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Comparing treatment targets in familial combined hyperlipidemia

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ABSTRACT

Introduction: Low-density lipoprotein cholesterol remains the principle goal of lipid-lowering therapy. Estimating low-density lipoprotein cholesterol using the Friedewald equation is unreliable when triglycerides are > 400 mg/dl. Furthermore, there is often a mismatch between the concentration of low-density lipoprotein cholesterol and the number of atherogenic particles. Consequently, non-high-density lipoprotein cholesterol (concentration of cholesterol in atherogenic particles) and apolipoprotein B (number of atherogenic particles) are considered alternative targets. This study evaluated the correlation and concordance of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B in persons with familial combined hyperlipidemia. **Methods:** A cross-sectional study including 410 familial combined hyperlipidemia subjects. A complete lipid profile was obtained for each participant: total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, apolipoprotein B,

RESUMEN

Introducción: El colesterol de las lipoproteínas de baja densidad sigue siendo el objetivo principal de la terapia hipolipemiante. La estimación de su concentración mediante la fórmula de Friedewald no es fiable cuando los triglicéridos son > 400 mg/dl. Además, a menudo hay una falta de coincidencia entre la concentración del colesterol LDL y el número de partículas aterogénicas. En consecuencia, el colesterol de no HDL (que traduce el colesterol en las partículas aterogénicas) y de la apolipoproteína B (número de partículas aterogénicas) se consideran objetivos alternativos. El estudio evaluó la correlación y concordancia del colesterol LDL con el colesterol no HDL y la apolipoproteína B en personas con hiperlipidemia familiar combinada. **Métodos:** Estudio transversal que incluyó a 410 sujetos con hiperlipidemia familiar combinada. Un perfil lipídico completo se obtuvo para cada participante: incluye colesterol, triglicéridos, colesterol HDL y la apolipoproteína B. La concordancia (kappa) y correlación (rho) entre el colesterol LDL, colesterol

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and non-high-density lipoprotein cholesterol. The concordance (kappa) and correlation (rho) between low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B was calculated. **Results:** The correlation coefficients for low-density lipoprotein cholesterol with non-high-density lipoprotein cholesterol and apolipoprotein B were low (0.41 and 0.50, respectively; p = 0.000). With low-density lipoprotein cholesterol < 100 mg/dl, 61.7 and 73.9% exceeded the non-high-density lipoprotein cholesterol and apolipoprotein B goals, respectively. The concordance (kappa) between low-density lipoprotein cholesterol target and non-high-density lipoprotein cholesterol and apolipoprotein B targets was 0.253 and 0.165, respectively (p = 0.000). In subjects with triglycerides < 400 mg/dl, non-high-density lipoprotein cholesterol < 130 mg/dl showed a stronger agreement with low-density lipoprotein cholesterol < 100 mg/dl than apolipoprotein B < 90 mg/dl (k = 0.40 vs. k = 0.26). In the first triglyceride tertile (triglycerides < 192 mg/dl), the concordance between low-density lipoprotein cholesterol < 100 mg/dl and non-high-density lipoprotein cholesterol < 130 mg/dl was 0.94, and with apolipoprotein B < 90 mg/dl it was 0.51 (p = 0.000). **Conclusions:** In familial combined hyperlipidemia, the concordance among lipid targets is low. In these subjects a more informative lipid assessment that includes low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B, is needed. (REV MEX ENDOCRINOL METAB NUTR. 2015;2:138-49)

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Key words: Lipids. FCHL. Treatment targets.

no HDL y la apolipoproteína B fueron estimadas. **Resultados:** Los coeficientes de correlación entre el colesterol LDL con el colesterol no HDL y la apolipoproteína B de las lipoproteínas y apolipoproteína B fueron bajos (0.41 y 0.50, respectivamente; p = 0,000). En casos con colesterol LDL < 100 mg/dl, el 61.7 y 73.9% superaron los objetivos terapéuticos correspondientes del colesterol no HDL y de la apolipoproteína B, respectivamente. La concordancia (kappa) entre las metas del colesterol LDL y colesterol no HDL o la apolipoproteína B fue 0.253 y 0.165, respectivamente (p = 0,000). En sujetos con triglicéridos < 400 mg/dl, el colesterol no HDL < 130 mg/dl mostró una concordancia sólida con el colesterol LDL < 100 mg/dl de apolipoproteína B < 90 mg/dl (k = 0,40 vs. k = 0,26). En el primer tercil de triglicéridos (triglicéridos < 192 mg/dl), la concordancia entre un valor de colesterol LDL < 100 mg/dl y el colesterol no HDL < 130 mg/dl fue 0.94, y con la apolipoproteína B < 90 mg/dl fue de 0.51 (p = 0,000). **Conclusiones:** En la hiperlipidemia familiar combinada, la concordancia entre los objetivos de lípidos es baja. En estos casos se requieren nuevas herramientas para medir el riesgo aterogénico del padecimiento.

Palabras clave: Lípidos. FCHL. Objetivos terapéuticos.

INTRODUCTION

Low-density lipoprotein cholesterol (LDL-C) remains the principle goal of therapy in the management of dyslipidemia[1-4]. However, many people who achieve LDL-C goals still develop atherosclerotic disease[5]. This is called "residual risk". As a result, some authors suggest that focusing exclusively on LDL-C levels is not ideal for the optimal management of dyslipidemia.

