Correlation between Apolipoprotein B-to-Apolipoprotein A1 Ratio and Total-to-HDL-Cholesterol Ratio in a Healthy Population: Should Castelli Index be Updated?

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SUMMARY

Background

The total cholesterol/HDL cholesterol ratio (TC/HDL-Cr) was proposed as a marker of coronary risk about 25 years ago by Dr. William Castelli and the suggested target was <4.5. The INTERHEART study showed that the ApoB / ApoA ratio is a predictor of cardiovascular events higher than the TC / HDLr. Many laboratories in our country do not have the technology to accurately measure apolipoproteins.

Objective

To determine values of TC /HDLr or Castelli index (CI) corresponding to the decile 1 of the ApoB / ApoA ratio (0.43, odds ratio 1) of the INTERHEART study, to identify the optimal cutoff point (OCP) that differentiates between sujects with ApoB / ApoA≤ 0.43 and > 0.43; and propose an updated CI target.

Material and Methods

Apolipoprotein levels were measured by immnuno-phelometry in samples obtained from blood donors. Models of simple linear regression were made to analyze the relationship between the ApoB/ApoA and TC/HDL ratios. A ROC analysis was carried out to evaluate the accuracy of the CI to distinguish between subjects with ApoB / ApoAr ≤0.43 and > 0.43. Subjects with hypertension, vascular disease, diabetes or treated with lipid-lowering drugs were excluded.

Results

A total of 283 subjects were included, 64% men, 31% smokers. General characteristics (mean ± SD): age 41.8 ± 14 years, BMI 26.2 ± 4, TC 199.5 ± 48 mg / dl, HDL 49 ± 13 mg / dl, CI 4.31 ± 1.3, ApoB 95.2 ± 28 mg / dl, ApoA 157.4 ± 32 mg / dl, ApoB / ApoAr 0.62 ± 0.21. In the overall population, the correlation between ApoB / ApoAr and the CI was 0.90 and the ApoB / ApoAr of 0.43 corresponded to an CI of 3.22. The area under the ROC curve of the CI to distinguish between subjects with ApoB/ApoAr 0.43 and > 0.43 was 0.936 (CI 95% 0.897- 0.975) and OPC was 3.238.

Conclusions

These results suggest that the target of CI should be reviewed and updated at <3.25.

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Key words > Castelli Index - Apolipoproteins - Cardiovascular Risk (Risk)

Abbreviations >

ApoA	Apolipoprotein A1	**OCP**	optimal cutoff point
ApoB	Apolipoprotein B100	**TP**	Total population
HDL-C	High Density Lipoprotein Cholesterol	**ApoB / ApoAr**	ApoB / ApoA ratio
TC	Total cholesterol	**TC / HDL-Cr**	TC / HDL-C ratio
SD	Standard Deviation	**ROC**	Receiver Operating Characteristic
CI	Castelli Index	**NPV**	Negative predictive value
MI	Myocardial infarction	**PPV**	positive predictive value
BMI	Body mass index		

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BACKGROUND

25 years ago, in a preliminary analysis of the Framingham study, Dr. William Castelli noted that the total cholesterol / high density lipoprotein (TC / HDL-C) ratio or Castelli index (CI) was an excellent predictor of coronary risk and suggested a target <4.5 and the indication of lipid-lowering therapy in front of higher values. (1)

The plasmatic concentration of apolipoprotein B (ApoB) allows us to estimate the total number of atherogenic particles. Apolipoprotein A1 (ApoA) is the most important protein in HDL-C and has a critical role in reverse cholesterol transport. (2)

Different studies showed the independent prognostic value of the ApoB / ApoA (ApoB / ApoAr) ratio, surpassing the conventional lipid markers. (3-6) The ApoB / ApoAr and the CI are indicators of the balance between pro-atherogenic and antiatherogenic lipoproteins. In the INTERHEART study, the association between ApoB / ApoAr and risk of myocardial infarction was significantly higher than that observed with CI. In this control-case study, the decile median of the ApoB / ApoAr associated with lower risk of myocardial infarction (MI) (decile 1, odds ratio 1) corresponded to a value of 0.43. (7)

Many laboratories do not have the technique to measure apolipoproteins or do not have an accurate methodology. (8, 9) The measurement of TC and HDL-C is relatively simple and less expensive; however, as it was previously stated, the reference value of TC/ HDL-Cr, suggested by Dr. Castelli in 1985, was not updated.

