Total cholesterol in dyslipidemias

Is it a useful measure?

LAUREN SOFÍA CALVO-BETANCOURT, DIEGO JOSÉ ARDILA-ARDILA, ÁNGEL GARCÍA-PEÑA, ÓSCAR MAURICIO MUÑOZ-VELANDIA, ÁLVARO J. RUIZ • BOGOTÁ, D.C. (COLOMBIA)

DOI: https://doi.org/10.36104/amc.2019.1320

Abstract

Introduction: the relationship between lipid fractions and cardiovascular risk is clear. However, the operational characteristics of total cholesterol (TC) for the diagnosis of dyslipidemias due to elevated LDL cholesterol (LDLC), hypertriglyceridemia and low HDL cholesterol (HDLC) are not clear. s

Objective: to establish the sensitivity (Sen) specificity (Spe) and predictive values (PPV and NPV) of TC (>200 mg/dL) for diagnosing various types of dyslipidemias.

Materials and methods: a study of diagnostic tests using all the lipid profiles processed at the Hospital Universitario San Ignacio in Bogotá (Colombia) from January 2006 to January 2017. Sensitivity, Spe, PPV and NPV were calculated for each dyslipidemia and for each LDLC goal.

Results: in 25,754 profiles, the average age was 53.6±18 years. The prevalence of elevated LDLC (based on the goals of 160, 130, 100, 70 or 55 mg/dL) was: 19.9%, 44.5%, 72.7%, 92.1% and 96.8%, respectively; for hypertriglyceridemia (>150 mg/dL) it was 44.7%, and for low HDLC (< 40 mg/dL) it was 33.9%. The sensitivity of TC (>200 mg/dL) for elevated LDLC according to the same goals was: 100%, 95%, 70%, 56% and 53%, with a specificity of: 59%, 81%, 94%, 95% and 92%; PPV=37%, 80%, 97%, 99% and 99%; and NPV=100%, 95%, 54%, 15% and 5.8%. For hypertrygliceridemia: Sen=61%, Spe=61%, PPV=55% and NPV=66%. For low HDLC: Sen=36%, Spe=42%, PPV=26% and NPV=54%.

Conclusions: given the operational characteristics of TC>200 mg/dL, it should not be used as an isolated tool for diagnosing dyslipidemia due to LDLC, HDLC or hypertriglyceridemia. **(Acta Med Colomb 2019; 44. DOI: https://doi.org/10.36104/amc.2019.1320).**

Key words: *dyslipidemias, diagnosis, cholesterol, LDL cholesterol, sensitivity and specificity.*

Dra. Lauren Sofía Calvo-Betancourt: Residente de Medicina Interna; Dr. Diego José Ardila-Ardila: Internista-Cardiólogo. Especialista en Hemodinamia; Dr. Ángel García-Peña: MSc, PhD(c) Internista-Cardiólogo; Dr. Óscar Mauricio Muñoz-Velandia: MSc, PhD. Internista-Epidemiólogo Clínico; Dr. Álvaro J. Ruiz: MD, MSc, FACP. Internista, Epidemiólogo Clínico, Profesor Titular. Pontificia Universidad Javeriana, Hospital Universitario San Ignacio. Bogotá, D.C. (Colombia).
Correspondencia: Dra. Lauren Sofía Calvo Betancourt, Bogotá, D.C. (Colombia).
E-mail: lscalvo@husi.org.co
Received: 17/III/2019 Accepted: 9/X/2019

Introduction

Coronary heart disease is the leading cause of death worldwide, and Colombia is no exception. The data show that in Colombia in 1990, there were 25,312 deaths due to coronary heart disease; in 2003, this number increased to 37,481 (1).

Several factors have been associated with the development of coronary heart disease, mainly dyslipidemia. Lipid profile alterations have been described that are associated with increased cardiovascular risk, such as elevated LDL cholesterol (LDL-C), triglyceride, or non-HDL cholesterol levels and low HDL cholesterol (HDL-C) levels (2).

Several clinical practice guidelines have identified LDL-C as the main target for cholesterol reduction therapy based on robust scientific evidence that shows that LDL-C plays a critical role in atherogenesis and in the development and recurrence of coronary artery disease (3-5).