In certain patients there is a mismatch between the concentration of LDL-C and the number of atherogenic particles; this is expressed as the number of lipoproteins containing apolipoprotein B (Apo-B)[5]. The LDL particles are heterogeneous with respect to the amount of cholesterol they carry. One person may have large LDLs, rich in cholesterol, while a second person can have small LDLs, which contain only a small amount of cholesterol. Therefore, at the same concentration of LDL-C, the second person will have a greater number of atherogenic particles (LDLs), and consequently increased cardiovascular risk[6]. As a result of this discrepancy, several expert panels suggest the use of other parameters to improve the evaluation of cardiovascular risk and thus determine the intensity of therapy. Furthermore, in many centers, the concentration of LDL is not measured directly, but calculated using the Friedewald formula. This estimate is unreliable in those patients with triglycerides > 350 mg/dl. Therefore, two other parameters, presented as supplementary treatment targets, include the concentration of Apo-B and the

calculation of non-high density lipoprotein- cholesterol (non-HDL-C). Both are useful but are not equivalent.

The LDL-C is the mass of cholesterol within LDL particles. The Apo-B concentration represents the total number of circulating atherogenic particles, 90% of which are usually LDL particles[7]. Each particle of very low-density lipoprotein (VLDL), LDL, intermediate-density lipoprotein (IDL) and lipoprotein (a) contains an ApoB100 molecule and each chylomicron or chylomicron remnant contains an ApoB48 molecule. The measurement of this parameter is standardized among laboratories and does not require fasting; yet it does represent an additional cost to the patient. Non-HDL-C is calculated by subtracting the concentration of HDL-C from total cholesterol; it represents the cholesterol concentration of all the atherogenic lipoproteins (the mass of cholesterol within all the Apo-B particles). It is considered a good therapeutic goal because its value does not change, regardless of lipid exchange between VLDL-C and LDL. In summary, non-HDL-C represents the cholesterol content of atherogenic lipoproteins (VLDL, IDL, and LDL), whereas Apo-B measures the total number of atherogenic particles.

In the pathogenesis of atherosclerosis, lipoproteins containing Apo-B play an important role. They enter in the sub-endothelial space where they undergo oxidation, which results in the production of ligands for macrophages. There is, therefore, an accumulation of cholesterol within macrophages, the formation of foam cells, and finally an atherosclerotic plaque[8].

Multiple epidemiological studies show the superiority of Apo-B and non-HDL-C for the prediction of cardiovascular risk compared with LDL-C. The AMORIS study showed that Apo-B was a better predictor of risk than LDL-C[9]. The INTERHEART study found that Apo-B had a higher odds ratio compared with any other cardiovascular risk parameter and it was superior to non-HDL-C in all ethnic groups[10]. In the Women's Heart Study, cardiovascular events where equally related with Apo-B and non-HDL-C; both were superior to other lipid parameters[11]. The Emerging Risk Factor Collaboration published two analyses on this subject[12,13]. In the first publication there were no significant differences in the prevention of cardiovascular risk between LDL-C, non-HDL-C, and Apo-B[12]. In the second publication, the investigators concluded that the prediction of cardiovascular risk improved with the addition of Apo-B, lipoprotein A-1, lipoprotein (a), or lipoprotein-related phospholipase A2 to the traditional lipid parameters (total cholesterol and HDL-C)[13]. Finally, Sniderman, et al. conducted a meta-analysis to investigate whether Apo-B or non-HDL-C increased the predictive power of LDL-C. They reported that during a 10-year period, a strategy focused on controlling non-HDL-C could prevent 300,000 more cardiovascular events than one directed at LDL-C; and a strategy focused on controlling Apo-B could prevent 500,000 more cardiovascular events than one directed at LDL-C[14].

The assessment of Apo-B and non-HDL-C may be more relevant in persons with dyslipidemias characterized by triglyceride-rich lipoproteins (VLDL and IDL), low levels of HDL-C, and increased levels of small dense LDL-C particles. In these cases, the total number of LDL-C particles may be higher than the calculated LDL-C level. Reaching the LDL-C goal alone in this situation may not be enough. Diseases with these characteristics include: type 2 diabetes, the metabolic syndrome, and some primary dyslipidemias (familial combined hypercholesterolemia, hypoalphalipoproteinemia, and familial dysbetalipoproteinemia).

Familial combined hyperlipidemia (FCHL) is the most common primary dyslipidemia in Mexico. It is characterized by hypercholesterolemia and/or hypertriglyceridemia, elevated Apo-B and small dense LDL-C particles. It is associated with other metabolic abnormalities including obesity, insulin resistance, diabetes, and the metabolic syndrome. The FCHL shows a prevalence of 14% in premature coronary heart disease[15,16]. The diagnostic criteria for this disease remain controversial. A recent consensus suggests that the diagnosis is established in the presence of triglyceride levels > 130 mg/dl and high levels of Apo-B (> 120 mg/dl)[17]. However the original diagnostic criteria (hypercholesterolemia or hypertriglyceridemia in the proband, and the demonstration of hypercholesterolemia,

hypertriglyceridemia, and mixed hyperlipidemia in three different members of a family) and Apo-B levels above the 90th demographic percentile (> 108 mg/dl in men and > 99 mg/dl in women) appears to be more closely related to the atherogenic risk of this disease[15].

As mentioned before, non-HDL-C and Apo-B are not equivalent. When the content of cholesterol in the LDL-C particles is normal, both parameters are consistent. This means that they are equal for reporting cardiovascular risk. However, when the cholesterol content in the LDL-C particles is higher or lower than normal, the two parameters are discordant and predict differing risks. The objective of this study is to evaluate the correlation and the concordance of LDL-C, non-HDL-C, and Apo-B in patients with FCHL. The information generated will help evaluate the usefulness of these parameters as additional treatment targets in the follow-up of these high-risk patients. This is the first study in Mexico to assess whether the three parameters are equivalent in patients with FCHL.