The objectives of our study were to determine in a healthy population of Argentina, the value of the TC/ HDL-Cr corresponding to the decile 1 of the ApoB/ ApoAr of the INTERHEART study, to identify the optimal cut-off point (OCP) that distinguishes between subjects with CT/HDL-C ≤0.43 or > 0.43, and finally to propose a target updated of CI.

MATERIAL AND METHODS

The sample was obtained in a non-probabilistic, consecutive way in Hemotherapy service of Hospital Italiano de Buenos Aires. Sujects filled out a form with basic clinical data (age, gender, weight, height, drug treatment and smoking history, hypertension, diabetes mellitus or prior cardiovascular disease). Of these samples and anonymously it was obtained a fraction of blood to carry out lipidic measurements.

Inclusion criteria: any subject that assits to the hemotherapy service to donate blood .

Exclusion criteria: 1) prior cardiovascular disease (acute myocardial infarction, unstable angina, chronic stable angina, myocardial resvacularization surgery, coronary angioplasty, CVA, peripheral vascular disease, aortic disease or any of its branches), 2) personal history of diabetes mellitus or hypertension, 3) prior lipid-lowering therapy. The levels of apolipoproteins were measured by kinetic immunonephelometry (IMMAGE® Immunochemistry System) and the TC level by the enzymatic endpoint method. The HDL-C level was obtained by direct enzymatic method. The coefficients of variation for interessay and intraessay corresponding to the measure used methods were the followings: TC (2% and 1%), HDL-C (2% and 1%), ApoB (5.5% and 4%) and ApoA-1 (4.5% and 4%). The values of lipoproteins and apolipoproteins were expressed in mg/dl.

Statistical analysis

Four simple linear regression models were made to assess the correlations between ApoB / ApoAr and CI: 1) in the total population (TP), 2) in the subpopulation of very low risk, composed by non smokers with a rate of body mass <25, 3) in men and 4) in women. Subsequently, CI values were determined which corresponded to each model to the ApoB / ApoAr of 0.43. They were analyzed the assumptions of linearity, homoscedasticity and normality.

It was carried out a ROC (receiver operating characteristic)analysis. It was calculated the area under the curve in order to assess the accuracy of the TC/HDL-C to distinguish between subjects with ApoB/ApoAr ≤0.43 or >0.43. With the purpose to determine the OCP of CI using two methods: 1) a point on the ROC curve closest to the point (0.1) of the graph (point c *) and 2) the Younden index, which corresponds to maximum vertical distance between the ROC curve and the line of statistical chance (point cJ) (Table 1, Figure 1). (10, 11). They were calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). It was considered statistically significative a p value <0.05.

The study was carried out following the recommendations in medical research suggested by the Declaration of Helsinki, Good Clinical Practice Guidelines and regulations of the local Ethics Committee.

RESULTS

A total of 283 subjects were recruited. The age (mean ± SD) was 41.9 ± 14 years, 64% were male. The body mass index (BMI) (mean ± SD) was 26.2 ± 4 and the prevalence of smoking was 31%. 82.3% of the population had a ApoB/ApoAr >0.43.

The mean plasmatic levels in the total population were the followings (mean ± SD): total cholesterol 199.5 ± 48 mg / dl, HDL cholesterol 49 ± 13 mg / dl, triglycerides 107.2 ± 78 mg / dl, CI 4.3 ± 1.3, ApoB 95.2 ± 28 mg / dl, ApoA1 157.4 ± 32 mg / dl and ApoB/ ApoAr 0.62 ± 0.21. The very low-risk subpopulation consisted of 86 subjects non-smokers (55% men) with a mean age of 39.5 ± 15 years and BMI of 22.7 ± 2. The values of TC, triglycerides, ApoB, CI and ApoB/ApoAr were lower than the TP (191.02 ± 40, 82.9 ± 40, 86.3 ± 26, 3.8 ± 1.2 and 0.55 ± 0.19, respectively), while levels of HDL-C and ApoA were higher (53.6 ± 15 and 165 ± 37mg/dl, respectively).

