ORIGINAL ARTICLE

Lipid Goals in Diabetic Patients. Clinical Implications after Application of a New Formula for LDL-cholesterol Calculation

Metas lipídicas en pacientes diabéticos. Implicaciones clínicas luego de aplicar una nueva fórmula para el cálculo del COLESTEROL-LDL

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ABSTRACT

Background: There are clear recommendations for lipid management in diabetic patients. A new formula for the calculation of LDL-cholesterol (LDL-C) would improve the inaccuracy of the Friedewald formula.
Objectives: The aim of this study was to analyze the use of statins and the fulfillment of lipid goals in diabetic patients, evaluating the consequences of applying a new formula for LDL-C calculation.
Methods: This was a descriptive, cross-sectional, multicenter study including type 2 diabetic patients over 18 years of age. LDL-C was calculated using the classic Friedewald formula and the new formula. Recommendations of the position document for the appropriate use of statins from the Argentine Society of Cardiology were followed.
Results: A total of 528 patients were included in the study. In secondary prevention, 77.2% of patients received statins (23.4% high-intensity statins) and 36.6% and 36.0% of these patients achieved the goals of LDL-C below 70% mg/dl and non-HDL-C below 100 mg/dl, respectively. In 20.8% of patients with LDL-C below 70 mg/dl according to the Friedewald formula, this goal was not attained when the new formula was applied. In primary prevention, 62.2% patients with risk factors or white organ damage received statins (14.7% high-intensity statins) and 20.9% and 20.4% achieved the goals of LDL-C below 70% mg/dl and non-HDL-C below 100 mg/dl. In 27.7% of patients with LDL-C below 70 mg/dl using the Friedewald formula, this goal was not reached when applying the new formula. More patients did not achieve the LDL-C goal with the new formula when the triglyceride level was higher.
Conclusion: In this population, the appropriate use of statins and the fulfillment of lipid goals were poor. Applying the new LDL-C formula optimized the evaluation of these patients.

Keywords: Diabetes Mellitus, Type 2 - Hydroxymethylglutaryl-CoA Reductase Inhibitors - Goals Models, Theoretical-Cholesterol, LDL

RESUMEN

Introducción: Existen claras recomendaciones para el manejo lipídico en los diabéticos. Una nueva fórmula para el cálculo del C-LDL mejoraría la imprecisión de la fórmula de Friedewald.
Objetivos: Analizar el uso de estatinas y el cumplimiento de las metas lipídicas en pacientes diabéticos, evaluando las consecuencias de aplicar una nueva fórmula para el cálculo del C-LDL.
Métodos: Estudio descriptivo, transversal y multicéntrico. Se incluyeron diabéticos tipo 2 mayores de 18 años. El C-LDL se calculó con la fórmula clásica (Friedewald) y la nueva fórmula. Se siguieron las recomendaciones del documento de posición para el uso adecuado de estatinas (Sociedad Argentina de Cardiología).
Resultados: Se incluyeron 528 pacientes. En prevención secundaria, el 77,2% recibió estatinas (23,4% alta intensidad). El 36,6% y el 36,0% alcanzaron la meta de C-LDL menor a 70 mg/dL y de C-noHDL inferior a 100 mg/dL, respectivamente. El 20,8% de los pacientes con un C-LDL menor de 70 mg/dL (Friedewald) salió de meta al aplicar la nueva fórmula. En los pacientes en prevención primaria con factores de riesgo o daño de órgano blanco, el 62,2% recibió estatinas (14,7% alta intensidad). El 20,9% y el 20,4% alcanzaron la meta de menor a 70 mg/dL y de C-noHDL inferior a 100 mg/dL. El 27,7% de los pacientes con un C-LDL menor de 70 mg/dL (Friedewald) salió de meta al aplicar la nueva fórmula. A mayor nivel de triglicéridos, más pacientes salieron de meta de C-LDL con la nueva fórmula.
Conclusión: El cumplimiento de las metas lipídicas y el uso adecuado de estatinas en esta población fue deficiente. Aplicar la nueva fórmula de C-LDL optimizó la evaluación de estos pacientes.