In daily practice, it is common to encounter health professionals who use total cholesterol (TC) as the only diagnostic tool for dyslipidemia. However, given that TC may be elevated due either to elevated LDL-C or to elevated triglycerides, which in both cases indicate an atherogenic profile, or may be elevated due to high HDL-C, which indicates a protective profile, it has been proposed that TC should not be used as the only tool for the evaluation of lipids (5).

Several studies have used TC as a surrogate for LDL-C (6, 7); however, there are no objective data on the operating characteristics of TC for the identification of different types of dyslipidemia. The aim of the present study was to determine the operating characteristics of TC for the diagnosis of hypercholesterolemia (high LDL-C, at different risk levels), hypertriglyceridemia and low HDL-C.

Materials and Methods

A study was conducted of diagnostic tests that included lipid profiles measured from January 2006 to January 2017 at San Ignacio University Hospital in Bogotá (Colombia). Lipid profiles were identified in record systems, and the

results were obtained directly from the hospital's clinical laboratory database. All samples that simultaneously measured TC, HDL-C and triglycerides were included in the study, regardless of the level (even triglycerides > 400 mg/dL). The study was evaluated and approved by the Research and Ethics Committee of Pontifical Javeriana University and San Ignacio University Hospital. It was assumed that the values were profiles of patients who were not take medication; if they were taking medication, it is expected that the operating characteristics would be valid because the relative value of the lipid fractions was evaluated in relation to TC.

Continuous variables are expressed as the mean and standard deviation, and categorical variables are expressed as percentages.

For analysis of the operating characteristics, the sensitivity and specificity of TC > 200 mg/dL were calculated to identify each dyslipidemia, as well as the positive and negative predictive values, according to the prevalence found for each dyslipidemia. The statistical package Stata 14.0® was used (*Release 14, 2015. StataCorp LP, College Station, TX*).

Results

A total of 25,754 tests were analyzed. The mean age of the patients was 53.6 ± 18 years, and 53.8% were women. The most frequent abnormality in the population was hypercholesterolemia (TC >200 mg/dL), 50%, followed by hypertriglyceridemia, 45% (Table 1). Forty-five percent had LDL > 130 mg/dL.

Table 2 shows the operating characteristics of TC levels for the diagnosis of the different types of dyslipidemia. As expected, the sensitivity decreases and the specificity increases as lower values are used to define LDL hypercholesterolemia. Using a cutoff point of TC >200 mg/dL, the sensitivity to detect patients with LDL-C >160 mg/dL was 100%, with a specificity of 59%. In contrast, if hypercholesterolemia was defined as LDL-C values above 100 mg/dL, the specificity was 94%, but the sensitivity was reduced to 70%.

For hypertriglyceridemia, both the sensitivity and the specificity of TC >200 mg/dL for the detection of triglycerides [TAGs] >150 mg/dl were 61%, and for the detection of HDL < 40 mg/dL, the sensitivity was 36%, and the specificity was 42%.

Discussion

In the present study, we demonstrated that TC should not be used as an isolated tool for the diagnosis of dyslipidemia. In fact, our data show that the sensitivity, specificity and predictive values change significantly depending on the operating definition of LDL-C hypercholesterolemia used. Additionally, we found that the sensitivity and specificity values of TC to detect low HDL dyslipidemia or hypertriglyceridemia are very low.

The implications of these findings in daily clinical practice are evident. Different management guidelines, including both national (8, 9) and international (10, 11) guidelines, recommend, for patients in primary prevention, the initiation of pharmacological management depending on the cardiovascular risk of each patient at 10 years. Using only a TC level > 200 mg/dL to make this decision does not allow identifying the highest risk patients, in whom the LDL-C levels at which the initiation of treatment is indicated are lower or the management goals may vary. For example, European guidelines for the management of dyslipidemia (10) recommend considering management with statins, seeking a 50% reduction when patients in primary prevention, at very high risk, have LDL-C values between 70 and 135 mg/dL, but recommend different goals (LDL-C <70 mg/dL) when the initial LDL-C value is >135 mg/dL.

