



Original/Otros

# Role of ApoA1 on High-Density Lipoprotein: an intervention with plant sterols in patients with hypercholesterolemia

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## Abstract

**Background:** Numerous studies have shown an inverse association between cholesterol's concentration associated with High-Density Lipoprotein Cholesterol (HDL-C) and cardiovascular risk. The present study intends to investigate the possible relation between Apolipoprotein A (ApoA1) and HDL-C as a new strategy to reduce cardiovascular risk.

**Aim:** was determine the effect of ApoA1 in cholesterol's metabolism through its influence on HDL-C in young adult population.

**Methods:** One clinical trial, controlled, randomized, double-blind, providing a commercial milk, "Naturcol", with sterols for 3 weeks (n = 19) and placebo (n = 16). A questionnaire *Ad Hoc* was designed and a complete anthropometric study was made. SPSS 21.0 was used to analyse the data.

**Results:** Significant differences were observed between sterol milk and placebo in a single marker, Low-Density Lipoprotein Cholesterol (LDL-C). A linear dispersion of data between HDL-C and ApoA1 was found, both at the beginning and end of the intervention (Person Correlation = 0.846 and 0.903, respectively). High dependency measures by linear regression ( $R^2 = 0.715$  and  $0.816$ , respectively) were observed.

**Conclusion:** A significant relation between HDL-C and ApoA1 was proven. Taking into account the importance that HDL-C levels seem to have on cardiovascular health, ApoA1 is presented as an important clinical marker to improve heart function as well as to reduce cardiovascular risk.

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Key words: *ApoA1. Cholesterol. Cardiovascular risk. Plant sterols. High-density lipoproteins (HDL-C).*

## PAPEL DE APOA1 EN LIPOPROTEÍNAS DE ALTA DENSIDAD: UNA INTERVENCIÓN CON ESTEROLES VEGETALES EN PACIENTES CON HIPERCOLESTEROLEMIA

### Resumen

**Antecedentes:** Numerosos estudios han demostrado una asociación inversa entre la concentración de colesterol asociado a lipoproteínas de alta densidad de colesterol (HDL-c) y el riesgo cardiovascular. El presente estudio investigó la posible relación entre la apolipoproteína A (ApoA1) y el HDL-C como una nueva estrategia para reducir el riesgo cardiovascular.

**Objetivo:** determinar el efecto de ApoA1 en el metabolismo del colesterol a través de su influencia sobre el HDL-c en la población adulta joven.

**Métodos:** ensayo clínico, controlado, aleatorizado, doble ciego, proporcionando una leche comercial con esteroides, "Naturcol", durante 3 semanas (n = 19) y placebo (n = 16). Se diseñó un cuestionario *Ad Hoc* y se realizó un estudio antropométrico completo. Se utilizó el programa SPSS 21.0 para analizar los datos estadísticos.

**Resultados:** Se observaron diferencias significativas entre la leche de esteroles y el placebo únicamente en un solo marcador, en las lipoproteínas de baja densidad de colesterol (LDL-c). Se encontró una dispersión lineal de datos entre HDL-C y ApoA1, tanto al principio y al final de la intervención (correlación de Person = 0,846 y 0,903, respectivamente). Se observó alta dependencia en la regresión lineal ( $R^2 = 0,715$  y  $0,816$ , respectivamente).

**Conclusión:** Una relación significativa entre el HDL-c y ApoA1 fue comprobada. Teniendo en cuenta la importancia que los niveles de HDL-c parecen tener en la salud cardiovascular, la ApoA1 se presenta como un importante marcador clínico para mejorar la función del corazón, así como para reducir el riesgo cardiovascular.

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Palabras claves: *ApoA1. Colesterol. Riesgo cardiovascular. Esteroides vegetales. Lipoproteínas de alta densidad (HDL-c).*

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## Abbreviations

ApoA: Apolipoprotein A.  
ApoA1: Apolipoprotein A-1.  
ApoB: Apolipoprotein B.  
BIA: Bioelectrical Impedance Analysis.  
TC: Total Cholesterol.  
Dl: Decilitre.  
CVD: Cardiovascular Disease.  
G: Grams.  
HC: Hypercholesterolemia.  
HDL-C: High-Density Lipoprotein Cholesterol.  
HUCSCM: *Hospital Universitario Clínico San Carlos de Madrid*.  
BMI: Body Mass Index.  
LCAT: Lecithin-Cholesterol Acyltransferase.  
LDL-C: Low-Density Lipoprotein Cholesterol.  
CRP: C-Reactive Protein.  
TAG: Triacylglycerol(s).  
ACS: Acute Coronary Syndrome.  
SNP: Single-Nucleotide-Polymorphism.