Palabras clave: Diabetes Mellitus Tipo 2 - Inhibidores de Hidroximetilglutaril-CoA Reductasas - Metas -Modelos Teóricos-LDL,Colesterol

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INTRODUCTION

Presence of type 2 diabetes approximately doubles cardiovascular mortality compared with subjects without this disease. Evidence from randomized clinical trials has shown a significant reduction of cardiovascular events in diabetic patients receiving moderate-intensity statins. (2-4) A meta-analysis comparing high-intensity vs. moderate-intensity statins demonstrated an additional benefit in favor of more intense treatment in the population with or without diabetes. (5)

Consequently, current guidelines recommend that patients with diabetes should receive moderate or high-intensity statins, aiming at 50% or higher reduction in the LDL-cholesterol (LDL-C) level. (6-8) Choice of statin type and dose, or the therapeutic goal, change according to the risk of the diabetic patient, with a more aggressive strategy in subjects at higher risk.

In daily practice, LDL-C level is assessed using the Friedewald formula (9) which assumes a fixed relationship of 5:1 between triglycerides and cholesterol bound to very low-density lipoproteins (VLDL-C). In the context of hypertriglyceridemia or in case of very low LDL-C levels, the value of LDL-C calculated with this formula may be erroneous. (10, 11) A new formula recently validated by Martin et al. would allow a marked improvement of this inaccuracy, as it considers a variable correction factor that contemplates the triglyceride level. (12)

Although LDL-C is considered as a primary therapeutic goal, cholesterol not associated with HDL (non-HDL-C) is regarded as a relevant lipid goal in diabetic patients. (8, 13) This lipid marker is easy to obtain and estimates with greater accuracy all the atherogenic particles.

Thus, the aims of this study were: 1) to assess the percentage of patients with diabetes who meet LDL-C goals calculated with the Friedewald formula and non-HDL-C goals according to current recommendations; 2) to determine the percentage of patients that receive adequate doses of statins; and 3) to evaluate the consequences of applying the new formula to calculate LDL-C.

METHODS

This was a descriptive, cross-sectional, multicenter study of consecutive samples obtained in the outpatient cardiovascular prevention service of five cardiology centers of the Autonomous City of Buenos Aires and Greater Buenos Aires.

Patients over 18 years of age with type 2 diabetes were consecutively included in the study, with assessment of their clinical and laboratory variables (12-hour fasting lipid profile, including total cholesterol, HDL-C and triglycerides). LDL-C was calculated using the Friedewald formula (9) and the new formula postulated by Martin et al. (12)

The position document guidelines for the correct use of statins of the Argentine Society of Cardiology were followed to evaluate the fulfillment of lipid goals and analyze the correct indication of statins. (7) In this case, the following conduct was recommended: a) in diabetic patients with history of clinical cardiovascular disease (coronary heart disease, cerebrovascular disease or peripheral artery disease), high-intensity statin administration was recommended, seeking a goal of LDL-C below 70 mg/dl and non-HDL-C below 100 mg/dl; b) in diabetic patients with no prior history of cardiovascular disease, with one or more risk factors or target organ damage (microalbuminuria, neuropathy or retinopathy), high-intensity statin administration was recommended, seeking a goal of LDL-C below 70 mg/dl and non-HDL-C below 100 mg/dl; c) in diabetic patients with no prior history of cardiovascular disease and no other risk factor or target organ damage, moderate-intensity statin administration was recommended, seeking a goal of LDL-C below 100 mg/dl and non-HDL-C below 130 mg/dl.

Taking into account the statins available in our country, high-intensity statins (LDL-C reduction above 50%) were atorvastatin 40/80 mg/day and rosuvastatin 20/40 mg/day. Similarly, the following schemes were considered as moderate-intensity statins (LDL-C reduction between 30% and 50%): atorvastatin 10/20 mg/day, simvastatin 20/40 mg/day, fluvastatin 80 mg/day and rosuvastatin 5/10 mg/day. Lower doses were considered as low-intensity statins (LDL-C reduction below 30%).

