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TRIGLYCERIDES INDUCED HDL-C-LOWERING IS EXACERBATED IN POST-MENOPAUSAL WOMEN

Treball de Fi de Grau

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Agraïments

Vull agrair la col·laboració de totes aquelles persones i institucions que han fet possible la realització d'aquest Treball de Fi de Grau.

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I per últim, agrair a la meva família, amics i companys el suport i els ànims durant tot el temps que ha durat la realització d'aquest treball.

Abstract

Introducció: Les malalties cardiovasculars són la principal causa de mort a Espanya i es relacionen directament amb factors de risc cardiovascular no modificables, com el sexe i l'edat, i factors de risc modificables, com la hipertensió arterial, el diagnòstic de Diabetis Mellitus o el perfil lipídic. Tot i que la lipoproteïna de baixa densitat transportadora de colesterol (LDL-c) és considerada el principal factor lipídic de risc cardiovascular, aproximadament la meitat dels infarts de miocardi es produeixen en persones amb concentracions normals de LDL-c. En aquestes persones, la principal alteració lipídica és l'elevació dels triglicèrids (TAG), que provoca una disminució de les concentracions de lipoproteïna d'alta densitat transportadora de colesterol (HDL-c). L'objectiu d'aquest treball és entendre quins factors modulen la disminució de HDL-c deguda a l'augment dels TAG.

Mètodes: El treball s'ha realitzat amb les dades d'una mostra de la població general de 4.754 adults participants en l'estudi Di@bet.es. Els lípids s'han avaluat amb una bioquímica de rutina hospitalària. L'anàlisi estadística s'ha fet amb el programa SPSS.

Resultats: Abans de la menopausa, la disminució del HDL-c associada a l'augment dels TAG és menor en les dones que els homes. Després de la menopausa però, l'augment dels TAG és significativament major en dones. També s'ha observat que amb l'augment de TAG el HDL-c disminueix progressivament amb l'edat en les dones mentre que es manté constant en els homes.

Conclusions: Existeix una relació inversa entre les concentracions plasmàtiques de TAG i HDL-c que varia segons l'edat i el sexe dels subjectes i que afecta especialment les dones.

Introducción: Las enfermedades cardiovasculares son la principal causa de muerte en España y se relacionan directamente con los factores de riesgo cardiovascular no modificables, como el sexo y la edad, y con factores de riesgo modificables, como la hipertensión arterial, el diagnostico de Diabetes Mellitus o el perfil lipídico. A pesar de que la lipoproteína de baja densidad transportadora de colesterol (LDL-c) es considerada el principal factor lipídico de riesgo cardiovascular, aproximadamente la mitad infartos de miocardio se producen en personas con concentraciones normales de LDL-c. En estas personas, la principal alteración lipídica es la elevación de los triglicéridos (TAG), que provoca una disminución de la concentración de la lipoproteína de alta densidad

transportadora de colesterol (HDL-c). El objetivo de este trabajo es entender que factores modulan la disminución del HDL-c debida a los TAG.

Métodos: El trabajo se ha realizado con los datos de una muestra de la población general de 4.754 adultos participantes en el estudio Di@bet.es. Los lípidos se han evaluado mediante una bioquímica de rutina hospitalaria. El análisis estadístico se ha realizado con el programa SPSS.

Resultados: Antes de la menopausia, la disminución del HDL-c asociada al aumento de los TAG es menor en las mujeres que en los hombres. Pero después de la menopausia, el aumento de los TAG es significativamente mayor en mujeres. También se ha observado que con el aumento de los TAG el HDL-c disminuye progresivamente con la edad en las mujeres mientras que se mantiene constante en los hombres.

Conclusiones: Existe una relación inversa entre las concentraciones plasmáticas de TAG y de HDL-c que varía según la edad y el sexo de los sujetos y que afecta principalmente a las mujeres.