## Introduction

Cardiovascular Disease (CVD) of atherothrombotic aetiology is the first cause of death in the occidental World<sup>1</sup>. Although Spain has a lower CVD incidence than northern European countries, we should consider that hospitalization as a consequence of Acute Coronary Syndrome (ACS) increases annually in 1.5%, approaching the European figures<sup>2</sup>.

There are several risk factors associated with the development of CVD, among which Hypercholesterolemia (HC) is one of the most relevant; not only because of its high prevalence but also because of its deficient control in general population, which have already been diagnosed with the disease. The increase of Low-Density Lipoprotein Cholesterol (LDL-C) seric concentrations has been reported as the main risk factor in a CVD. Some studies suggest that for the reduction of 1% of the concentration of total cholesterol, a reduction of 2% on cardiovascular risk could be obtained<sup>3</sup>.

However, it should be remained that, among HC, several phenotypes are found, affected by different mechanisms in the regulation, manipulation and relevancy of cardiovascular risk<sup>4,5,6</sup>. The relation between cardiovascular events and high concentrations of cholesterol, associated to LDL-C is clearly established after numerous clinical tests and reviews based on the evidence of their results. In addition, an increasing number of studies have proven an inverse relation between cholesterol's concentration associated to High-Density Lipoprotein Cholesterol (HDL-C) and cardiovascular risk. Thus, it is justified to focus on HDL-C as a new additional strategy to reduce cardiovascular risk, as well as on the interest of the mechanisms implied<sup>7</sup>.

Therefore, the decision of intervention on the lipid metabolism to prevent CVD is based on the analytic levels of plasmatic cholesterol and its fractions, though some workgroups recommend changing the focus towards apolipoproteins<sup>8</sup>.

Apolipoproteins are the parts of lipoproteins that contain proteins and are generally combined with lipids. Apolipoprotein A-1 (ApoA1) is associated with HDL-C while Apolipoprotein B (ApoB) is associated with LDL-C, having opposite functions<sup>9</sup>.

Apolipoprotein A (ApoA) is formed by other subclasses, ApoA1, ApoA2, and others, which synthesize in the liver and intestine. They are transferred actively towards and from HDL-C, VLDL-C and chylomicrons. Their main function is to activate Lecithin-Cholesterol Acyltransferase (LCAT), which esterifies free cholesterol on HDL and, peripherally, transfers it from the interior of the cell to its membrane, therefore activating ApoA1 receptors with the intervention of cholesterol's transporters ABCA1<sup>10</sup>. Some authors even suggest the determination of useful ApoA1 on patients' diagnosis with a genetic defect of low production of HDL-C, though the benefits of associating low concentrations of ApoA1 to cardiac risk, instead of measuring HDL-C, are not still clear. There are prospective studies on the predicative value of ApoA1 which have not shown higher advantages on HDL-C, as well as not having standardized determination methods yet<sup>11</sup>.

The present study intends to prove the possible relation between ApoA1 and HDL-C in a double-blind study, based in an intervention with vegetal sterols, analysing, at the beginning and end of this study, the variations of fractions of blood cholesterol in relation to ApoA1.

## Objective

The aim of the study was establish the effect of ApoA1 in cholesterol's metabolism through its influence on HDL-C in a young adult population.

