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Martin's, Friedewald's and Cordova's formulas compared to LDL-C directly measured in Southern Brazil

Fórmulas de Martin, Friedewald e Cordova comparadas com a dosagem direta do LDL-C no sul do Brasil

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ABSTRACT

Introduction: Recently, fasting flexibility for laboratory determination of lipid profile has been recommended. When triglycerides (TG) are above 400 mg/dl, the formula proposed by Martin *et al*. should be used to estimate the low-density lipoprotein cholesterol (LDL-C). However, this formula has not been evaluated in our population. **Objectives:** We evaluated the performance of Martin's equation for LDL-C estimation compared to Cordova & Cordova and Friedewald formulas in a population of Southern Brazil. **Methods:** Sampling consisted of 10,664 Brazilian individuals (5,847 women) aged 1 to 93 years, with TG, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and LDL-C directly measured. **Results:** Martin's formula presented significantly higher LDL-C values in patients with TG < 300 mg/dl, underestimating values when TG > 400 mg/dl, even with negative values; and LDL-C values was also overestimated in all TC ranges, with greater standard deviation. It also presented a higher mean error in the stratified intervals, and a lower correlation coefficient. **Conclusion:** Martin's equation is not accurate for estimating LDL-C in our sample, unless TG is between 300 and 400 mg/dl. We recommend using the Cordova & Cordova formula as an alternative to determine LDL-C when its direct measurement is not available, and not applying the Martin's Formula indiscriminately to other populations before it is properly evaluated and compared with other available equations.

Key words: cholesterol; LDL-cholesterol; formula; atherosclerosis; risk factor.

RESUMO

Introdução: *Recentemente, foi recomendada a flexibilização do jejum para a determinação laboratorial do perfil lipídico. Quando os triglicerídeos (TG) estiverem acima de 400 mg/dl, deve ser utilizada a fórmula proposta por Martin* et al. *para a estimativa do colesterol da lipoproteína de baixa densidade (LDL-C), contudo, essa fórmula não foi avaliada em nossa população.* ***Objetivos:*** *Avaliamos o desempenho da equação de Martin para a estimativa do LDL-C em comparação com as fórmulas de Cordova & Cordova e Friedewald em uma população da região sul do Brasil.* ***Métodos:*** *A amostragem foi composta por 10.664 indivíduos brasileiros (5.847 mulheres) com idades entre 1 e 93 anos, com TG, colesterol total (CT), colesterol da lipoproteína de alta densidade (HDL-C) e LDL-C medidos diretamente.* ***Resultados:*** *A fórmula de Martin apresentou valores significativamente mais altos de LDL-C em pacientes com TG < 300 mg/dl, subestimando os valores quando TG > 400 mg/dl, inclusive com valores negativos; também foi superestimado o LDL-C em todas as faixas de CT, com maior desvio padrão. Ainda apresentou um erro médio maior nos intervalos estratificados e um menor coeficiente de correlação.* ***Conclusão:*** *A equação de Martin não tem acurácia para a estimativa do LDL-C em nossa amostragem, a menos que o TG esteja entre 300 e 400 mg/dl. Recomendamos que a fórmula Cordova & Cordova seja utilizada como uma alternativa para determinar o LDL-C quando sua medida direta não estiver disponível e que a fórmula de Martin não seja aplicada indiscriminadamente em outras populações sem ser adequadamente avaliada e comparada com outras equações disponíveis.*

Unitermos: *colesterol; LDL-colesterol; fórmulas; aterosclerose; fatores de risco.*

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RESUMEN

Introducción: *Recientemente, se ha recomendado la flexibilización del ayuno para la determinación del perfil lipídico. Cuando los triglicéridos (TG) estén por encima de 400 mg/dl, se debe utilizar la fórmula propuesta por Martin* et al. *para estimar el colesterol de la lipoproteína de baja densidad (LDL-C); sin embargo, esa fórmula no ha sido analizada en nuestra población.* ***Objetivos:*** *Evaluamos el desempeño de la ecuación de Martin para estimar el LDL-C en comparación con las fórmulas de Cordova y Cordova, y Friedewald en una población de la región Sur de Brasil.* ***Métodos:*** *La muestra se compuso de 10.664 individuos brasileños (5.847 mujeres) con edades entre 1 y 93 años, con TG, colesterol total (CT), colesterol de la lipoproteína de alta densidad (HDL-C) y LDL-C medidos directamente.* ***Resultados:*** *La fórmula de Martin presentó valores notablemente más altos de LDL-C en pacientes con TG < 300 mg/dl, subestimando los niveles cuando TG > 400 mg/dl, incluso con valores negativos; también el LDL-C fue sobrevalorado en todos los rangos de CT, con mayor desviación estándar. Además presentó un error medio mayor en los intervalos estratificados y un menor coeficiente de correlación.* ***Conclusión:*** *La ecuación de Martin no tiene exactitud para estimar el LDL-C en nuestra muestra, a menos que el TG esté entre 300 y 400 mg/dl. Recomendamos que la fórmula de Cordova y Cordova sea utilizada como una alternativa para determinar el LDL-C cuando su medida no esté disponible, y que la fórmula de Martin no sea empleada indiscriminadamente en otras poblaciones sin ser adecuadamente evaluada y comparada con otras ecuaciones disponibles.*