Introduction: Cardiovascular diseases are the leading cause of death in Spain and are directly related to non-modifiable cardiovascular risk factors, such as sex and age, and modifiable risk factors, such as arterial hypertension, diagnosis of Diabetes Mellitus or lipid profile. Although the low-density lipoprotein cholesterol (LDL-c) is considered the main lipid cardiovascular risk factor, approximately half of all myocardial infarctions occur in people with normal LDL-c concentrations. In these people, the main lipid alteration is elevated triglycerides (TAG), which causes a decrease in the concentration of high-density lipoprotein cholesterol (HDL-c). The aim of this work is to understand which factors modulate the decrease in HDL-c due to TAG.

Methods: The work was conducted using data from a general population sample of 4,754 adults participating in the Di@bet.es study. Lipids were assessed by routine hospital biochemistry. Statistical analysis was performed with SPSS software.

Results: Before menopause, the decrease in HDL-c associated with an increase in TAG is lower in women than in men. But after menopause, the increase in TAG is significantly higher in women. It has also been observed that with increasing TAGs HDL-c decreases progressively with age in women while it remains constant in men.

Conclusions: There is an inverse relationship between plasma TAG and HDL-c concentrations that varies according to the age and sex of the subjects and mainly affects women.

Introduction

Cardiovascular diseases (CVD) are the leading cause of death in Spain.
In 2020, 119.853 people died in Spain due to cardiovascular disease, representing the 24.3% of all deaths in the country. This mortality is ahead of the mortality because of tumors (22.8%) and because of infectious and parasitic diseases, which include COVID-19 (16.4%). Compared to 2019, mortality from CVD has risen by 2.8%. Of the total deaths from cardiovascular diseases, 53.32% were women and 46.67% men[1].

Cardiovascular risk is the probability an individual has of suffering a cardiovascular disease (stroke, ischemic heart disease, heart failure...) within a certain time-period and depends fundamentally on the concurring risk factors present in this individual.
There are non-modifiable risk factors, such as age, sex, race, or family history; but there are also modifiable risk factors that can be avoided or minimized through interventions. The most important modifiable factors are hypertension, cholesterol levels, metabolic syndrome, diabetes, overweight and obesity, smoking, alcohol abuse, level of physical activity…[2]

One of the most important modifiable factors, along with blood pressure values, is the lipid profile[3].
The relationship between serum total cholesterol levels and cardiovascular risk has been known since the 1970s and since then it has been used as a predictor of cardiovascular disease[4,5]. Later, LDL-c, one of the main lipoproteins transporting cholesterol in circulation, began to be extensively studied and became the main therapeutic target for cardiovascular risk reduction[6]. It was after the publication of the Framingham Heart Study[7] that HDL-c was also accepted as an important protective factor. Triglycerides (TAG), which are also part of the lipid profile, are also considered a risk factor. Although they do not accumulate in the artery, they modulate LDL and HDL metabolism.
In fact, the greatest cardiovascular risk occurs when there are alterations in the three parameters: an increase in LDL-c and TAG and a decrease in HDL-c[8,9].

There is, however, a population group that, despite lipid-lowering treatment (correct LDL-c levels) and the achievement of other goals related to cardiovascular risk, suffer from cardiovascular events[10]. In fact, approximately half of all myocardial infarctions

occur in people with normal LDL-c concentrations[11]. These people have what is called "residual risk" and is closely related to atherogenic dyslipidemia, which analytically presents low levels of c-HDL and high levels of TAG[12,13]. The pathophysiology of this form of dyslipidemia is associated with insulin resistance, obesity and type 2 diabetes[14].

Regarding cardiovascular risk factors, some studies have reported differences between men and women.

Smoking and Diabetes Mellitus (DM) have recently been shown to disproportionately increase the risk of acute obstructive coronary artery disease in women[15]. Hypertension particularly affects coronary microcirculation, which turns out to be extremely vulnerable in postmenopausal women because of the drop in estrogen which until then played a protective role[16].

The aim of this study is to explore how the relationship between TAG and their effect lowering HDL-c, well known parameters of the lipid profile implicated in cardiovascular risk, is affected by sex and age.

Our hypothesis is that there are differences among women and men regarding the lowering effect that TAG have on HDL-c.

Methods

Study subjects

The study was performed in unrelated and non-selected consecutive individuals of the national, cross-sectional, population-based cohort study of cardiometabolic risk factors and their association with lifestyle, the Di@bet.es study[2].

