history, despite a higher incidence of CVRF in the men. This may be explained, at least in part, by a higher

Table 5 linear regression model for the association of covariates with the presence of subclinical atherosclerosis.

Variable	ß coefficient	95% CI	p-Value
Age	1.204	1.066—1.361	.003
Alcohol consumption	5.901	1.138—30.597	.034
Tobacco consumption	10.215	1.384—75.411	.023

Covariates: sex, systolic blood pressure, no. cigarettes/day, years of tobacco consumption, maximum HDL-C, left and right carotid intima-media thickness, LDL cholesterol at study entry, and diabetes.

prevalence of dyslipidaemia (and less lipid-lowering treatment) in women, as opposed to that observed in a working population.[18]

Regarding the relationship between cancer and HDL-C levels, some studies have shown an increase in the incidence of neoplasms in people with low levels due to the loss of anti-inflammatory effect and disturbed synthesis of steroid hormones.[19,20] However, other studies have shown an association between high levels of HDL-C and breast cancer.[21] In our sample, only three subjects had neoplasms.

In our sample there was poor adherence to the Mediterranean diet in both men and women, data that are similar to previous population-based surveys.[22] This finding highlights the need for a cross-sectional approach to patients to promote healthy dietary habits, the impact of which on health has been widely demonstrated.[23] However, this low adherence to the Mediterranean diet contrasts with the relatively high percentage of patients who report moderate or high levels of physical activity.

The analytical data of the cases do not reveal any relevant data beyond the maximum HDL-C reached, since it defines the cohort point for HALP. The women had higher LDL-C levels, which is consistent with a higher prevalence of dyslipidaemia and less lipid-lowering treatment than the men, and with a higher proportion of previous CVD. Glycaemia was higher in the men, in fact only they included diabetic patients. It has been described how hyperglycaemia could increase cardiovascular risk in subjects with HALP[24] by a mechanism that goes beyond diabetes itself as a classic risk factor; hyperglycaemia would affect the composition of HDL particles by impairing their function.[25]

One of the most relevant findings of our study is the detection of atherosclerotic plaque in a considerable number of patients. This was more frequent in the men, with higher body mass index and abdominal girth than the women, known predisposing factors for subclinical atherosclerosis.[26] In our series, subjects with plaque had lower maximum HDL-C levels than those without plaque (due to the higher prevalence of men, with lower HDL-C levels), although they were high compared with the Spanish population mean.[27] In fact, our patients' HDL-C levels at recruitment (Table 2) are similar to those used in a recent study that analyses the impact of high values (HDL-C>79 mg/dl in men and >99 mg/dl in women) on cardiovascular mortality.[28]

The presence of subclinical atherosclerosis with respect to HDL-C levels also exhibits a U-shaped curve pattern, although this was demonstrated by assessing its presence with coronary artery calcification in a study of 6000 participants.[29] As it is less cost-effective than carotid ultrasound, it could not be considered in our patients. In our study, age and tobacco use, i.e., classical CVRFs, showed an association with subclinical atherosclerosis, independently of other risk factors. Alcohol consumption was also associated with the presence of plaque in multivariate analysis. The association between alcohol consumption and cardiovascular disease is debated.[30] The association with subclinical atherosclerosis is less well studied. Our results suggest a detrimental effect of patient-reported moderate alcohol consumption, contrary to the work of Laguzzi et al. in subjects at high cardiovascular risk.[31] The way of assessing consumption and the profile of the subjects studied may explain these discrepancies. Our study also has a limited sample size, and therefore these results need to be confirmed by further studies.

This study is not without limitations. It is a preliminary study in which the intended sample size was not reached. Consequently, the statistical power was low for most of the variables tested. Only age differences between patients with and without plaque reached 96% power, but a total of 96 patients (balanced between men and women) would need to be studied to achieve a power of 80% to test for differences in prevalence of subclinical atherosclerosis between men and women. This limitation in recruitment may be a consequence of a probable under-diagnosis of HALP in our setting.

Furthermore, it seems clear that there is a selection bias; the cases studied are not healthy subjects, but patients attending the hospital or health centre, and therefore the findings described cannot be generalised. In this sense, the study of a control group would make it possible to highlight the truly distinctive characteristics of subjects with HALP and to propose a specific clinical approach for these patients which, at present, would have to be directed towards managing their risk factors and comorbidities. Finally, other variables that influence the function of HDL particles, such as PON1 activity or the presence of genetic variants that modulate the concentration of HDL-C, have not yet been analysed.

Conclusions

In our study, the men had a higher prevalence of cardiovascular risk factors than the women, except for dyslipidaemia. Subclinical atherosclerosis was present in more than half of the series, being more frequent in the men. The age of the patients, the volume of alcohol consumed, and tobacco consumption were associated, independently of other covariates, with the presence of plaque in some of the territories explored, but our data do not show a significant influence of HDL-C levels.

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Authors' contribution

All the authors made essential contributions to the conception, study design, acquisition, analysis, and/or interpretation of the data. All the authors critically reviewed the draft article and approved the final version presented.

Conflict of interests

The authors have no conflict of interest to declare.

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