## Materials and methods

Double-blind, controlled, randomized, clinical test with participants recruited from *Hospital Universitario Clínico San Carlos de Madrid (HUCSCM)*, after the approval of the Bioethic's Committee of this hospital (code: C.I. 12/233). Previous to the beginning of the test, the participants were given instructions about the aim of the study and signed an informed consent form. Sterols were mixed in commercial milk "Naturcol" (supplied by *Corporación Alimentaria Peñasanta S.A.*), available in the market during the period of this study. During three weeks, the participants received either the treatment or the placebo, ingesting 2 glasses of milk every day. The glasses were standardised to a

volumetric capacity of 350 ml, administering in each of them a daily capacity of 2.24 g of vegetal sterols for patients receiving the treatment (included in the “milk study” phase). The same quantity of non-sterol, skimmed milk was given to patients receiving the placebo. The milk was blinded, bottled in white, without the knowledge of both participants and investigators, only differing on the colour of the cap. The assignment of the groups was arbitrary, using randomization-by-number charts.

#### *Inclusion and exclusion criteria*

- – *Inclusion criteria:* Men and women; aged 18-50, Total Cholesterol (TC) > 200 mg/dl.
- – *Exclusion criteria:* TC < 200 mg/dl; cardiac pathology (ictus, myocardial infarction, angina pectoris, etc.); lactose intolerance; allergy to cow milk’s proteins; allergy to vegetal sterols; pharmacologic treatment to cholesterol or triacylglycerol/triglycerides (TAG) (fibrates, statins, etc.); obesity - Body Mass Index (BMI) > 30.

#### *Clinical analysis*

Sample extractions for analytical tests were conducted by healthcare personnel in *Unidad de Análisis Clínicos del HUCSCM*, following the standardized methodology. The test were done after the participants had fasted for 12 hours<sup>12,13,14</sup>.

#### *Study factors and variables*

For this project an *Ad Hoc* questionnaire was designed. All surveys, as well as the anthropometric study, were made by a single investigator. The variables of study were established to reach the outlined targets: gender, age, clinical and pharmacological history, quality of sleep, health habits, toxic habits (such as tobacco and alcohol), intestinal habits, food consumption frequency and physical activity. In addition, it was measured the weight, height, waist perimeter, BMI, grease percentage, visceral grease percentage, grease-free mass (kg) and water percentage in each participant. Weight, BMI and corporal composition were established with a tetra-polar, mono-frequency (50 kHz), Bioelectrical Impedance Analysis (BIA): TANITA BP-601 Model. For the composition’s measurement with BIA, the usual standard protocol was used. Analytic markers were: ApoA1, Lipoprotein A, lipid profile (TC, HDL-C, LDL-C and TAG), haematology (white and red series’ count), glucose, insulin and C-Reactive Protein (CRP).

Besides this, confounding factors were also considered, using an affinity chart for the ingestion’s compliance (>95 %), a own elaboration score to mo-

nitor food’s ingestion that could influence, upwards or downwards, cholesterol’s metabolism and controlling the non-modification of initial habits during the test.

#### *Statistical Analysis*

For data analysis, *IBM’s SPSS 21.0* statistic’s programme was used. Firstly, a descriptive analysis of socio-demographic, anthropometric and of initial and final lipid levels under the ingestion of “Naturcol” and the placebo was undertaken. Normality of lipid levels was also measured using *Shapiro-Wilk Test*. To measure the efficiency of the ingestion of “Naturcol” and the placebo, the difference of lipid levels before and after the ingestion was calculated, also employing *Student’s T-Test* for related samples or *Wilcoxon Signed-Rank Test*, according to the compliance of the “assumption of normality” of the independent variables. The size of the effect was calculated as the quotient of the average’s difference with the initial standard deviation for “Naturcol”. In order to study if the effect of the ingestion of “Naturcol” or the placebo interacts with the gender, F-Test for ANOVA’s interaction of a design of partially repeated measures with the gender factor was used. The level of statistical’s significance applied was 5%. As for studying the relation between ApoA1 and HDL-C, as well as with other markers, *Pearson Product-Moment Correlation Coefficient* was applied and, afterwards, a linear regression was used to discover the degree of dependence between both parameters.

This study followed the ethical principles recognised by the Declaration of Helsinki, the recommendations of good clinical practice, the actual Spanish legislation which regulates clinical investigation on humans, personal and bioethics data protection (Spanish Law: *Decreto Real 561/1993 sobre ensayos clínicos y 14/2007, 3 Julio para la investigación biomédica*).