The initial cross-sectional study of the Di@bet.es was undertaken in 2008–2010 from a random cluster sampling of the Spanish population[17]. The Di@bet.es study sample consisted of 5072 subjects older than 18 years, randomly selected from the National Health System registries distributed into 100 clusters. Subjects with severe disease such as cancer or hepatitis were excluded by protocol. Detailed information on the methodology of the Di@bet.es cohort study has been previously described[18].

The population that concerns our study consisted of 4.754 adults from the Dia@bet.es study with triglycerides levels < 6,5mmol/L (575,22mg/dL), excluding all patients with moderate, severe (>885mg/dL) and very severe (1770mg/dL) hypertriglyceridemia[19].

The research was carried out in accordance with the Declaration of Helsinki (WHO 2011) of the Word Medical Association. Written informed consent was obtained from all the participants. The study was approved by the Ethics and Clinical Investigation Committee of the Hospital Regional Universitario de Málaga (Malaga, Spain) in addition to other regional ethics and clinical investigation committees all over Spain.

Data collection and laboratory measurements

The participants were invited to attend an examination visit at their health center with a nurse specially trained for this project. Information was collected using an interviewer administered structured questionnaire, followed by a physical examination and blood sampling.

For the present study the anthropometric and sociodemographic variables considered were: age; sex; BMI (body mass index); alcohol consumption (no alcohol consumption, occasionally/weekends or daily/nearly daily); adherence to the Mediterranean diet (a 14-point Mediterranean diet score was calculated and the cut-off for effective adherence was over 8 points)[20]; physical activity (total physical activity MET-minutes/week), smoking

habits (current smokers vs former/never been smokers) and whether or not the subjects were diagnosed with Diabetes Mellitus (DM).
Clinical variables such as blood pressure levels, fasting levels of glucose (mg/dL) and lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein and triglycerides) were also considered.

As mentioned in the introduction, the first lipoprotein analysis has been performed with 200µl of serum were diluted with 50 µl deuterated water and 300 µl of 50 mM phosphate buffer solution (PBS) at pH 7.4. 1H-NMR spectra were recorded at 306 K on a Bruker Avance III 600 spectrometer operating at a proton frequency of 600.20 MHz.

Statistical Analysis

Statistical software SPSS, version 23 was used to analyze all data. Continuous variables normally distributed are presented as the mean and standard deviation (SD). Categorical variables are presented as the percentage and the number of individuals. ANOVA was used to evaluate differences between groups.
To estimate the association between HDL-c and TAG we used linear regression with multivariate models. We initially selected known confounders variables and their interaction terms for inclusion in the multivariable regression models. The interaction terms were considered significant when significantly improved the variability of the dependent variable explained by the model. Because we found a significant interaction between age and sex, multivariable models to evaluate HDL-c and TAG association were performed with the population stratified into men and women. The R-squared (R2) statistic was used to provide an estimate of the percentage of the response variable variability that was explained by the linear models and by each of the predictors added in the models.
p-value of <0.05 was considered statistically significant.

Results

Clinical characteristics

The characteristics of the study subjects are shown in Table 1, also separated according to sex. The final sample participating in the study is composed of 4754 adults, of which 2020 were men, representing 42.5% of the total, and 2734 women, representing the remaining 57.5%. The average age of the participants was 50.4 years.

There were remarkable differences in the characteristics related to cardiovascular risk: the mean BMI of women was 27.67kg/m^2, while the mean BMI of men was 28.52kg/m^2. Men had higher blood pressure (138/79 mmHg vs. 127/75 mmHg) and higher baseline glucose values (103,20mg/dL vs. 95,57 mg/dL). 43,42% of men drink alcohol daily and 29,26% smoke, vs the 15,05% and 23,11% of women, respectively.

Adherence to the Mediterranean diet was present in 34% of the participants.

As for the lipid profile, the HDL-c was significantly lower in men than that of women (1.21 vs 1.44 mmol/L) and the LDL-c was higher (2.75 vs 2.68 mmol/L). Men also had higher TAG levels (1.51 vs1.19 mmol/L).