Palabras clave: *colesterol; LDL-colesterol; fórmulas; aterosclerosis; factores de riesgo.*

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of mortality in the world, accounting for 31% of global deaths[1]. Low-density lipoprotein cholesterol (LDL-C) is a laboratory parameter frequently used in the assessment of CVD risk, since its accumulation in the arterial walls contributes to the formation of atherosclerotic plaques, although the mechanism of atherosclerosis is complex and not completely understood[2-4].

Recently, an updated national guideline was published recommending the flexibilization of fasting in the determination of the lipid profile for cardiovascular risk assessment. It has also been recommended that LDL-C determination should be performed by estimation using the Friedwald (FF) or Martin (MF) formulas when a direct determination is not possible. In cases of fasting and triglycerides (TG) values > 400 mg/dl, which prevent the use of FF, the MF or direct determination should be used[5, 6].

FF is routinely used in clinical practice because it is considered a good cost-effective alternative to the ultracentrifugation reference method. However, it cannot be applied under hyperglycemic conditions and when TG > 400 mg/dl. In diabetic patients or samples with increased TG values, the results may be underestimated, misclassifying the risk of CVD[7-9].

Martin *et al*. (2013)[10] proposed a new equation derived from FF for the estimation of LDL-C, with an adjustable factor in the calculation of the very low density lipoprotein cholesterol (VLDL-C) fraction based on TG (instead of the fixed divisor of five in FF), in order to correct FF limitations and improve the LDL-C estimation. However, researchers have applied the MF adjustable factor in their studies and had overestimated results in some populations, concluding that accuracy of the equation improved only slightly compared to FF[11-13].

Although the new Brazilian guidelines have their merits[14], they are questionable in several points and their possible consequences[15]. Notably, MF was recommended for the estimate LDL-C in the Brazilian population without been validated or minimally evaluated in our metabolic and lifestyle conditions.

Considering that the determination of the lipid profile is of fundamental importance to identify risk factors and to establish adequate therapeutic plans, it is necessary to have high safety regarding the diagnostic methods proposed in our population. Thus, in this work, we aim to evaluate MF performance in a large laboratory database of a population of southern Brazil, compared to FF and the formula developed and proposed by Cordova & Cordova (FCOR) (2013)[16].

METHODS

Sampling

This study consisted of a database of 10,664 Brazilian individuals with TG, total cholesterol (TC), high-density lipoprotein cholesterol (HLD-C), and LDL-C directly measured[8]. The population consists of 5,847 women and 4,817 men, aged 1-93 years. Blood samples were collected after a 12 hour fast in a clinical laboratory in Southern Brazil, from January 2000 to December 2002.

Laboratory methods

TG and TC assays were performed with Triglycerides FS reagents (DiaSys Diagnostic Systems GmbH & Co KG, Holzheim, Germany) and Cholesterol (BioSystems SA, Barcelona, Spain), respectively, according to the manufacturers' recommendations, in Spectrum CCX II equipment (Abbott Diagnostics, Abbott Park, IL, USA). The tests were calibrated with the CCX Multicalibrator Set (Abbott), with three-point curves. LDL-C determination by the homogeneous method was performed with LDL-C Select FS reagent (DiaSys), a method based on Wako technology (Richmond, VA, USA) according to the manufacturer's recommendations. The determination of high-density lipoprotein cholesterol (HDL-C) was performed by the homogeneous method with the HDL-C reagent Immuno FS (DiaSys/Wako). The coefficient of variation of the tests was determined by analysis of the results obtained for 20 consecutive days using, in duplicate, aliquots of the control serum Accumark (Sigma Diagnostics, St. Louis, MO, USA), lot 111K6403. The coefficient of variation of the LDL-C measures by the direct method was 4%; for TC, TG and HDL-C were 3%, 4%, and 3%, respectively. The laboratory where the tests were performed participates in the National Program of Quality Control sponsored by the Brazilian Society of Clinical Analyzes (PNCQ-SBAC) with excellent evaluation. The values obtained for TC varied from 73 to 523 mg/l, from 18 to 2,574 mg/l for TG, from 12 to 130 mg/l for HDL-C, and from 24 to 423 mg/l for LDL-C.