Statistical analysis

Categorical data were analyzed using the chi-square test. Continuous variables were expressed as mean ± standard deviation, and categorical variables as absolute and relative frequency. Pearson's test was used to establish the correlation between the two equations to calculate LDL-C. The concordance between both formulas was analyzed to establish the proportion of subjects that met the LDL-C goal, using Fleiss's kappa index. Mild or poor, acceptable or discreet, moderate, substantial or very good concordance was defined depending on kappa below 0.20, between 0.21 and 0.40, 0.41 and 0.60, 0.61 and 0.80 and between 0.81 and 1, respectively. A two-tailed p value below 0.05 was considered as statistically significant. STATA 13 (Stata Corp, College Station, TX) software package was used for statistical analysis.

Ethical considerations

The study was performed following the recommendations in medical research of the Declaration of Helsinki, Good Clinical Practice Guidelines and legal regulations in force. The protocol was submitted to the Research Area of the Argentine Society of Cardiology.

RESULTS

A total of 528 patients with type 2 diabetes were included in the study. Mean age was 62.1±12.7 years, and 64% were men. In 37.7% of cases, the population was in secondary prevention (previous history of coronary heart disease, stroke or peripheral vascular disease). Mean values of total cholesterol, HDL-C and non-HDL-C were 171.8±43.4 mg/dl, 43.9±12.4 mg/dl and 127.9±41.7 mg/dl, respectively. Median triglyceride level was 139 mg/dl (interquartile range 100-189 mg/dl), and LDL-C calculated with the Friedewald formula and the new formula was 95.8±38.5 mg/dl and 101.3±36.2, respectively. Table 1 shows the population characteristics.

Statins were administered to 62.5% of patients, though only 17.1% received high-intensity statins.

This percentage was higher in secondary prevention subjects compared with diabetic patients without history of cardiovascular diseases (23.4% vs. 12.7%, p=0.04). Table 2 details the medication received by the study population.

The analysis of the group of patients with prior history of cardiovascular disease (n=197) showed that 77.2% received statins (23.4% high-intensity statins). Only 36.6% met the goal of LDL-C below 70% mg/dl (calculated with the Friedewald formula). Subjects receiving high-intensity statins were able to achieve the objective compared with those not receiving this treatment (52.2% vs. 31.8%, p=0.01). Among the patients who attained the objective LDL-C estimated with the Friedewald formula, 20.8% did not achieve it when the modified formula to calculate LDL-C was applied. The goal of non-HDL-C below 100 mg/dl was reached by 36% of the population.

In the group of patients without prior history of cardiovascular disease but with some additional risk factor or target organ damage (n=225), 62.2% received statins (14.7% high-intensity statins). Only 20.9% met the goal of LDL-C below 70% mg/dl (with the Friedewald formula). Subjects receiving high-intensity statins were able to achieve the objective more frequently than those not receiving this treatment (25.5% vs.11.8%, p=0.02). Among patients who attained the objective of LDL-C estimated with the Friedewald formula, 27.7% did not achieve it when the modified formula to calculate LDL-C was applied. The goal of non-HDL-C below 100 mg/dl was reached by 20.4% of the population.

Finally, the analysis of the group of patients without history of cardiovascular disease and no other associated risk factor or target organ damage (n=106) showed that 36.8% received statins (6.6% high-intensity and 28.3% moderate intensity statins). Only 30.2% attained the goal of LDL-C below 100 mg/dl (calculated with the Friedewald formula). Among patients who attained the objective LDL-C estimated with the Friedewald formula, 23.1% did not achieve it when the modified formula to calculate LDL-C was applied. The goal of non-HDL-C below 130 mg/dl was met by 32.6% of the population.

A graphical representation of the percentage of subjects who met the lipid goals and received high-

Table 1. Population characteristics (n=528).