Similarly, Colombian guidelines (8, 9) recommend considering pharmacological treatment in primary prevention for patients with LDL-C > 160 mg/dL. Our data allow us to quantify this impact, demonstrating, for example, that when defining hypercholesterolemia as LDL-C of 70 mg/dL, the sensitivity is only 56%, which implies that 44% of patients with values higher than this level would not be identified by the test. Likewise, it is worth highlighting the low specificity of the test (59%) to detect values greater than 160 mg/dL, which would imply that in many cases, pharmacological management would be indicated to patients who probably do not require it, given that the elevated TC values would be associated with an elevation of lipid fractions different from LDL-C.

These conclusions had already been suggested in a previous study in which TC was used to stratify cardiovascular risk, finding that its isolated measurement incorrectly classified 48% of the subjects (12). Several studies have shown a 15-30% reduction in cardiovascular events by achieving reductions in the LDL-C fraction (13, 14); however, reducing TC has not generated these benefits. Recently, focus has been directed toward not only reducing LDL-C but also reducing non-HDL cholesterol and increasing protective fractions, with this strategy demonstrating a greater benefit in reducing cardiovascular events compared to the single-focus approach (15). However, none of these approaches

Table 1. *Frequency of lipid profile abnormalities.*

	%	n
Total cholesterol >200 mg/dL	49.5	12,759
HDL-C < 40 mg/dL	33.9	8,748
LDL-C (mg/dL)		
>160	19.9	4,050
>130	44.5	9,055
>100	72.7	14,804
>70	92.19	18,757
> 55	96.8	19,732
Triglycerides > 150 mg/dL	44.71	11,514

Table 2. *Operating characteristics of total cholesterol.*

		LDL-C mg/dL					HDL-C mg/dL	Triglycerides mg/dL
		>160	>130	>100	>70	>55	<40	>150
Total cholesterol >200 mg/dL	SS (%)	100	95	70	56	53	36	61
	SP (%)	59	81	94	95	95	42	61
	PPV (%)	37	80	97	99	99	26	55
	NPV (%)	100	95	54	15	5.8	54	66

have the objective of reducing TC levels, which reinforces what was proposed in our study.

In our population, we found findings similar to those reported by Galvis et al. (16), who found that the most frequent alteration was total hypercholesterolemia, followed by hypertriglyceridemia and the presence of an LDL-C >130 mg/dL; the latter is the suggested goal for the LDL-C level in patients without cardiovascular risk factors (17), which would imply that almost half of our population would require initiation or intensification of statin therapy. It is worth clarifying that San Ignacio University Hospital is a referral institution where mainly patients with manifest atherosclerotic disease are treated; therefore, the prevalence of dyslipidemia may be biased and significantly higher than that of the general population.

The main strength of this study is the sample size, considering that more than 25,000 lipid profile measurements were considered, which allows a very accurate estimate of the sensitivity, specificity and predictive values of TC. However, there are some limitations that must be taken into account: having included in the analysis patients with triglyceride values above 400 mg/dL, in whom Friedewald's formula produces an inaccurate estimate of LDL-C, can generate a biased calculation of the operating characteristics of TC for the diagnosis of dyslipidemia. However, the proportion of patients with this characteristic was low (6.29%), and this way of using the data represents the conditions in which the test is used in daily practice.

An additional limitation is the lack of data on the individual clinical characteristics of the patients, which did not allow us to perform subgroup analyses of primary and secondary prevention patients.

Conclusion

Given the operating characteristics of TC, it should not be used as an isolated tool for the diagnosis of LDL-C or HDL-C dyslipidemia and much less for hypertriglyceridemia, for which the operating characteristics of the test were the lowest. Therefore, a complete measurement of the lipid profile and each of its subfractions should be conducted in order to properly select patients for whom pharmacological treatment is indicated as well as to determine the management goals for each.