Data analysis

LDL-C was estimated by the FF [LDL-C = TC-HDL-C – (Trig/5)] for the samples with TG < 400 mg/dl[17]. The results of LDL-C by MF[10] were calculated using the Microsoft Excel™ program according to the model provided by the authors (http://www.ldlcalculator.com/). The LDL-C values were calculated by CORF according to the equation LDL-C = (TC-HDL-C)*0.7516[16]. The comparison between the methods of homogeneous LDL-C and estimation of LDL-C by the formulas was carried out according to Passing & Bablok (1984)[18], through correlation analysis, expressed by the equation $y = bx + a$, where b is the slope of the line, representing the proportional error, and a is the intersection on the y-axis, representing the constant error. To improve comparison between methods, the samples were stratified according to TC levels: 70-150 mg/dl, 151-200 mg/dl, 201-250 mg/dl and > 250 mg/dl, and the TG levels: < 150 mg/dl, 151-200 mg/dl, 201-300 mg/dl, 301-400 mg/dl and > 400 mg/dl. The root-mean-square-error (rMSE) of each LDL-C determination method and the statistical significance of the differences were also calculated using the Student's *t*-test, and the Microsoft Excel™ Office 365 software. The $p < 0.05$ values were considered significant. The data were also visually analyzed by the Bland-Altman difference plot[19].

RESULTS AND DISCUSSION

The estimated values for LDL-C according to MF were, overall, higher than the values estimated by the direct measurement method used for the CORF and even higher than the values estimated by the FF (**Table 1**). Interestingly, some values estimated by MF may return negative results, notably when TC > 250 mg/dl, or when TG > 400 mg/dl. With the data stratified, on average, in all the ranges of TC, MF presented higher results, and also concerning TG values. Only in the TG range between 301-400 mg/dl, the LDL-C values returned by MF are similar to those obtained by the direct method or by the CORF, and with TG > 400 mg/dl the MF results underestimate the LDL-C.

Another important aspect to be analyzed is the accuracy of the different methods of LDL-C determination. rMSE is a good measure of accuracy, and often used to evaluate differences in estimated values in a model, or as an estimate of the actual values observed by the model[20].

TABLE 1 – Results of mean ± standard deviation (lowest value found – highest value found) from LDL-C (measured), LDL-C (Martin), LDL-C (Cordova & Cordova) and LDL-C (Friedewald) according to triglyceride and total cholesterol levels, in mg/dl

	n	LDL-C (measured)	LDL-C (Martin)	LDL-C (Cordova & Cordova)	LDL-C (Friedewald[1])
TG					
≤ 150 mg/dl	6,52	126 ± 37 (24-307)	139 ± 38*** (28-354)	120 ± 30*** (32-286)	140 ± 39*** (28-327)
151-200 mg/dl	1,897	146 ± 39 (39-321)	156 ± 38*** (48-377)	141 ± 30*** (53-309)	153 ± 40*** (41-376)
201-300 mg/dl	1,458	152 ± 42 (56-332)	158 ± 40*** (58-328)	148 ± 32*** (68-279)	150 ± 43*** (37-325)
301-400 mg/dl	448	157 ± 45 (40-299)	157 ± 41 (34-289)	157 ± 33 (52-261)	141 ± 45*** (27-278)
> 400 mg/dl	341	163 ± 57 (57-423)	149 ± 50*** (-133-133)	171 ± 40*** (92-370)	-
TC					
≤ 150 mg/dl	472	68 ± 13 (24-105)	76 ± 13*** (28-106)	70 ± 11*** (32-95)	75 ± 14*** (27-107)
151-200 mg/dl	3,043	101 ± 16 (47-155)	111 ± 14*** (51-153)	100 ± 12*** (65-131)	110 ± 16*** (46-156)
201-250 mg/dl	4,488	136 ± 20 (73-200)	147 ± 16*** (52-195)	131 ± 13*** (80-173)	146 ± 18*** (69-198)
> 250 mg/dl	2,661	185 ± 32 (47-332)	195 ± 31*** (-133-377)	174 ± 24*** (106-370)	195 ± 30*** (115-376)
All	10,664	135 ± 41 (24-423)	146 ± 40*** (-133-377)	131 ± 34*** (32-370)	144 ± 40*** (2-376)

*LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; TC: total cholesterol; [1]applied to samples with triglycerides ≤ 400 mg/dl. Comparison of Martin-LDL-C with Cordova & Cordova-LDL-C, and Cordova & Cordova-LDL-C/Friedewald-LDL-C with measured-LDL-C: *p < 0.05; **p < 0.01; ***p < 0.001.*

Overall, MF has a lower correlation and a larger error in the estimate of LDL-C compared to CORF (**Table 2**), with CORF showing better accuracy (lower rMSE) than the direct method. With stratified data, we, again, observed that the correlation of MF is worse when TG > 400 mg/dl, and the accuracy is consistently lower in all TC and TG ranges, curiously except when TG > 400 mg/dl.

Using the individual data from each method of LDL-C estimation plotted compared to the direct method (**Figure 1**), we observed that the correlation graphs show both a negative proportional and constant error for the values estimated by MF and FF, while the CORF presents a positive proportional error with a constant negative error. As the LDL-C values become higher, the difference in LDL-C between the direct and CORF methods becomes positive, that is, the LDL-C values by CORF are lower in higher ranges.

Here, it is noteworthy that LDL-C values determined directly by Wako-based method tend to overestimate LDL-C when TG and LDL-C are higher[21]. However, the CORF corrects this bias, presenting lower LDL-C values in higher ranges, which explains the results of its greater accuracy, what does not occur with MF and FF.

On the other hand, as TG values increase, CORF tends to present slightly higher LDL-C results, decreasing the difference in relation to the direct method, unlike FF and MF, and as the values of TC are higher, CORF tends to return lower LDL-C results, increasing the difference from the direct method (**Figure 2**). In fact, as TC becomes higher, higher LDL-C values are expected, and, again, it is shown that the CORF corrects the positive bias of the direct method in this higher range. We also note that MF

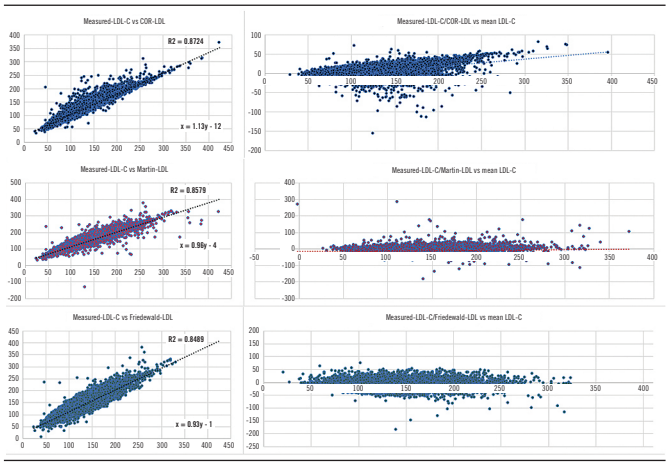

FIGURE 1 – *Linear correlation and Bland-Altman plots between direct measurement of LDL-C values (measured-LDL-C) and Martin-estimated LDL-C values (Martin-LDL), using Cordova & Cordova (COR-LDL) and Friedewald formula in the study population*

LDL-C: low-density lipoprotein cholesterol.

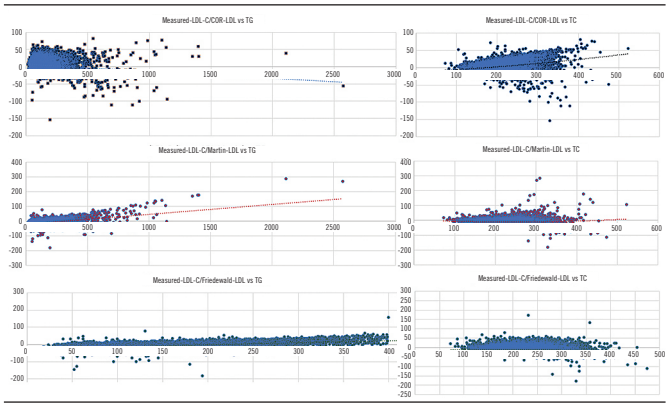

FIGURE 2 – *Graph showing the differences between Martin-estimated LDL-C values (Martin- LDL), compared to direct measurement of LDL-C values (measured-LDL-C) by Cordova & Cordova (LDL-COR) and Friedewald formulas in the studied population, in relation to the values of TG and TC*

LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; TC: total cholesterol.