Continuous variables*	
Age, years	62.1 ± 12.7
Duration of diabetes, years	5.5 (3.0 – 12.0)
Body mass index, kg/m2	31.4 ± 5.6
Serum creatinine, mg/dl	1.0 ± 0.4
Glycemia, mg/dL	129.2 (110.5-151.5)
HbA1c, %	7.1 ±1.3
Total cholesterol, mg/dl	171.8 ± 43.4
LDL-C (Friedewald), mg/dl	95.8 ± 38.5
LDL-C (modified formula), mg/dl	101.3 ± 36.2
HDL-C, mg/dl	43.9 ± 12.4
Triglycerides, mg/dl	139.0 (100.0 – 189.0)
non-HDL-C, mg/dl	127.9 ± 41.7
Systolic blood pressure, mmHg	128.7 ± 14.1
Diastolic blood pressure, mmHg	77.9 ± 10.2
Waist circumference, cm	106.0 ± 13.7
Categorical variables, %	
Male gender	64.0
Current smoker	10.0
Hypertension	70.3
Family history of premature vascular disease	11.2
Retinopathy	4.4
Neuropathy	5.7
Microalbuminuria	27.6
Obesity	55.7
Secondary prevention	37.3

*Values are expressed as mean±standard deviation or median (interquartile range).

Table 2. Pharmacological treatment of the population (n=528).

Treatment %	N (%)
Aspirin	196 (37.1)
ACEI/ARBs	336 (63.6)
Betablockers	194 (36.7)
Calcium blockers	103 (19.5)
Diuretics	110 (20.8)
Metformin	416 (78.8)
Sulphonylureas	53 (10.1)
Thiazolidinediones	11 (2.1)
DPP4 inhibitors	133 (25.2)
GLP-1 agonists	38 (7.2)
SLGT-2 inhibitors	44 (8.3)
Atorvastatin	127 (24.1)
5 mg/day	2 (1.5)
10 mg/day	62 (47.7)
20 mg/day	42 (32.3)
40 mg/day	20 (15.4)
80 mg/day	4 (3.1)
Rosuvastatin	183 (34.6)
5 mg/day	30 (16.4)
10 mg/day	95 (51.9)
20 mg/day	53 (29.0)
40 mg/day	5 (2.7)
Simvastatin	20 (3.8)
10 mg/day	9 (47.4)
20 mg/day	10 (52.6)
Fluvastatin	3 (0.6)
Ezetimibe	50 (9.5)
Fibrates	56 (10.6)
Omega 3	20 (3.8)

ACEI: Angiotensin-converting enzyme inhibitors: ARBs: Angiotensin II receptor antagonists. DPP4: Dipeptidyl peptidase 4. GLP-1: Glucagon-like peptide-1 receptor. SLGT-2: Sodium-glucose transport protein-2.

intensity statins is shown in Figure 1.

Similarly, the percentage of patients who did not attain the LDL-C therapeutic objective increased significantly with the new formula when triglycerides were higher ($p < 0.01$) (Table 3).

The correlation between both formulas to calculate LDL-C was excellent ($r=0.969$) and was observed both for patients in primary prevention ($r=0.963$) as in secondary prevention ($r=0.974$). In the analysis of the subpopulation with low LDL-C (below 70 mg/dl) the correlation between both formulas was moderate ($r=0.665$) (Figure 2). The concordance between both methods to calculate LDL-C and identify patients who met the therapeutic goal (below 70 mg/dl) was high (kappa: 0.826). This concordance decreased as the triglyceride level increased: triglycerides below 150 mg/dl, kappa 0.927; triglycerides 150-199 mg/dl, kappa 0.765; triglycerides 200-299 mg/dl, kappa 0.673; triglycerides equal to or higher than 400 mg/dl, kappa 0.428.

DISCUSSION

The results of this study demonstrate that a very low proportion of diabetic patients fulfilled the recommended therapeutic lipid goals, also considering that many patients who met the LDL-C below 70 mg/dl objective did not achieve this goal when a more exact formula to calculate LDL-C was applied.