#### **Results**

The test started with 43 participants. Four of them were excluded due to non-compliance of the treatment or the used methodology; and other 4 participants did not complete the research, therefore their results were not included the final report. 35 participants finished this study – 19 women and 16 men (age 36,3 (±6,9)). 19 of them were in the study group with sterols and 16 of them in the control-group, which received the placebo. The normality of the variables was proved and significant differences due to age, weight, height and anthropometry were not found. The descriptive characteristics of the participants are shown in table I.

After finalizing the treatment, significant differences were observed between the values of milk with sterol and placebo milk, in only one single marker: LDL-C (Table II).

**Table I**

Descriptive data of the sample in reference to gender, age and basic anthropometry. Expressed in absolute values and its percentage, in brackets, or in average values and its standard deviation, in brackets

	N (%) / M (Sd)
Gender (Male)	16 (45,7)
Age (Years)	36,3 (6,9)
Weight (Kg)	69,4 (11,9)
Height (m)	1,7 (0,9)
BMI	23,9 (3,4)

**Table II**

Comparison of the intervention 's efficiency, measured through the difference between initial and final values ( $\Delta$ : initial-final), expressed as average and standard deviation, with its significance (p) in each case

	Naturcol M (Sd)	Placebo M (Sd)	p
$\Delta$ LDLc <sub>mg/dL</sub>	15,9 (29,54)	-11,1 (19,2)	0,004
$\Delta$ HDLc <sub>mg/dL</sub>	2,3 (8,1)	-1,0 (3,0)	0,14
$\Delta$ ApoA 1 <sub>mg/dL</sub>	5,5 (12,6)	-1,9 (15,8)	0,13
$\Delta$ Lipoprotein A <sub>mg/dL</sub>	-3,9 (8,7)	-1,1 (4,5)	0,24

A linear data dispersion was found between HDL-C and ApoA1, both among the initial and final values of the intervention (Pearson Correlation: 0,846 and 0,903, respectively), obtaining a high dependence; values of linear regression ( $R^2 = 0,715$  and  $0,81$ , respectively).

This dependence could not be proven or it was too low, between LDL-C and ApoA1 ( $R^2$  de 0,131), and the initial-final values of HDL-C and ApoA1 ( $R^2$  de 0,27).

## Discussion

On one hand, several studies have shown that there is an inverse relation between HDL-C and ECV levels. It is estimated that, for an increase of 1 mg/dl of HDL-C, the risk of myocardial infarction or even death could be reduced in approximately 3%<sup>15</sup>, which would positively influence cardiovascular health. This result is of a great relevance to consider against LDL-C where, as we stated previously, a decrease of 1% would mean a reduction of 2% on cardiovascular risk<sup>3</sup>.

This way, as it has already been suggested in literature, a good therapeutic target would be to maintain, upwards HDL-C levels. Regarding this, ApoA1 seems to cause a special relevance and interest in the scientific community. Our data shows a high dependence of HDL-C, that is not modified after the intervention ( $p=0,13$ ) as there is not a significant modification of HDL-C ( $p=0,14$ ). Similar data was observed by Collins M, et al. 2007<sup>16</sup>, in an intervention with 84 participants, divided in 4 groups (exercise and sterols, sterols, exercise and control), without acknowledging any changes after the intervention, neither in ApoA1, Apolipoprotein B (ApoB), ghrelin and the growth hormone. Nevertheless, a correlation between ApoA1 and HDL-C was observed ( $r=0,33$ ,  $p=0,01$ ). In another study, Sialvera Tf, et al 2007, administering up to 4 g of sterol to a sample of 108 participants (double-blind), reached a decrease of LDL-C higher than 20%. No differences were seen on HDL-C and ApoA1 levels<sup>17</sup>.