	Men 2020 (42.5%)	**Women** 2734 (57.5%)	**Total** 4754	**p**
Age (years)	50.6 (17.3)	50.3 (16.8)	50.4 (17.0)	0.452
BMI (Kg/m^2)	28.52 (4.43)	27.67 (5.62)	28.03 (5.16)	<0.0001
SBP (mmHg)	138 (17.44)	127 (20.35)	132 (20.24)	<0.0001
DBP (mmHg)	79 (10.48)	75 (11.24)	77 (11.11)	<0.0001
Alcohol consumption (n, %) Never Occasionally Daily	 300 (18.02%) 642 (38.56%) 723 (43.42%)	 940 (45.19%) 827 (39.76%) 313 (15.05%)	 1240 (33.1%) 1469 (39.2%) 1036 (27.7%)	<0.0001
Smoking habits (n, %) Yes No	 589 (29.26%) 1424 (70.74%)	 630 (23.11%) 2096 (76.89%)	 1219 (25.7%) 3520 (74.3%)	<0.0001
Adherence to Mediterranean diet (n, %) >8 points <=8 points	 700 (35.11%) 1294 (64.89%)	 894 (33.16%) 1802 (66.84%)	 1594 (34.0%) 3096 (66.0%)	0.164
Physical activity TMET (minutes per week)	3001.30 (4482.75)	1908.66 (2897.57)	2372.84 (3695.21)	<0.0001
Diabetes Mellitus (n, %) Yes No	 357 (17.67%) 1663 (82.33%)	 305 (11.16%) 2429 (88.84%)	 662 (13.93%) 4092 (86.07%)	<0.0001

Baseline glucose (mg/dL)	103.20 (31.93)	95.57 (25.62)	98.81 (28.72)	<0.0001
Lipid profile				
Total cholesterol (mmol/L)	5.02 (1.02)	5.09 (1.03)	5.06 (1.03)	0.012
HDL cholesterol (mmol/L)	1.21 (0.28)	1.44 (0.33)	1.34 (0.33)	<0.0001
LDL cholesterol (mmol/L)	2.75 (0.77)	2.68 (0.77)	2.71 (0.77)	0.002
TAG (mmol/L)	1.51 (0.86)	1.19 (0.61)	1.33 (0.74)	<0.0001

Table 1. Subject's characteristics. Data is represented as mean values (Standard Deviation) unless indicated otherwise

Confounding factors and interaction variables

We first selected those factors that may influence, either as confounders or as interaction factors, circulating TAG and/or HDL-c levels.

Those factors were gender, age, tobacco and alcohol consumption, physical activity level, BMI, diet, and whether or not the participants were diagnosed with Diabetes Mellitus (DM).

For HDL-c, adjusting for potential confounders and first-order interactions (TAG*gender, TAG*age, TAG*BMI, TAG*physical activity, TAG*DM, TAG*smoke and TAG*Mediterranean diet) the lineal regression models showed a significant effect of TAG. The linear regression model also showed a significant interaction of TAG with age and with gender ($p<0.001$), (Table 2). Figure 1 shows the correlation between TAG and HD-c and also evidence the interaction with gender.

	b	**SE**	**p**
TAG*gender	-0.042	0.013	<0.01
TAG*age	-0.002	0.000	<0.01
TAG*BMI	-0.000	0.001	0.896
TAG*physical activity	-0.000	0.000	0.937
TAG*DM	0.014	0.017	0.407
TAG*smoke	0.025	0.013	0.058
TAG*Mediterranean diet	0.016	0.013	0.217

Table 2. Adjusted b linear regression estimates of the effect of TAG on HDL-c applied to the overall population. The model is testing the first-order interactions with gender, age, BMI, physical activity, DM, smoking habits and adherence to Mediterranean diet. SE =standard error.