METHODS

Study population

The study was approved by the institutional review board of the Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubiran (INCMNSZ).

The study population consisted of persons with a previous diagnosis of FCHL attending their routine lipid clinic visit in the INCMNSZ. At enrollment, informed consent was obtained, and all participants completed a questionnaire that included demographic data, medical history, and lifestyle factors. All patients arrived with the results of a lipid profile taken a week before their clinic visit. The diagnostic criteria considered for FCHL were the presence of hypercholesterolemia (total cholesterol > 200 mg/dl) or hypertriglyceridemia (triglycerides > 150 mg/dl), the demonstration of hypercholesterolemia, hypertriglyceridemia, and mixed hyperlipidemia in three different first-degree relatives, and Apo-B levels above the 90th percentile for the Mexican population (> 108 mg/dl for men and > 99 mg/dl for women). Anthropometric measurements were also registered (weight, height, blood pressure). The complete lipid profile was registered; this included total cholesterol, triglycerides, HDL-C, LDL-C, and Apo-B levels. Any medication that the patient was taking was also recorded. Exclusion criteria included history of an acute illness within the previous six weeks, pregnancy, and the presence of any disease or medication known to significantly influence lipid parameters. The concordance and correlation between the following therapeutic targets was analyzed: LDL-C, non-HDL-C, and Apo-B.

Laboratory measurements

The lipid parameters were measured in the Institute's central lab. For total cholesterol, HDL-C, triglycerides, and glucose measurements, commercial enzymatic methods were used (Beckman Coulter). The LDL determination was calculated with the Friedewald formula. Apolipoprotein B concentration was measured using nephelometry methods (Beckman Coulter). Insulin was measured using an enzymatic immunoassay (Abbot).

Statistical analysis

The data is presented as median with interquartile range due to the non-parametric distribution of lipid profiles. Proportions and medians are compared between groups using the chi-square test and Mann Whitney-U tests. Spearman correlations are shown to assess the degree of linear association between LDL-C and Apo-B and non-HDL-C, respectively. The concordance correlation coefficient between LDL-C, non-HDL-C, and Apo-B was assessed by the kappa value in the total population and in subpopulations. In addition, triglyceride tertiles were generated and the kappa value for comparisons between lipid targets was calculated. The p value was considered significant when $p < 0.05$. All analyses were performed using SPSS v. 15.0 IL.

Table 1. Biochemical characteristics of participants

Variable	FCHL total (n = 410)	Men (n = 183)	Women (n = 227)	Mann-Whitney U test, p
Triglycerides (mg/dl)	235.5 (160.75-381.0)	278 (188-424)	221 (149-328)	p = 0.000
Total cholesterol (mg/dl)	196 (168.75-222.0)	201 (172-225)	196 (167-219)	p = 0.159
HDL-C (mg/dl)	40 (36-48)	37 (33-43)	43 (38-52)	p = 0.000
LDL-C (mg/dl)	93.7 (76.6-111.8)	94 (76.4-107.4)	93.2 (76.8-113.2)	p = 0.538
Non-HDL-C	153 (125-182)	161 (130-188)	147 (121-173)	p = 0.004
Glucose (mg/dl)	96 (88-107)	97 (88.75-107.25)	96 (87-107)	p = 0.579
Insulin (U/l)	12.8 (8.95-24.65)	11.7 (8.4-17.97)	14.3 (10.01-31.75)	p = 0.005
Apo-B	111 (94.87-125.0)	115 (98-131)	109 (92.3-120.0)	p = 0.004

FCHL: familial combined hyperlipidemia; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Apo-B: apolipoprotein B.

RESULTS

The study population included 410 persons with FCHL (191 men and 231 women). The median age of participants was 49.5 years, and anthropometric measurements were; median weight 70.5 kg (men 77.2 kg and women 66.0 kg), median body mass index (BMI) 27.2 (men 27.4 and women 26.9), median waist circumference 93.2 cm (men 96 cm and women 91 cm; p = 0.000). All patients received the indication to follow a dietary plan and a statin. The statin dose was adjusted to achieve the LDL-C treatment goal (< 100 mg/dl for primary prevention or < 70 mg/dl for secondary prevention). Table 1 shows the laboratory characteristics of all participants (n = 410).

The median serum concentrations of lipid levels were as follows: total cholesterol 196 mg/dl, triglycerides 235.5 mg/dl, HDL-C 40 mg/dl, LDL-C 93.7 mg/dl, Apo-B 111 mg/dl, non-HDL-C 153 mg/dl. Only 72.0% of the group (295 persons) had an LDL-C < 100 mg/dl. It was evident that triglycerides, non-HDL-C, and Apo-B were not at recommended target levels: median levels of non HDL-C and Apo-B are > 90 and > 130 mg/dl, respectively. Only 113 persons (27.6%) had non-HDL-C < 130 mg/dl. Only 78 persons (19.0%) had an Apo-B level < 90 mg/dl.

If we analyze the results of those subjects with LDL-C < 100 mg/dl (n = 295), the corresponding non-HDL-C and Apo-B were 143 and 105 mg/dl, respectively; these are clearly above target concentrations. These results are shown in table 2 (n = 295). Only 113 (38.3%) had non-HDL-C < 130 mg/dl. Only 77 (26.1%) persons had an Apo-B level < 90 mg/dl.