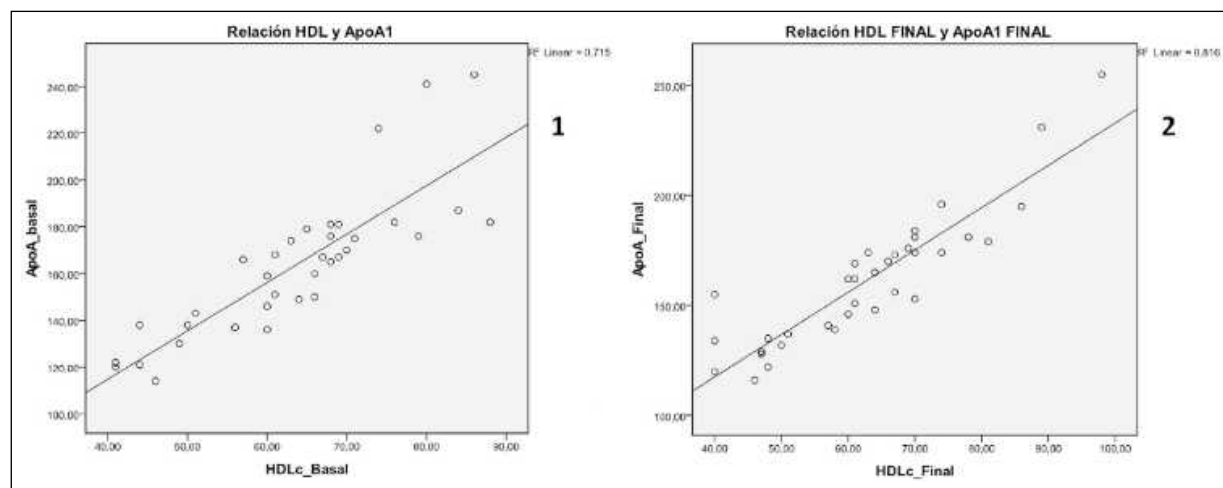


Fig. 1.—Pearson Correlation between initial HDL-C and initial ApoA1 (Figure 1.1); and between final HDL-C and final ApoA1 (Figure 1.2.).

Other authors<sup>18</sup>, following the hypothetical influence of HDL-C and ApoA as indicators to estimate the individual risk of CD, undertook a test with 15 obese participants that undertook physical exercise. A significant reduction on TAG, ApoA1 and ApoB levels was achieved, though not in LDL-C or HDL-C levels, which they justify stating that only a part of HDL-C particles participate in the reverse transportation of cholesterol. And though the majority believes that an adequate increase of physical activity produces an increase on HDL-C concentrations (and probably also on ApoA1 levels)<sup>19</sup>, more thorough studies have not found positive and consistent results based, for example, on physical exercise, like Kelly et al, 2011<sup>20</sup> meta-analysis, which concludes with the improvement of TC, LDL-C and TAG levels, but not with an increase of HDL-C levels, neither with significant differences in this marker.

On another hand, besides the values recollected and measured in blood, there is still a lack of data relating apolipoproteins (ApoB, ApoA1) and LDL-C and HDL-C, with the charge of the atherosclerotic plaque and the presence of a nucleus rich in lipids, as a high-risk plaque marker<sup>21</sup>.

It is increasingly evident that a functional HDL-C is a more desirable target than the simple increase of the levels of HDL-C cholesterol, due to its well-known anti-atherogenic function in its capacity to promote the transportation of inverse cholesterol from peripheral cells<sup>22</sup>. At this point, the functionality of ApoA1 could play a relevant role, being an important motor of therapeutic target to improve cardiac function and decrease, therefore, cardiovascular risk.

This scientific interest is motivating the research of new molecules and medicines capable of changing lipids and lipoproteins' fractions as, for example, fenofibrate<sup>23</sup>, nevirapine<sup>24</sup>, niacin<sup>25,26</sup>, statin or hormonal therapy<sup>27</sup>, with different results.

These discrepancies, besides the different methodological circumstances in studies and populations with important basic differences, could be due to, partially, the possible variability and functionality that host different genetic mutations (SNPs, Single-Nucleotide-Polymorphism). Gomez P, et al 2010<sup>28</sup>, published that different polymorphisms in ApoA1 and ApoA4, meant a different response on LDL-C after an intervention with different diets, relating some disease's phenotypes with the genotype of the patient.

## Conclusion

We have proven an important relation between HDL-C and ApoA1. Considering the relevance that HDL-C levels have on cardiovascular health, ApoA1 appears as a clinical marker of interest, related to its correct functionality and concentration. More studies should be undertaken in order to delve into this line of investigation, contributing with more clear evidences.

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## Conflict of interest

There weren't any conflict of interest with none of authors.

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