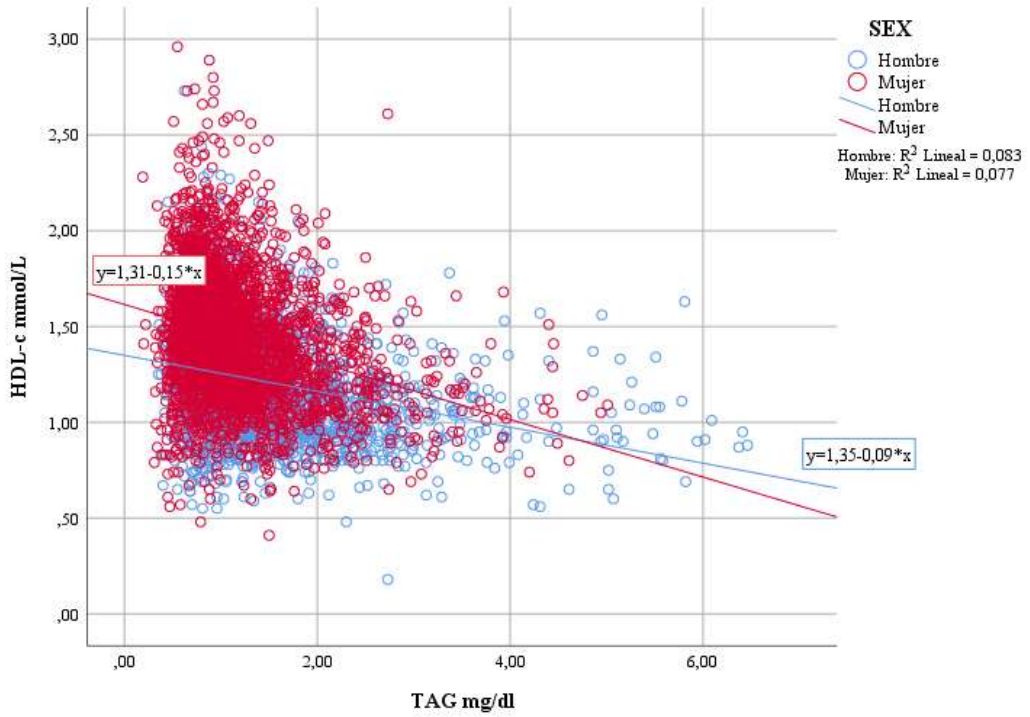

Figure 1. Correlation between TAG and HDL-c levels according to gender.

Because of these interactions, the effect of TAG on HDL-c was evaluated separately according to gender and at different ages.

First, the model adjusted for gender, age, tobacco, physical activity level, BMI, diet, and whether or not the participants were diagnosed with DM, was re-applied in men and in women separately. We observed that the effect of TAG on HDL-c was restricted to women (R^2: 14%, p<0.001). In men, the effect lost the statistical significance (R^2: 15%, p=0.105).

Second, the interaction with age was restricted to women (p<0.001). Thus, we re-applied the model adjusted for gender, age, tobacco, physical activity level, BMI, diet, and whether or not the participants were diagnosed with DM, at five representative ages of the study population (20, 30, 50, 70 and 80 years) (Table 3)(Figure 2).

We made three main observations. First, before menopause, the decrease of HDL-c associated to increased TAG was lower in women compared to men. Second, after

menopause, such increase was significantly higher in women. Third, HDL-c kept getting lower with age among women whereas it remained constant in men.

		Women			Men		
		b	**SE**	**p**	**b**	**SE**	**p**
TAG (mmol/L)	**20 years**	-0.001	0.027	0.963	-0.072	0.018	<0.001
	30 years	-0.035	0.035	0.090	-0.075	0.014	<0.001
	50 years	-0.102	0.012	<0.001	-0.081	0.008	<0.001
	70 years	-0.170	0.018	<0.001	-0.086	0.013	<0.001
	80 years	-0.204	0.023	<0.001	-0.089	0.017	<0.001

Table 3. Adjusted b linear regression estimates of the effect of TAG on HDL-c at 5 representative ages of the study population. SE =standard error.