Finally, we present the characteristics of the subpopulation with triglycerides < 400 mg/dl (n = 326). The median levels of LDL-C, non-HDL-C, and Apo-B were 95.6, 143, and 107 mg/dl, respectively (Table 3). Again, both non-HDL-C and Apo-B were above recommended levels. Only 115 (38.3%) had a non-HDL-C level < 130 mg/dl. Only 76 (23.2%) had an Apo-B concentration < 90 mg/dl.

CORRELATIONS

The Spearman correlation coefficients comparing LDL-C with non-HDL-C and Apo-B were 0.412 and 0.502, respectively (p = 0.000). The correlation

Table 2. Lipid profile of familial combined hyperlipidemia individuals with low-density lipoprotein cholesterol < 100 mg/dl

Variable	FCHL Total (n = 295)	Men (n = 134)	Women (n = 161)	Mann-Whitney U test, p
Triglycerides (mg/dl)	272 (164-408)	330 (193.0-491.25)	241 (152.0-366.5)	p = 0.001
Total cholesterol (mg/dl)	183 (161-207)	186.5 (162.75-219.25)	180 (160-199)	p = 0.041
HDL-C (mg/dl)	38 (34-46)	36.5 (32.0-41.25)	41 (36-48)	p = 0.000
LDL-C (mg/dl)	86.6 (69.0-95.4)	87.6 (68.15-95.4)	86.2 (70.5-95.6)	p = 0.871
Non-HDL-C	142 (115-170)	149.5 (118.0-187.25)	137 (113-158)	p = 0.001
Glucose (mg/dl)	96 (87-108)	98 (87-108)	95 (87.0-106.5)	p = 0.472
Insulin (U/l)	12.4 (8.7-17.95)	11.6 (8.3-16.85)	13.5 (9.25-20.75)	p = 0.061
Apo-B	105 (89.4-118.0)	109 (91.75-124.0)	100 (87-114)	p = 0.002

FCHL: familial combined hyperlipidemia; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Apo-B: apolipoprotein B.

between non-HDL-C and Apo-B was strong (rho = 0.82; p < 0.001).

For the subjects with LDL-C < 100 mg/dl, these figures did not improve; rho = 0.169 (p = 0.004) for non-HDL-C and rho = 0.250 (p < 0.001) for Apo-B. The correlation coefficient for non-HDL-C and Apo-B was 0.80 (p < 0.001).

For the subpopulation with triglycerides < 400 mg/dl, the correlations with LDL-C improved significantly: rho = 0.80 (p = 0.000) for non-HDL-C and rho = 0.72

Table 3. Characteristics of the population with triglycerides < 400 mg/dl

Variable	Total (n = 326)	Men (n = 130)	Women (n = 196)	Mann-Whitney U test, p
Triglycerides mg/dl	206.5 (144.0-278.25)	216 (152.75-310.0)	201.5 (139.0-268.25)	p = 0.08
Total cholesterol (mg/dl)	187 (163-208)	186 (161.75-207.25)	196 (163.0-210.75)	p = 0.389
HDL-C (mg/dl)	42 (37.0-50.25)	40 (35.0-45.25)	45 (39-53)	p = 0.00
LDL-C (mg/dl)	95.6 (82.35-119.8)	95.3 (83.9-119.8)	95.7 (80.85-119.3)	p = 0.69
Non-HDL-C	143.5 (118-166)	146 (118.0-165.25)	143 (116.25-166.0)	p = 0.58
Glucose (mg/dl)	96 (88-106)	97.5 (89.5-107.0)	96 (87-106)	p = 0.29
Insulin (U/l)	12.6 (8.8-25.0)	11.6 (8.4-17.97)	13.9 (10.0-31.7)	p = 0.029
Apo-B (mg/dl)	107.5 (91-120)	108 (91-123)	106 (89.97-119.0)	p = 0.616

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Apo-B: apolipoprotein B.

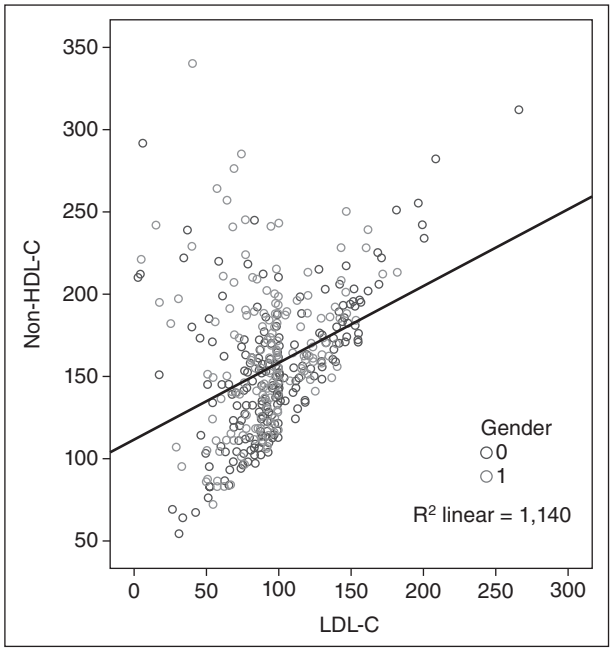

Figure 1. Low-density lipoprotein cholesterol (calculated with Friedewald formula, x-axis) plotted against non-high-density lipoprotein cholesterol (y-axis) in patients with familial combined hyperlipidemia (0 = women, 1 = men). LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