Correlations between ApoB/ApoAr and CI showed minor differences with values of r, ranging between 0.88 and 0.91 (Table 2). In linear regression models, the ApoB/ApoAr of 0.43 corresponded to Castelli indexes of 3.22, 3.17, 3.32 and 3.12 in the TP, in the subpopulation of very low risk, in men and women, respectively (Table 2, Figure 2).

The area under the ROC curve of CI to distinguish between subjects with ApoB/ApoAr ≤0.43 or >0.43 was 0.936 (95% CI 0.897-0.975). The OPC value determined by the shortest distance to point 0.1 and the Younden

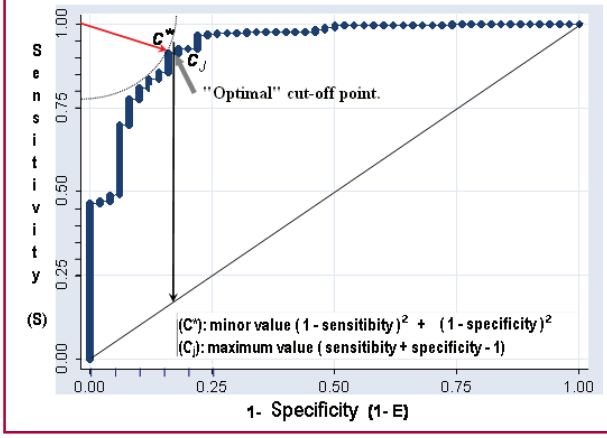

Fig 1. Methodology and formulae used in the study to determine the optimal cuttoff point. c* is the point determined by the shortest radio between the point 1 and the ROC curve ROC (red arrowr). cJ is the point determined by the maximun vertical distance between the ROC curve and the line of chance.

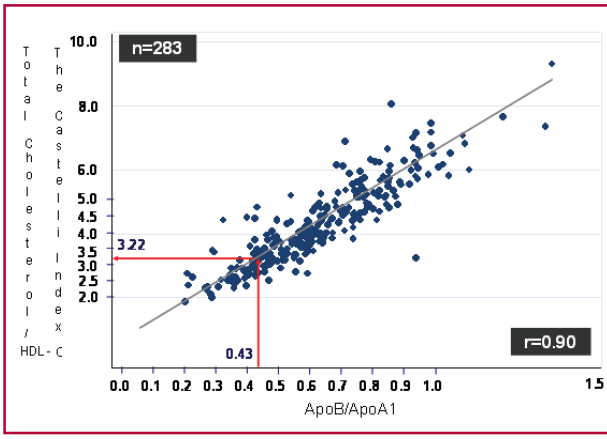

Fig 1. Correlation between ApoB/ApoAr and CI in the total population. In the simple linear regression anális, ApoB/ApoAr of 0.43 corresponded to a CI of 3.22.

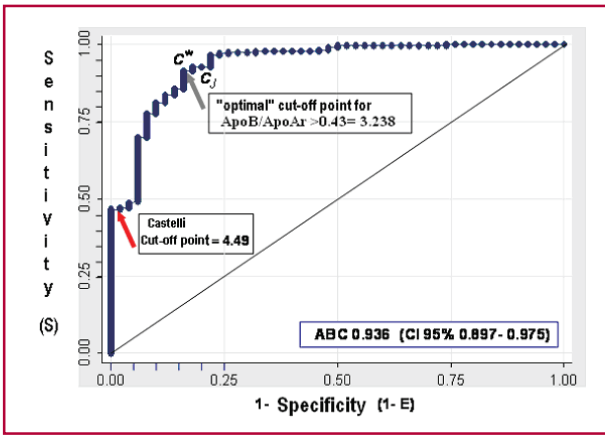

Fig 1. Area Ander the ROC curve (ABC) of the Castelli index to distinguís between subjects with a ApoB/ApoAr ≤0,43 or > 0,43. The grey arrow shows the location of the optimal cutoff point in the curve (c* and cJ). The red arrow shows the location of historical cutoff point.