Statins are a first-line therapeutic tool in the context of cardiovascular prevention in patients with diabetes. Depending on the type and dose of statin used, LDL-C reduction in the diabetic patient ranges between 24% and 52%. (14-16) The efficacy of statins in these patients was demonstrated in a meta-analysis including only patients with diabetes (14 randomized clinical trials with 18,686 patients). Statin therapy reduced all-cause mortality by 9% and major cardiovascular events by 21% per each 1 mmol/l (39 mg/dl) of LDL-C reduction. (17) These findings were observed regardless of baseline population characteristics, including presence or not of prior history of cardiovascular disease or baseline LDL-C level. Moreover, a post-hoc analysis of the SATURN trial revealed that high-intensity statins are able to revert atherosclerosis [estimated by coronary intravascular ultrasound (IVUS)] in patients with diabetes similarly to subjects without diabetes, only when very low LDL-C levels (below 70 mg/dl) are attained. (18) Consequently,

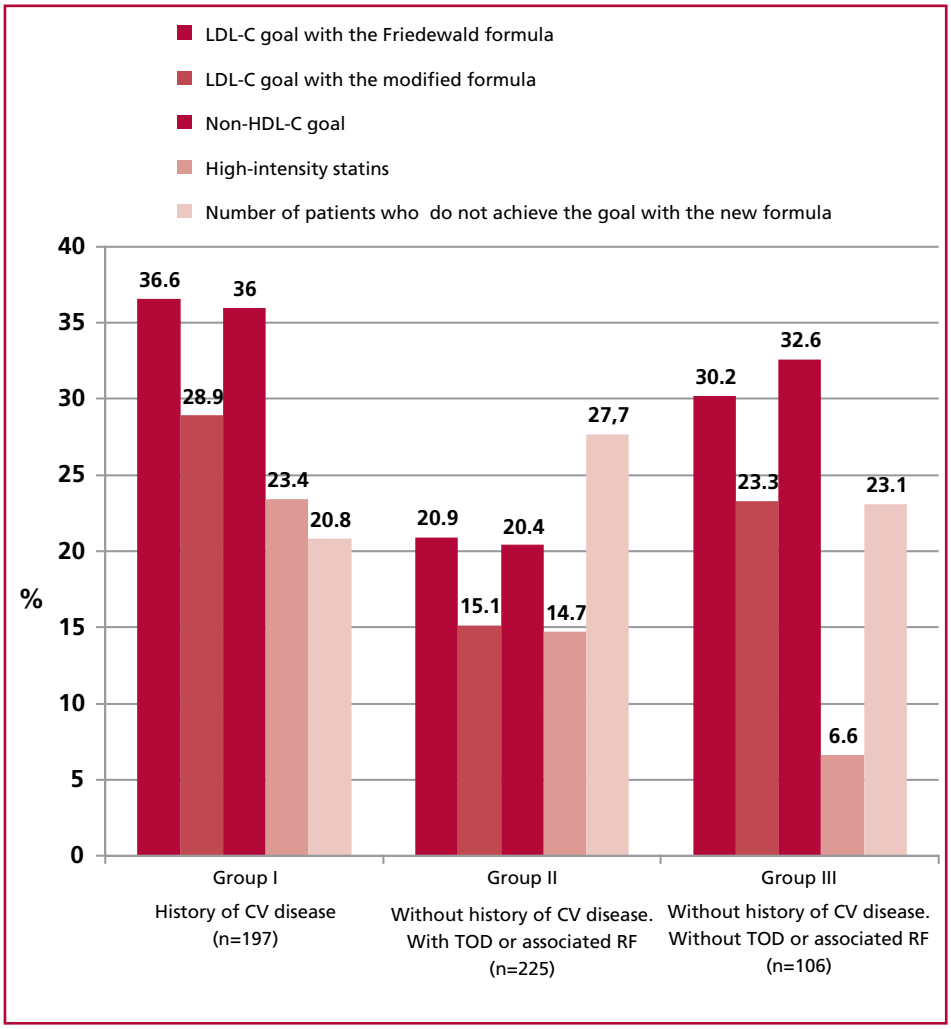


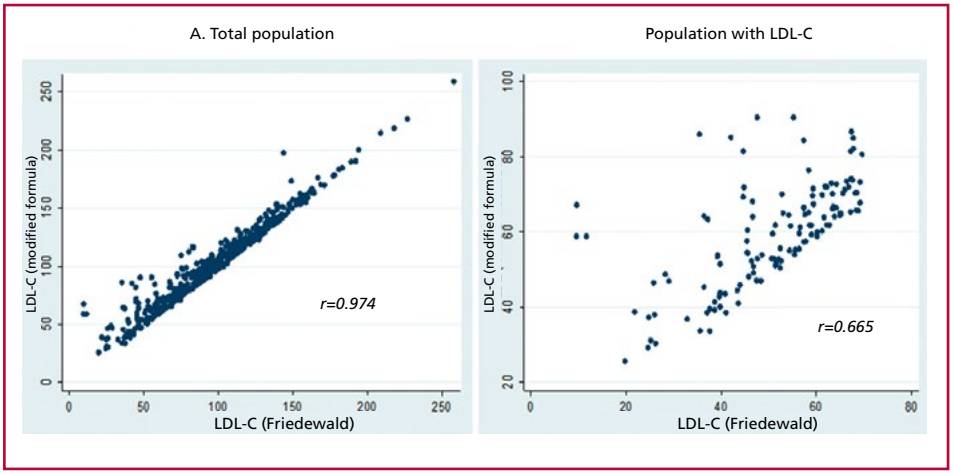
Fig. 1. Proportion of patients who met the goals or received high-intensity statins. Group 1: Patients with history of cardiovascular disease (goals: LDL-C <70 mg/dl and non-HDL-C <100 mg/dl); Group II: Patients without history of cardiovascular disease with one or more risk factors or target organ damage (objectives: LDL-C <70 mg/dl and non-HDL-C <100 mg/dl); Group III: Patients without history of cardiovascular disease, with no other risk factors and no target organ damage (objectives: LDL-C <100 mg/dl and non-HDL-C <130 mg/dl). CV: Cardiovascular; RF: Risk factors; TOD: Target organ damage.

Table 3. Proportion of patients who having met the LDL-C objective using the Friedewald formula do not attain this goal when the new formula, according to triglyceride level, is applied.

Triglyceride level	Proportion of subjects who do not attain the objective (LDL-C ≥70 mg/dL)* % (N)
< 150 mg/dl	10.7 % (8/75)
150-199 mg/dl	33.3% (9/27)
200-399 mg/dl	42.9 % (9/21)
≥ 400 mg/dl**	55.6 % (5/9)

*Patients with history of cardiovascular disease or subjects in primary prevention with risk factors or associated target organ damage.