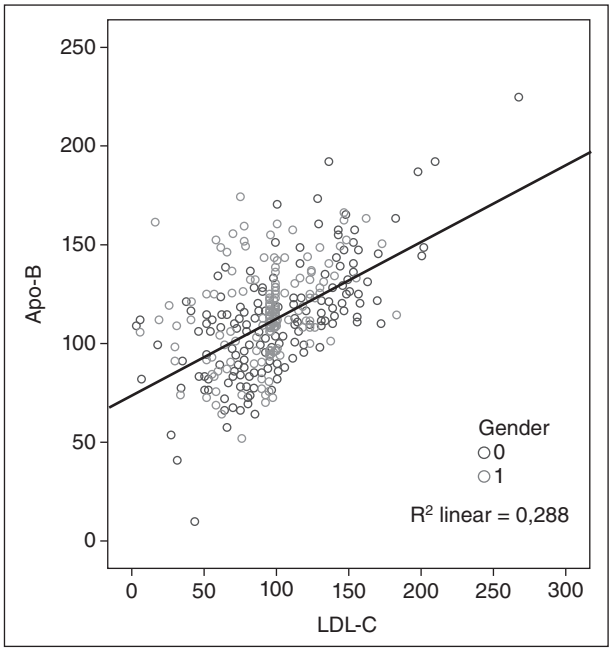

Figure 2. Low-density lipoprotein cholesterol (calculated with Friedewald formula, x-axis) plotted against apolipoprotein B (y-axis) in patients with familial combined hyperlipidemia (0 = women, 1 = men). Apo-B: apolipoprotein B; LDL-C: low-density lipoprotein cholesterol.

(p = 0.000) for Apo-B. The correlation coefficient for non-HDL-C and Apo-B was 0.85 (p < 0.001). The dispersion graphs (total population), showing the distribution of LDL-C with non-HDL-C, LDL-C with Apo-B, and non-HDL-C with Apo-B are shown in figures 1, 2, and 3.

The dispersion graphs for the subpopulation of subjects with triglycerides < 400 mg/dl showing the distribution of LDL-C with non-HDL-C, LDL-C with Apo-B, and non-HDL-C with Apo-B are shown in figures 4, 5, and 6.

When triglycerides are > 400, the calculation of LDL is unreliable. Based on that, we use non-HDL-C in place of LDL-C in this situation. Figure 7 shows non-HDL-C plotted against Apo-B in this subpopulation. The correlation is very low.

CONCORDANCE

The distribution of Apo-B < 90 and Apo-B ≥ 90 and the corresponding non-HDL-C < 130 and ≥ 130, and the concordance (kappa) of each with LDL < 100 mg/dl is shown in table 4. Of those with LDL < 100 mg/dl, 61.7 and 73.9% exceeded the non-HDL-C and Apo-B goals, respectively. The concordance (kappa) was poor between LDL-C target and non-HDL-C and Apo-B targets: 0.253 and 0.165, respectively (p = 0.000). However, the agreement between non-HDL-C and Apo-B targets was stronger (k = 0.64; p = 0.000).

We calculated concordance using the stricter LDL-C target of < 70 mg/dl, compared to non-HDL-C < 100 mg/dl and Apo-B < 80 mg/dl. The results are shown in table 5. The concordance (kappa) was poor between LDL-C target and non-HDL-C and Apo-B targets: 0.295 and 0.194, respectively (p = 0.000).

Next, we analyzed the subgroup of individuals with triglycerides < 400 mg/dl; here the concordance between LDL-C and the other parameters improved (Table 6). The kappa values were 0.40 and 0.26 for non-HDL-C and Apo-B, respectively (p = 0.000). However, the agreement between non-HDL-C and Apo-B targets was stronger (k = 0.62; p = 0.000).

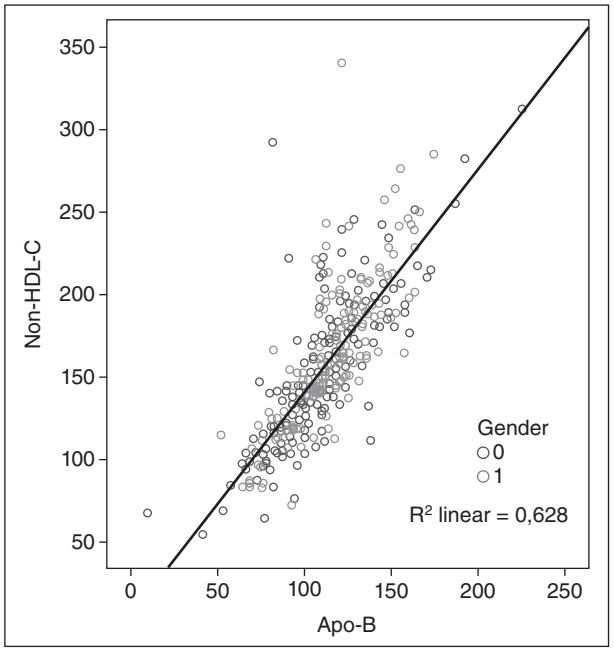

Figure 3. Non-high-density lipoprotein cholesterol (y-axis) plotted against apolipoprotein B (x-axis) in patients with familial combined hyperlipidemia (0 = women, 1 = men). HDL-C: high-density lipoprotein cholesterol; Apo-B: apolipoprotein B.