Table 2. Correlations betweem ApoB/ApoA y TC/C-HDL ratios, equations of models of linear regression and Castelli index values (TC/C-HDL-C) that correspond to a ApoB/ApoAr of 0.43.

	Correltion ApoB/ApoAr-CTC/HDL-C	Equation of linear regression (TC/ HDL-C)	TC/ HDL-C (Apo B/Apo A = 0.43)
Total population	r = 0.90	0.824 + 5.576 × Apo B/Apo A	3.22
Subpopulation of very low risk	r = 0.91	0.803 + 5.498 × Apo B/Apo A	3.17
Men	r = 0.88	0.979 + 5.439 × Apo B/Apo A	3.32
Women	r = 0.90	0.758 + 5.486 × Apo B/Apo A	3.12

index was 3.238 (Figure 3).

The sensitivity, specificity, PPV and NPV of CI of 3.24 to identify patients with a Apo/ ApoAr> 0.43 were of 91%, 84%, 96% and 68% respectively (Figure 4A) . When a similar analysis was carried out with the historical cut-off point of 4.5, the results were of 47%, 96%, 98% and 28% (Figure 4 B).

It was assessed an exploratory cut-off point of 3.03 and there was an increase in sensitivity and in NPV (97% and 83% respectively) but lower specificity (78%) (Figure 4C).

DISCUSSION

Cardiovascular prevention guidelines recommend intensive targets for patients at high and very high risk. In clinical practice may be identified fairly easily, simply by the clinical history or exploring conventional risk factors. (12, 13)

However, approximately 80% of cardiovascular events occur in individuals with a lower basal risk, which creates difficulties in making decisions in clinical practice or population planning strategies. (14, 15) The Framingham score is unable to identify subjects with high vascular risk among men younger than 40 years and it ranks of low cardiovascular risk to most women younger than 70. (15-17). Therefore, to distinguish between individuals with very low risk (<6%) or low-moderate risk (6-20%) of suffering coronary events could improve the cost-effectiveness in primary prevention. There are still disputes over the choice of "ideal" lipid marker as aim treatment and the optimal target to achieve.

In this scenario, recent studies and consensus proposed to ApoB/ApoAr as the best lipidic predictor of cardiovascular events. (3-6) The plasmatic level of ApoB is an indicator of the total number of atherogenic particles, whereas the ApoA is involved in reverse cholesterol transport that participates in the formation of nascent HDL or prebetic HDL, but also it has antioxidant and inflammatory properties. (18) Therefore, the ApoB/ApoAr reflects the balance of plasmatic proatherogenic/antiatherogenic. (2, 7)