References

1. **Ruiz Á.** Dislipidemias y riesgo cardiovascular: ¿Tiempo para un nuevo enfoque en lípidos? Dyslipidemias and cardiovascular risk: time for a new appoach to lipid disorders? *Rev Colomb Cardiol*. 2009;**16(5):**214-220. http://www.scielo.org.co/pdf/rcca/v16n5/v16n5a4.pdf.
2. **Graham I, Cooney M-T, Bradley D, Dudina A, Reiner Z.** Dyslipidemias in the Prevention of Cardiovascular Disease: Risks and Causality. *Curr Cardiol Rep*. 2012;**14(6):**709-720. doi:10.1007/s11886-012-0313-7
3. **Howard B V, Robbins DC, Sievers ML, et al.** LDL cholesterol as a strong predictor of coronary heart disease in diabetic individuals with insulin resistance and low LDL: The Strong Heart Study. *Arterioscler Thromb Vasc Biol*. 2000;20(3):830-835. http://www.ncbi.nlm.nih.gov/pubmed/10712410. Accessed December 2, 2018.
4. **Cannon CP, Braunwald E, McCabe CH, et al**. Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes. *N Engl J Med*. 2004; **350(15):** 1495-1504. doi:10.1056/NEJMoa040583
5. **Report F.** National Cholesterol Education Program Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Arch Intern Med*. 2002; **151(6):** 1071. doi:10.1001/archinte.1991.00400060019005
6. **Wilson P W et al.** Prediction of Coronary Heart Disease Using Risk Factor Categories. *Circulation*. 1998; **97(18):** 1837–1847.
7. **Nagasawa S, Okamura T, Iso H, et al.** Relation between serum total cholesterol level and cardiovascular disease stratified by sex and age group: a pooled analysis of 65 594 individuals from 10 cohort studies in Japan. *J Am Heart Assoc*. 2012; **1(5):** e001974. doi:10.1161/JAHA.112.001974
8. **Muñoz O, Garcia Á.** Guía de práctica clínica para la prevención , detección temprana , diagnóstico , tratamiento y seguimiento de las dislipidemias en la población mayor de 18 años. *Acta Médica Colomb*. 2014; **39(2):** 5-27.
9. **Adulto CDEL.** Cardiología. 2015; **22(1):** 14-21.
10. **Catapano AL, Graham I, De Backer G, et al.** 2016 ESC/EAS guidelines for the management of dyslipidemias. *Rev Esp Cardiol*. 2017; **70(2):** 115.e-115.e. doi:10.1016/j.recesp.2016.11.052
11. **Stone NJ, Robinson JG, Lichtenstein AH, et al**. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American college of cardiology/American heart association task force on practice guidelines. *J Am Coll Cardiol*. 2014; **63**(25 PART B): 2889-2934. doi:10.1016/j.jacc.2013.11.002
12. **Branchi A, Rovellini A, Fiorenza AM, et al.** Estimation of cardiovascular risk: total cholesterol versus lipoprotein profile. *Int J Clin Lab Res*. 1994;**24(2):**106-112. http://www.ncbi.nlm.nih.gov/pubmed/7919426. Accessed December 2, 2018.
13. **LaRosa JC, Grundy SM, Waters DD, et al.** Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *Nejm*. 2005; **352:** 1425-1435. doi:10.1056/NEJMoa050461
14. **Cannon CP, Braunwald E, McCabe CH, et al.** Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes. *N Engl J Med*. 2004; **350(15):** 1495-1504. doi:10.1056/NEJMoa040583
15. **Zhao X-Q, Phan BAP, Davis J, et al.** Mortality reduction in patients treated with long-term intensive lipid therapy: 25-year follow-up of the Familial Atherosclerosis Treatment Study-Observational Study. *J Clin Lipidol*. 2016; **10(5):** 1091-1097. doi:10.1016/j.jacl.2016.06.013
16. **Galvis Y, Barona J, Cardona J.** Prevalencia de dislipidemias en una institución prestadora de servicios de salud de Medellín (Colombia), 2013. *Rev CES Med*. 2016; **30(1):** 3-13. doi:10.21615/ces med.v30i1.3166
17. **Jellinger PS, Handelsman Y, Rosenblit PD, et al.** 1 CPG for Managing Dyslidemia and Prevention of CVD. *Endocr Pract*. 2017; **23(2)**. doi:10.4158/EP171764. APPGL

CC BY