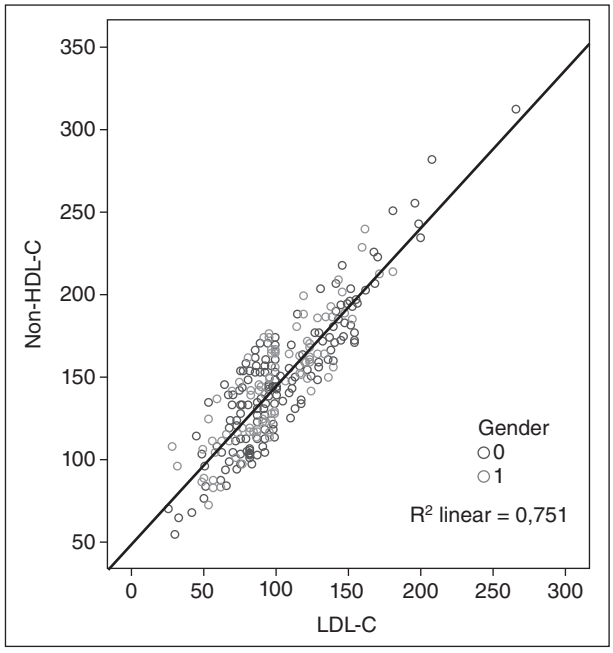

Figure 4. Low-density lipoprotein cholesterol (calculated with Friedewald formula, x-axis) plotted against non-high-density lipoprotein cholesterol (y-axis) among familial combined hyperlipidemia patients with triglycerides < 400 mg/dl (0 = women, 1 = men). LDL-C: low-density lipoprotein cholesterol: HDL-C: high-density lipoprotein cholesterol.

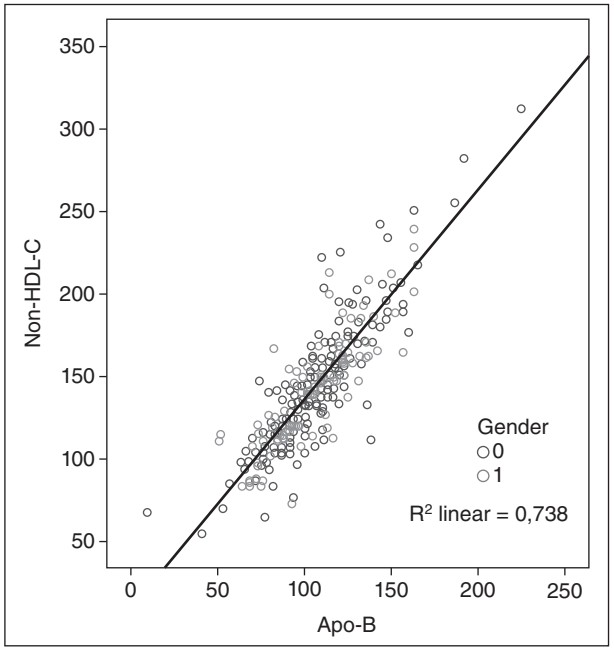

Figure 5. Non-high-density lipoprotein cholesterol (y-axis) plotted against apolipoprotein B (x-axis) among familial combined hyperlipidemia patients with triglycerides < 400 mg/dl (0 = women, 1 = men). HDL-C: high-density lipoprotein cholesterol; Apo-B: apolipoprotein B.

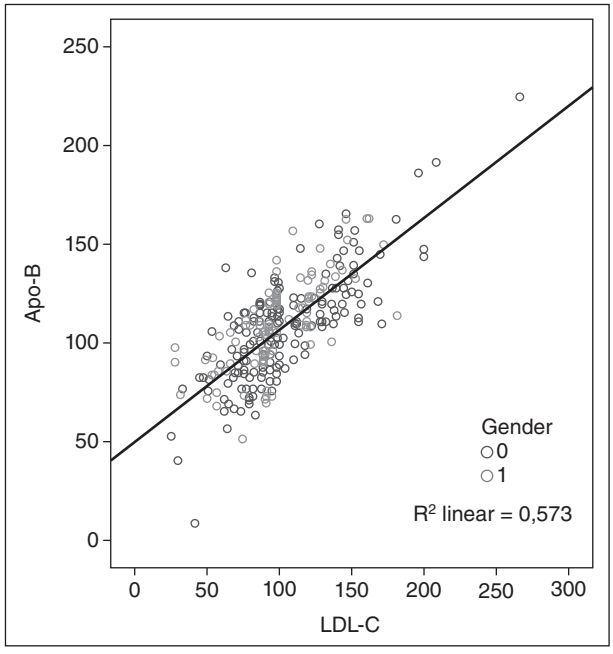

Figure 6. Low-density lipoprotein cholesterol (calculated with Friedewald formula, x-axis) plotted against apolipoprotein B (y-axis) among familial combined hyperlipidemia patients with triglycerides < 400 mg/dl (0 = women, 1 = men). Apo-B: apolipoprotein B; LDL-C: low-density lipoprotein cholesterol.