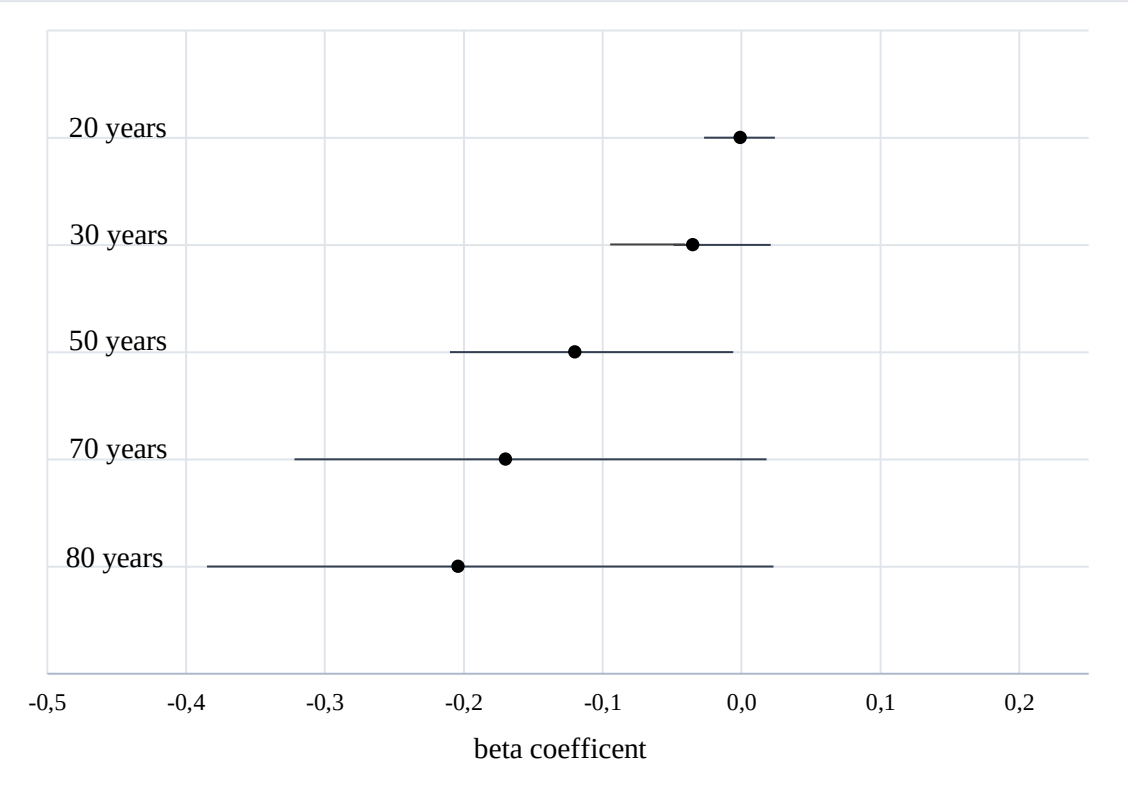

Figure 2. Adjusted b linear regression estimates of the effect of TAG on HDL-c at 5 representative ages of the women of the study.

Discussion

Our hypothesis was that the inverse relationship between plasma TAG and HDL-c varies depending on the age and sex of the subjects.

We found that when evaluating the effect of TAG on HDL-c, there is a clear interaction between gender and age in a cohort of general population.

We made three main observations: first, before menopause, the decrease of HDL-c associated to increased TAG was lower in women compared to men. Second, after menopause, such increase was significantly higher in women. Third, HDL-c progressively decrease with age among women whereas it remained constant in men.

Trying to explain the inverse correlation between TAG and HDL-c concentrations, some aspects of lipid metabolism must first be clarified[21].

Both are insoluble molecules that need to bind to proteins for transport, the apoproteins, forming lipoproteins. Lipoproteins can be classified according to their density, molecular weight and size.

Thus, lipid metabolism can be divided into an exogenous pathway, which involves the transformation of dietary lipids into cholesterol and TAG and their transport in the form of chylomicrons to the liver, adipose tissue or muscle; and an endogenous pathway, which involves VLDL lipoproteins. In the endogenous pathway, the liver synthesizes VLDL lipoproteins by packaging cholesterol and TAG together with apoproteins and phospholipids that transport the lipids to muscle or adipose tissue. In these tissues, VLDLs yield their components and are transformed into LDL, the main endogenous cholesterol transporter. Most LDL-c is taken up by the liver, the rest by extrahepatic tissues. Atheromatous injury occurs when macrophages, endothelial cells or smooth muscle cells recognize oxidized LDL or when they lost the *scavenger* receptor regulatory mechanism and become loaded with LDL indefinitely.