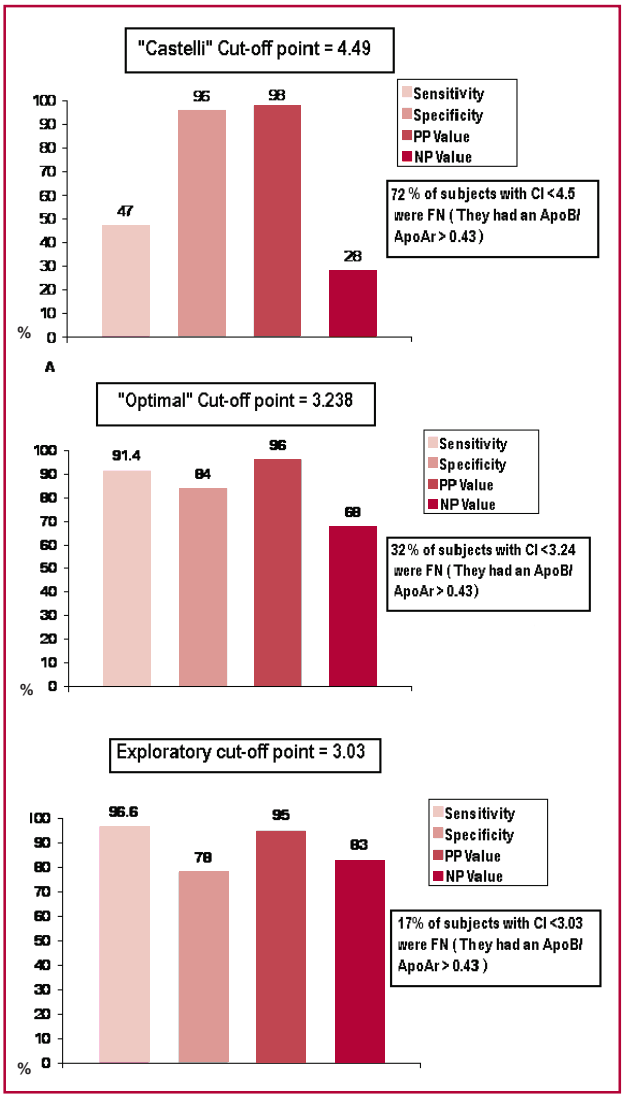

Fig 4. Sensitivity, specificity, positive predictive value (PP) and negative predictive value (NP) of CI to identify individuals with ApoB/ApoAr > 0.43. A. Historical cut-off point (4.5). B. Optimal cut-off point (3.24). C. Exploratory cut-off point (3.03).

In the lipidic subanalysis of the INTERHEART study, median of the decile 1 of the ApoB/ApoAr associated with lower risk of myocardial infarction (odds ratio 1) corresponded to 0.43 and showed a gradual and progressive increase in risk with increasing deciles of this ratio. (7) In a recent work by our group, we described the distribution of apolipoproteins in a healthy population of our environment. In this study, the percentile 20 of the ApoB/ApoAr corresponded to 0.46, very close value to decile 1 of the INTERHEART study. (19)

25 years ago, Dr. William Castelli recommended a target of TC / HDL <4.5, value that is still applied today. The "Castelli Index" was associated with likelihood ratios of 17.11 and 20.41 for men and women, respectively, and it was considered an excellent marker of coronary risk. (1) Recently, a retrospective analysis of the EPIC confirmed the independent predictive value of CI. (20)

TC/HDL reflects the same pathophysiological mechanisms that ApoB/ApoAr; however, the INTERHEART study showed categorically that ApoB/ ApoAr is a better marker of cardiovascular risk than CI. (7) In this study, the historical cut-off point value of 4.5 CI corresponded approximately to decile 5 and it was associated with an increased risk above 50% with regard to decile 1. In the INTERHEART study involved 3,125 Latin American subjects and included 412 Argentinians. In the Latin American cohort was showed that the change in 1 SD of the ApoB/ApoAr was associated with a significant increase in risk of MI (OR 1.27 [95% CI 1.17-1.38]), while the increase of 1 SD of the CI did not add prognostic information (OR 0.97 [95% CI 0.90-1.05]). (21) A recent subanalysis VA-HIT (Veterans Affairs High-Density Lipoprotein Intervention Trial) also showed a stronger relationship with the risk of coronary events of Apo/ApoAr than which was observed with the CI. (22)

These differences could be established for the greater precision of ApoB levels compared to those of TC to estimate the number of atherogenic particles and because the concentrations of ApoA better reflect the functionality of HDL than simply measuring HDL-C. (23)

Apolipoprotein measurement requires rigorous methods of quality control, precision and accuracy. (8, 9) It is a technique that involves higher operating costs than the measurement of TC and HDL-C. Therefore, to determine a cutoff point updated of the CI that allows us to identify subjects with a ApoB/ ApoAr associated with very low risk it has clinical and economic implications.