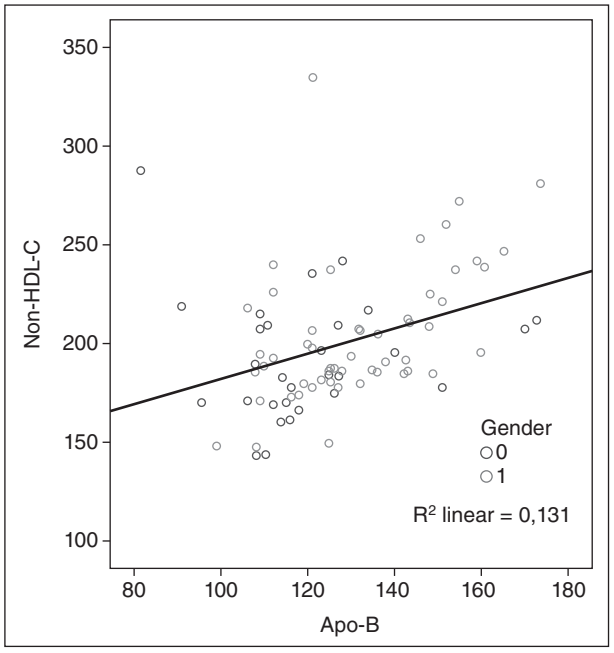

Figure 7. Non-high-density lipoprotein cholesterol (y-axis) plotted against apolipoprotein B (x-axis) among familial combined hyperlipidemia patients with triglycerides > 400 mg/dl (0 = women, 1 = men). HDL-C: high-density lipoprotein cholesterol; Apo-B: apolipoprotein B.

Finally, the total population (n = 422) was divided into three groups, as determined by tertiles of triglycerides (Table 7). The concordance values between LDL-C and non-HDL-C and Apo-B were highest when the triglycerides were < 191 mg/dl. In addition, the concordance between LDL-C and non-HDL-C was substantial in this tertile (kappa = 0.94). The corresponding agreement between LDL-C and Apo-B was moderate (kappa = 0.51). The agreement between non-HDL-C and Apo-B was maintained in all three tertiles.

DISCUSSION

In this study, we evaluated the agreement between treatment targets (LDL-C, non-HDL-C, Apo-B) in subjects with FCHL. When the mass of cholesterol per Apo-B particle is normal, all three markers are concordant. We included 410 FCHL subjects, 308 of which had achieved an LDL-C goal of < 100 mg/dl. The prevalent lipid profile in this population was isolated hypertriglyceridemia (n = 104) or mixed hyperlipidemia (n = 303).

In subjects with elevated triglycerides, the calculation of LDL-C using the Friedewald equation is unreliable. In this group, the ATP III guidelines recommend the use of non-HDL-C as a secondary treatment goal once the LDL-C target is reached. The current ATP IV guidelines do not address this issue[18].

In our study, the calculated correlation coefficients for LDL-C with non-HDL-C and for LDL-C with Apo-B were both low. The correlation between non-HDL-C and Apo-B was moderate. All correlations improved significantly when the population with triglycerides < 400 mg/dl was analyzed. The dispersion graphs show this result clearly. This finding is not unexpected and highlights the problems associated with utilizing a calculated LDL-C in the setting of hypertriglyceridemia.

Table 4. Distribution of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B according to recommended targets in persons with familial combined hyperlipidemia

	n = 410	LDL-C < 100 mg/dl (%)	LDL-C ≥ 100 mg/dl (%)	Discordance
Non-HDL-C < 130	114	113 (99.12)	1 (0.01)	+0.01%
Non-HDL-C ≥ 130	296	182 (61.49)	113 (38.18)	–61.5%
Kappa = 0.253; p = 0.000				
Apo-B < 90	77	77 (100)	0 (0)	0
Apo-B ≥ 90	333	218 (65.47)	115 (34.53)	–65.5%
Kappa = 0.165; p = 0.000				

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Apo-B: apolipoprotein B.

Table 5. Distribution of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B according to stricter targets in persons with familial combined hyperlipidemia

		LDL-C < 70 mg/dl (%)	LDL-C ≥ 70 mg/dl (%)	Discordance
Non-HDL-C < 100	26	19 (24.05)	7 (2.11)	+2.11%
Non-HDL-C ≥ 100	384	60 (15.62)	324 (84.38)	–15.6%
		Kappa = 0.295; p = 0.000		
Apo-B < 80	37	17 (45.95)	20 (54.05)	+54.1%
Apo-B ≥ 80	373	62 (16.62)	311 (83.38)	–16.6%
		Kappa = 0.194; p = 0.000		

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Apo-B: apolipoprotein B.

Table 6. Distribution of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B according to recommended targets in persons with familial combined hyperlipidemia with triglycerides < 400 mg/dl

	n = 326	LDL-C < 100 mg/dl (%)	LDL-C ≥ 100 mg/dl (%)	Discordance
Non-HDL-C < 130	114	113 (99.1)	1 (0.9)	+0.9%
Non-HDL-C ≥ 130	212	107 (50.47)	105 (49.52)	–50.5%
		Kappa = 0.400; p = 0.000		
Apo-B < 90	76	76 (100)	0 (0)	0
Apo-B ≥ 90	250	144 (57.60)	106 (42.40)	–57.6%
		Kappa = 0.256; p = 0.000		

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Apo-B: apolipoprotein B.

Table 7. Concordance between low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B. Total population divided into tertiles of triglycerides (n = 422)

Tertiles of triglycerides	Tertile 1 (Tg ≤ 191 mg/dl) n = 137	Tertile 2 (Tg 192-327 mg/dl) n = 136	Tertile 3 (Tg ≥ 328 mg/dl) n = 137	Total population n = 410
LDL-C with Apo-B	51/137 K = 0.51 p = 0.000	24/136 K = 0.18 p = 0.000	4/137 K = 0.01 p = 0.415	77/410 K = 0.15 p = 0.000
LDL-C with non-HDL-C	84/137 K = 0.94 p = 0.000	22/136 K = 0.16 p = 0.000	4/137 K = 0.01 p = 0.415	113/410 K = 0.24 p = 0.000
Non-HDL-C with Apo-B	51/137 K = 0.53 p = 000	16/136 K = 0.64 p = 0.000	2/137 K = 0.49 p = 0.000	69/410 K = 0.64 p = 0.000

TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Apo-B: apolipoprotein B; K: kappa.