There is also another pathway in lipoprotein metabolism: the reverse cholesterol transport, mediated by HDL. This pathway consists of cholesterol uptake from peripheral tissues and transport to the liver and its importance lies in the prevention of atheromatous lesions. The transfer of cholesterol from HDL to the liver is facilitated by two pathways: one direct by the SR-BI receptor and the other indirect by the transfer of cholesterol esters by cholesterol ester transfer protein (CETP).

Under certain conditions such as when there is insulin resistance, the relevance of the relationship between TAG and HDL-c is clearer.

Insulin resistance is associated with the overproduction of triglyceride-rich lipoproteins TRL (chylomicrons and VLDL). Increased TRL concentration in the circulation enhances lipid and apolipoprotein exchange with HDL, resulting in TAG enrichment and subsequent accelerated catabolism of HDL particles, characteristic of atherogenic dyslipidemia.

In atherogenic dyslipidemia there is also an increase in the activity of CETP (cholesteryl ester transfer protein). CETP modulates the transport of cholesterol from anti-atherogenic HDL lipoproteins to atherogenic lipoproteins rich in TAG. CETP dysfunction, or over function, converts HDL into small particles with low cholesterol content, which justifies low HDL cholesterol concentrations[22]. In a similar way, LDL particles also become smaller and denser worsening the evolution of the atheromatous lesion.

As discussed in the results section, the decrease in HDL-c and the increase in TAG are related to sex and age. In men, the decrease in HDL-c is constant throughout life and is statistically significant when related to the increase in TAG.

In women, on the other hand, the decrease in HDL-c in relation to the increase in TAG is not statistically significant during the first 4 decades of life. It seems that it is at the time of menopause that this inversely proportional relationship is significant and that it worsens as the years go by.

Focusing on age-related changes, as adults grow older, they experience significant changes in body composition, particularly from the third decade of life onwards. The changes include a sustained decrease in muscle mass and an increase in visceral adipose tissue, a tissue that produces inflammatory mediators and thus participates in the development of insulin resistance. These two changes are related to the decrease in physical activity and the maintenance of the same caloric intake even though the caloric requirement decreases progressively with age[23], activating the mechanisms of lipid metabolism dysregulation cited above.

It therefore seems important to consider what can happen in this period called menopause and what can alter the lipid profile of women in this way. It is known that after menopause, estradiol concentrations decrease significantly and this decrease is associated

with clinical manifestations such as vasomotor symptoms, osteopenia and osteoporosis, cancer, cardiovascular disease... Estrogens, especially estradiol, play a cardiovascular protective role, since it is produced from LDL-c, but when it is no longer produced, LDL-c levels in the blood increase and with them the cardiovascular risk increases[24]. Regarding HDL-c, although there are studies that report an increase in the levels, it has been shown that the transition to menopause is associated with a decrease in HDL-c and an increase in LDL-c and TAG[25]. Recent studies suggest that changes in the proportion of HDL subclasses are more associated with menopausal status than changes in total HDL-c[26]. This last statement should certainly be studied in future studies.

Conclusions

The current therapeutic intervention strategy for dyslipidemias is based on the basis of total cardiovascular risk and LDL-cholesterol concentration. The drug of choice for the treatment of dyslipidemias are statins, although there are other drugs for when the LDL-cholesterol control target is not achieved.

Specific HDL-c and TAG targets have not yet been defined. In addition, pharmacological therapeutic options to raise HDL-c levels are not as effective as LDL-c lowering ones. But lifestyle does have a major influence on hypertriglyceridemia and HDL-c levels. Modifying habits such as following a balanced diet, increasing physical activity, or quitting smoking is especially effective in patients with DM2 or metabolic syndrome[27].

But these recommendations and guidelines are based on analytical values, among other factors, that do not distinguish by sex. With the results obtained in this study, the clinical relevance and ultimate implications of making therapeutic plans based on statistically significant differences according to age or sex should be considered. For example, different treatments could be considered depending on whether the woman is premenopausal or postmenopausal, thus individualizing the therapeutic strategy in the hope of better control of cardiovascular risk factors.

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