In our study, the area under the ROC curve of the CI to distinguhish between individuals with ApoB/ ApoAr ≤0.43 or >0.43 was greater than 0.9, which indicates a high accuracy. The OCP of 3.24 had high sensitivity and specificity. The PPV was 96%, which means that most patients with CI> 3.2 had a ApoB/ ApoAr > 0.43. The NPV was slightly lower, which indicated that 68% of subjects with CI <3.24 also had a ApoB/ ApoAr of low risk. An exploratory cutoff point value of 3 increases sensitivity to 97% and NPV to 83%, which means greater security as well as to corroborate low risk and obtain a challenging target in medicated patients. These results are superior to those obtained using the historical cutoff point of 4.5, which showed a low sensitivity and NPV for the diagnosis of a ApoB/ ApoAr <0.43 less than 30%.

Limitations

We consider the possibility that the sample analyzed in this study was not representative of the population of the city of Buenos Aires. To clarify this doubt, we compared the lipidic values of our population with those published by researchers at the CARMELA study in a population of 1,482 individuals. The mean levels of

TC 201 mg / dl, HDL-C 52.5 mg / dl, triglycerides 114.3 mg / dl and 4.1 CI showed no significant differences with those obtained in our study. (24)

CONCLUSIONS

These results suggest that historic goal of the Castelli index should be reviewed and updated at <3.25.

Clinical Implications

The use of this new cutoff point would allow us to identify subjects with very low cardiovascular risk and adjust the therapeutic goal in pacients treated with lipid-lowering drugs. The measurement of TC and HDL-C is accessible and affordable, therefore, the CI may be used in most medical centers in our country.

RESUMEN

Correlación entre las razones apolipoproteína B/ apolipoproteína A1 y colesterol total/colesterol-HDL en una población saludable: ¿debería actualizarse el índice de Castelli?

Introducción

La razón colesterol total/colesterol-HDL (rCT/HDL) fue propuesta como marcador de riesgo coronario hace aproximadamente 25 años por el Dr. William Castelli y la meta sugerida fue < 4,5. El estudio INTERHEART demostró que la rApoB/ApoA es un predictor de eventos cardiovasculares superior a la rCT/HDL. Muchos laboratorios de nuestro país no disponen de la tecnología para medir apolipoproteínas con precisión.

Objetivo

Determinar valores de rCT/C-HDL o índice de Castelli (IC) correspondientes al decil 1 de la rApoB/ApoA (0,43, odds ratio 1) del estudio INTERHEART, identificar el punto de corte óptimo (PCO) del IC que discrimine entre sujetos con una rApoB/ApoA ≤ 0,43 y > 0,43 y proponer una meta actualizada del IC.

Material y métodos

Los niveles de apolipoproteínas se midieron por inmunonefelometría en muestras obtenidas de donantes de sangre. Se confeccionaron modelos de regresión lineal simple para examinar la relación entre las razones ApoB/ApoA y CT/HDL. Se efectuó un análisis ROC para evaluar la precisión del IC para discriminar entre sujetos con rApoB/ApoA ≤ 0,43 y > 0,43. Los sujetos con hipertensión, enfermedad vascular, diabetes o tratados con hipolipemiantes fueron excluidos.

Resultados

Se incluyeron 283 sujetos, 64% hombres, 31% fumadores. Características generales (media ± DE): edad 41,8 ± 14 años, IMC 26,2 ± 4, CT 199,5 ± 48 mg/dl, HDL 49 ± 13 mg/dl, IC 4,31 ± 1,3, ApoB 95,2 ± 28 mg/dl, ApoA 157,4 ± 32 mg/dl, rApoB/ApoA 0,62 ± 0,21. En la población total, la correlación entre la rApoB/ApoA y el IC fue de 0,90 y la rApoB/ApoA de 0,43 correspondió a un IC de 3,22. El área bajo la curva ROC del IC para discriminar entre sujetos con una rApoB/ApoA ≤ 0,43 y > 0,43 fue de 0,936 (IC 95% 0,897-0,975) y el PCO fue de 3,238.

Conclusiones

Estos resultados sugieren que la meta del IC se debería revisar y actualizar a < 3,25.

Palabras clave > Índice de Castelli - Apolipoproteínas – Riesgo

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Statement of conflict of interests

The authors declare that they do not have conflict of interests.