In addition, the calculation of kappa, evaluating agreement between LDL < 100 mg/dl, non-HDL-C < 130 mg/dl, and Apo-B < 90 mg/dl was also low; this improved only moderately when the subpopulation with triglycerides < 400 mg/dl was analyzed. In this situation, non-HDL-C < 130 mg/dl showed a stronger agreement with LDL-C < 100 mg/dl than Apo-B < 90 mg/dl (kappa = 0.40 vs. 0.26). It is notable that the concordance between non-HDL-C and Apo-B was strong in all analyses, demonstrating that the agreement between these parameters is preserved in FCHL.

After dividing the population into tertiles of triglycerides, the concordance between treatment targets was lost once triglycerides were > 193 mg/dl. In the first tertile (triglycerides < 191 mg/dl), the concordance between LDL-C < 100 mg/dl and non-HDL-C < 130 mg/dl was extremely high (kappa = 0.94; p = 0.00). In the case of Apo-B < 90 mg/dl, the concordance with LDL < 100 mg/dl was only moderate for this subpopulation (kappa = 0.51; p = 0.000). Yet again, the degree of concordance between Apo-B < 90 mg/dl and non-HDL-C < 130, although moderate, was maintained throughout the triglyceride tertiles.

As mentioned previously, more than 70% of the study population had reached an LDL-C target of < 100 mg/dl. Cardiovascular risk may be underestimated when we only consider LDL-C. In subjects with FCHL, the residual cardiovascular risk may be indicated by the discordance of LDL-C with other treatment parameters, namely Apo-B and non-HDL-C. In fact, both non-HDL-C and Apo-B predict overall cardiovascular risk better than LDL-C[19].

Otvos, et al. reported that when there is discordance between the number of LDL particles (Apo-B) and the concentration of LDL-C; only the number of particles was significantly associated with the incidence of cardiovascular events and the thickness of the carotid intima-media[6]. They concluded that when such a discrepancy exists, the risk attributable to LDL is best established by the level of Apo-B (the number of particles). Patients with LDLs poor in cholesterol may have residual risk; despite reaching LDL-C targets, they continue to have high numbers of LDL particles.

Masana, et al. evaluated individuals who, having achieved LDL-C targets, continued to have uncontrolled non-HDL-C levels (discordance between the two parameters)[20]. They reported that 90% of the patients with hypertriglyceridemia > 400 mg/dl, showed LDL-C at target, but the non-HDL-C was > 130 mg/dl. Furthermore, two of every five patients with triglycerides a little higher than 150 mg/ml and normal LDL-C levels had elevated levels of non-HDL-C.

As yet, it is unknown whether non-HDL-C and Apo-B are equivalent markers of cardiovascular risk. Sniderman, et al. investigated this question in a case-control study (acute myocardial infarction versus no acute myocardial infarction) when both parameters were discordant. When Apo-B was higher than non-HDL-C (when the Apo-B particles are poor in cholesterol), the cardiovascular risk is increased. In contrast, when the non-HDL-C levels were higher than Apo-B (when the Apo-B particles are rich in cholesterol), the risk is lower than the reference concordant group. Therefore, these investigators concluded that when non-HDL-C and Apo-B are discordant, Apo-B was a more accurate marker of cardiovascular risk than non-HDL-C. This suggests that the atherogenic particle number is a more important determinant than the mass of cholesterol within the Apo-B particles[21].

Hence, when all three parameters are concordant, the clinical utility of these variables is similar. The moment they are discordant, cardiovascular risk can be under- or overestimated if only LDL-C is considered[22]. For this reason, the Quebec cardiovascular study decided in favor of Apo-B and non-HDL-C over LDL-C[23].

Although the current literature suggests a better performance of Apo-B compared to non-HDL-C, there are significant practical limitations for its use. These include arbitrary treatment thresholds, cost, time lag in results, and poor goal attainment on lipid-lowering therapies[24]. In comparison, non-HDL-C involves a quick calculation and requires minimal physician education for implementation. However, the recent ACCORD-lipid arm results and the AIM-HIGH study did not find any additional benefit in cardiovascular risk reduction of lowering triglycerides or raising HDL-C in patients who achieve LDL-C targets[25,26]. This evidence endorses the need for more intensive LDL-C lowering[27].

In FCHL, LDL-C does not provide an accurate reflection of cardiovascular risk due to the presence of hypertriglyceridemia. This study highlights the lack of concordance among the treatment targets. During the long-term management of these patients, both non HDL-C and Apo-B should be used for follow-up in order to better address residual cardiovascular risk (Apo-B allows to focus on LDL-particle number and not just cholesterol concentration); however, treatment should still be focused on intensive statin therapy.

This study has several limitations. The estimation of LDL-C utilizing the Friedewald equation is not ideal; directly measured LDL-C would have been better. This was a cross-sectional study; a prospective study with long-term follow-up to assess cardiovascular endpoints would aid in evaluating the relevance of the discordant targets. The strengths of this study include a study population with high cardiovascular risk, in which the concordance of LDL-C with Apo-B and non-HDL-C is being assessed for the first time.

In conclusion, in FCHL the concordance among lipid targets is low. These patients need a more informative lipid assessment, which includes not only LDL-C, but also non-HDL-C and Apo-B.

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