TABLE 2 – Performance of the Martin and Cordova & Cordova formulas compared to the LDL-C values measured directly in the studied population, stratified by TC and TG levels

	n	LDL-C (measured)		LDL-C (Martin)			LDL-C (Cordova & Cordova)	
TG		rMSE	*p*	rMSE	*r*	*p*	rMSE	*r*
≤ 150 mg/dl	6,52	102.4	< 0.0001	112.74	0.9464	< 0.0001	96.58	0.9492
151-200 mg/dl	1,897	63.76	< 0.0001	67.73	0.9341	< 0.0001	60.62	0.9331
201-300 mg/dl	1,458	58.14	< 0.0001	60.23	0.936	< 0.0001	56.11	0.9352
301-400 mg/dl	448	33.42	0.1125	33.15	0.9086	0.34001	32.91	0.9126
> 400 mg/dl	341	30.88	< 0.0001	28.17	0.6876	< 0.0001	31.34	0.8308
				TC				
≤ 150 mg/dl	472	14.61	< 0.0001	16.16	0.7192	0.0001	14.84	0.7315
151-200 mg/dl	3,043	54.57	< 0.0001	59.92	0.7483	0.0005	53.94	0.7644
201-250 mg/dl	4,488	89.01	< 0.0001	96.1	0.7323	< 0.0001	85.71	0.7372
> 250 mg/dl	2,661	94.27	< 0.0001	98.65	0.735	< 0.0001	87.98	0.8011
All	10,664	141.42	< 0.0001	151.06	0.9208	< 0.0001	134.97	0.934

LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; TC: total cholesterol; rMSE: root-mean-square error; p: *comparison of Martin-LDL-C with Cordova & Cordova-LDL-C, and Cordova & Cordova-LDL-C with measured-LDL-C;* r: *Pearson's correlation coefficient between the measured-LDL-C determination and the formulas of Martin and Cordova & Cordova.*

significantly underestimates LDL-C as TG is higher. **Figure 3** demonstrates the distribution of the LDL-C values obtained by the different methods.

Others[13, 22] had already shown that TG values do not correlate totally with LDL-C values. Therefore, it is not surprising that an equation that does not use TG values for the estimation of LDL-C, such as CORF, returns more accurate results. Although MF made a significant mathematical effort to correct the factor that relates the TG values to the calculation, it could not improve the FF performance in our sample, even worsening some situations, with negative results. Several professionals of clinical laboratories in the country had already begun to realize, empirically, that MF is not appropriate in our environment.

However, it has been shown that either FM or FCOR may be a better choice depending on the population in which it is applied[23]. It is possible to suppose that genetic, metabolic, lifestyle, and perhaps even epigenetic differences influence the relation of the different laboratory parameters used by the different forms in the estimation of LDL-C. Thus, it is evident that it is not possible to indiscriminately apply a particular equation for the estimation of LDL-C in a population other than the one in which the respective formula was developed, without careful and appropriate evaluation.

In sum, we observed that MF is not appropriate in our population, especially in cases of high TC and TG. Therefore, especially in patients with no fasting, its use for the LDL-C estimation shall not be indiscriminately applied unless it can be properly evaluated and compared to other available equations. We suggest that CORF, should be validated by ultracentrifugation-based methods, evaluated in other Brazilian populations and then officially recommended for the LDL-C estimation, when it is not possible to directly determine its concentration.

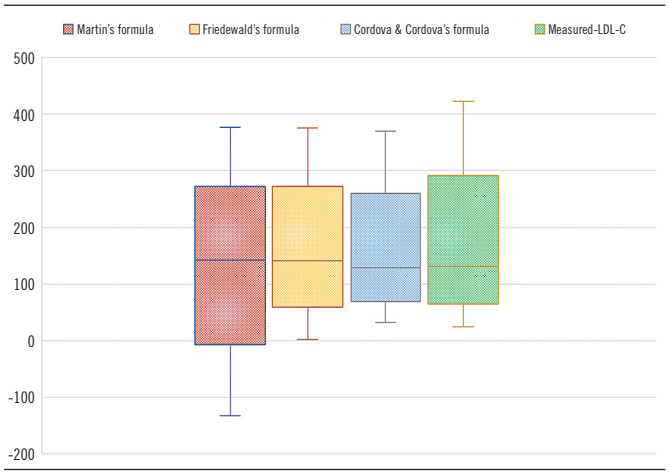

FIGURE 3 – *Distribution of LDL-C values obtained by the different methods, indicating the median, first and third quartiles, minimum and maximum values. Friedewald's estimation formula was applied only when TG < 401 mg/dl*

LDL-C: low-density lipoprotein cholesterol; TG: triglycerides.

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