**Only for comparative purposes, since the Friedewald formula is not recommended for triglyceride levels above 400 mg/dl.

Fig. 2. Correlation between both formulas for LDL-C in the total population (A) and in the subpopulation with LDL-C <70 mg/dl according to the Friedewald formula (B).



clinical practice guidelines agree in recommending statins, suggesting high-intensity statin administration (aiming at lower LDL-C objectives) in high risk diabetic patients. (6-8)

However, in daily practice, these recommendations are poorly accomplished. In our study approximately one-third or less of the population (depending on the group explored) met the LDL-C goal calculated with the Friedewald formula, with an extremely low use of high-intensity statins, similarly to previously published reports. A French study showed that in a group of 654 high-risk diabetic patients, 41% attained the goal of LDL-C below 70 mg/dl, though only 18.7% received high-intensity statins. (19) Similarly, in patients with coronary artery disease included in the EUROASPIRE IV study, the LDL-C objective was met by 28% of patients with prior history of diabetes and by 18% of patients with new diagnosis of diabetes. (20)

However, the poor success in achieving the therapeutic goals could be worse, if we consider the limitations of the technique used to measure LDL-C. In most of our centers, LDL-C is calculated with the Friedewald formula. This calculation method described in 1972 with a small group of 442 patients (9) is nowadays known to have certain limitations. (10) The analysis of a large population sample demonstrated that the greatest difference between LDL-C measured directly and that calculated with the Friedewald formula occurred in the presence of low LDL-C and high triglyceride levels. (21)

Martin et al. developed a new formula to calculate LDL-C, exploring more than 1 million samples and incorporating an adjustable factor obtained from the ratio between non-HDL-C and triglyceride levels. (12) This new formula improves the inaccuracy of LDL-C calculation with the Friedewald formula, mainly with very low LDL-C levels or hypertriglyceridemia. The latest American College of Cardiology/American Heart Association (ACC/AHA) guidelines for cholesterol management suggest for the first time the use of this new formula for LDL-C calculation.

Our study showed that approximately one out of four or five patients attaining the LDL-C goal below 70 mg/dl using the Friedewald formula, did not achieve it when the formula postulated by Martin et al. was applied. Similarly, analyzing a large number of patients with dyslipidemia, the VOYAGER study demonstrated that 23% of patients reaching an LDL-C value below 70 mg/dl with the Friedewald equation, were unable to meet the therapeutic goal when applying the new formula. (22) Moreover, in a large American sample obtained from hospital data, approximately one-fifth of subjects with LDL-C below 70 mg/dl estimated through the Friedewald formula exhibited values equal to 70 mg/dl or higher when using the new equation. (23) In a subanalysis of the FOURIER study, where a large number of coronary patients (36.6% diabetic) attained very low LDL-C levels after adding the PCSK9 inhibitor (evolocumab) to statin therapy, LDL-C calculated with the

Friedewald formula was in average 10 mg/dl over the direct LDL-C assessment in 13.3% of cases, which was reduced to 2.6% of cases when the new formula was applied. (24)

Our findings also emphasize that the classical formula to estimate LDL-C loses accuracy in the context of high triglycerides, as frequently found in the population with diabetes.

Among the numerous reasons why patients with diabetes do not attain the recommended lipid goals and are often undertreated, lack of adherence, medical inertia and low response to treatment are the most important ones. A large analysis of statin use patterns in a subgroup of diabetic patients, showed that adherence reached 55% of the time analyzed, and that the group at higher risk had the lowest adherence levels. (25) On the other hand, therapeutic inertia, defined as medical lack of treatment initiation or intensification when indicated, is often found in diabetes care. (26) A Spanish study in 639 patients with diabetes showed that medical inertia of lipid monitoring was 43.6%. (27) Finally, a study previously published in our country, demonstrated that diabetes was associated with greater probability of achieving a lower statin response (hypo-responders). (28)

The lipid profile in diabetic patients is usually characterized by high triglyceride levels, low HDL-C levels and a greater amount of cholesterol remnants and small and dense LDL-C particles. (29) In this context, the calculation of non-HDL-C becomes important as an additional lipid marker, as it represents more precisely the total potentially atherogenic particles. (30, 31) Again, in our study, the number of patients who attained this important objective was low (between 20% and 36% depending on the group analyzed).

Limitations

Our study has certain limitations. Given the study design, the possibility of bias cannot be ruled out. The population of diabetic patients attending cardiovascular secondary prevention offices does not necessarily represent the general population or the diabetic population treated by other specialties. In this sense, the low prevalence of complications such as neuropathy, nephropathy or retinopathy could be explained by the specialty of the treating teams. However, we consider that our research presents clinical implications that should be taken into account. It is known that the lipid-lowering therapy in diabetic patients, and consequently, the fulfillment of recommended lipid goals, is deficient. (32-34) In this context, we would be adding another difficulty. The traditional method used to define that a patient has reached the LDL-C goal has limitations. When the new formula is applied, it is possible to identify with greater accuracy those patients who do not reach the recommended therapeutic goal and optimize the lipid-lowering therapy, either maximizing the dose of statins or combining it with other drugs.

CONCLUSION

Lipid goals were poorly fulfilled in this population of diabetic patients and use of adequate statin doses was inadequate. The Friedewald formula has limitations to estimate correctly the LDL-C value with low levels of this lipid marker and high triglyceride values. The new formula to calculate LDL-C would allow optimizing lipid-lowering treatment in this specific group of patients.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material)

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