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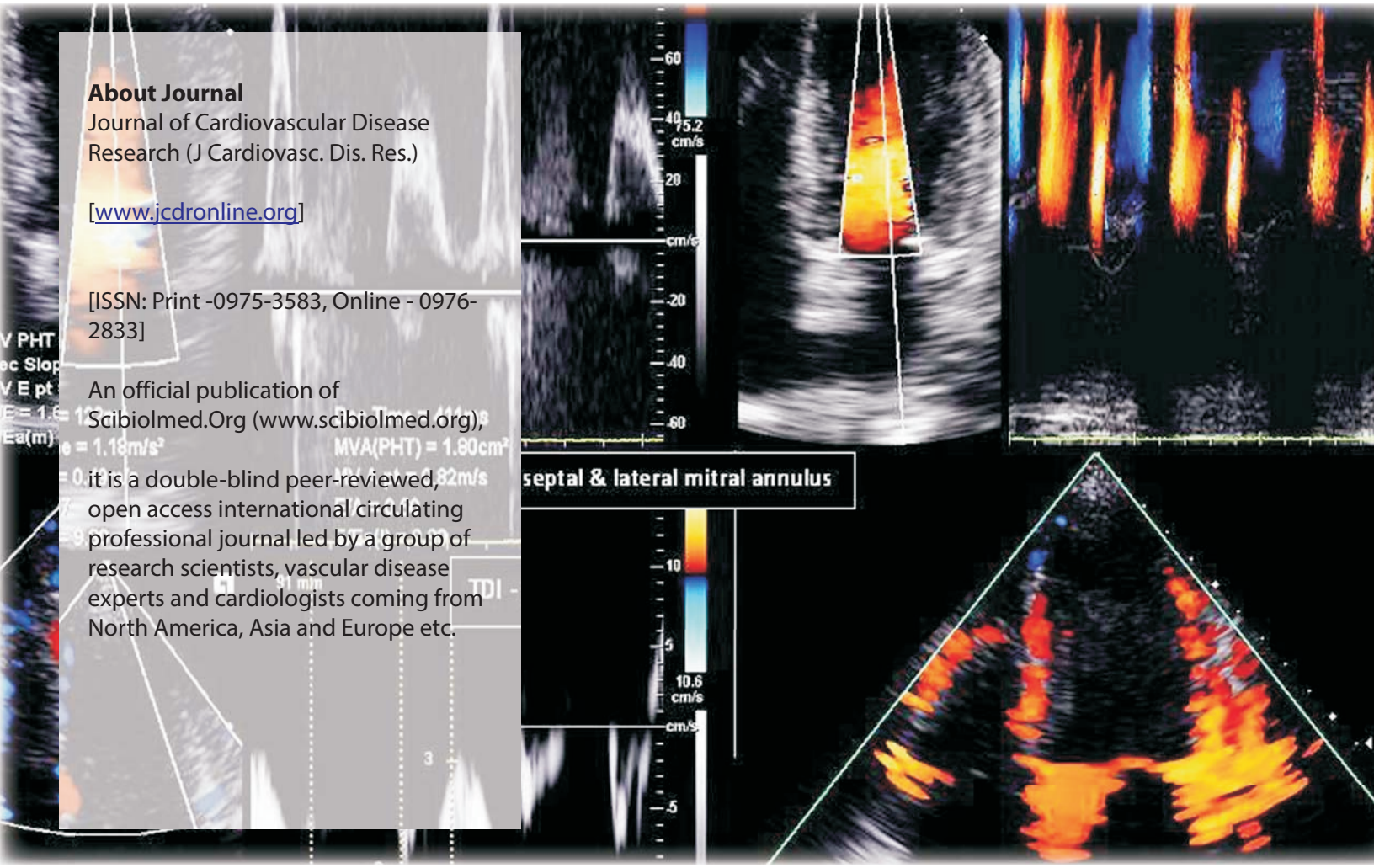

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Original Article

Castelli Index and estimative of LDL-c particle size may still help in the clinical practice?

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ABSTRACT

Background: There are many factors affecting the maintenance of a healthy in the population without coronary artery disease as plasmatic lipids and anthropometric parameters. This study aimed to evaluate the correlation between the Castelli Index I, Castelli Index II and the estimated size of the LDL-c particle with the presence of Coronary Artery Disease risk factors in patients undergoing coronary angiography.

Methods: Anthropometric (waist circumference and body mass index) and biochemical parameters (glycaemia, total cholesterol, triglycerides, LDL-c, HDL-c and high sensitivity C-reactive protein) from 95 patients undergoing coronary arteriography were collected. Castelli Index I (TC/HDL-c), Castelli Index II (LDL-c/HDL-c) and the estimate of LDL particle size (TG/HDL-c) were calculated.

Results: Our findings show that, in general, for abnormal values of the three rations cited above, there was a positive correlation with increased levels of serum lipids and that there are high percentages of subjects with increased values of WC, BMI and hsCRP and also the presence of MS, physical inactivity and family story of heart disease. Most patients with severe lesions in the arteries presented altered Castelli Index II and small dense LDL-c particle.

Conclusion: The use of these tree ratios may represent simple parameters for estimating cardiovascular risks patients with heart disease diagnosis in order to work on secondary prevention.

Key words: HDL-c, LDL-c, Triglycerides, Total Cholesterol, Coronary Angiography.

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INTRODUCTION

Cardiovascular disease (CAD) is a serious public health problem in both sexes worldwide. It is strongly associated to the Metabolic Syndrome (MS) that comprises a number of risk factors that plays a fundamental role in high morbidity. MS is usually manifested by insulin resistance and modifications in the reference ranges HDL-c and triglycerides (TG), waist circumference (WC), blood pressure, C-reactive protein (CRP) and obesity. This last condition is characterized by high levels of pro inflammatory mediators.[1–3] Plasma lipids play direct importance in the prevention of cardiovascular comorbidities. As a result, they have become therapeutic targets for minimizing the potential risks. Dyslipidemia is associated with reduced HDL-c levels and LDL-c particle size. The small dense LDL-c particles (sdLDL-c) are related to the formation of atherosclerotic plaques because of the reduction of the affinity with the LDL-c receptor and increased possibility of being incorporated in the intima of the vessel. Some authors have been using the Castelli Index I and II index (which respectively relate to the ratio Total Cholesterol (TC/HDL-c and LDL-c/HDL-c) in addition to estimate of LDL-c particles (TG/HDL-c) to assist in the assessment of cardiovascular risk.[1,4-9]

The biomarkers have been extensively studied as potential CAD risk factors and can be considered in the clinical stratification of these diseases. Calculated indexes obtained from laboratory measurements and the evaluation of plasma biomarkers are commonly used in CAD risk assessment.[10] Based on these assumptions, this study aimed to evaluate the correlation between the Castelli Index I (CI-I), Castelli Index II (CI-II) and the estimated size of the LDL-c particle with the presence of CAD risk factors in patients undergoing coronary angiography.

METHODS

Ethical Principles

This study was approved by the Ethics Committee of the University of Marilia (Protocol 449/Record 25000.113733/2010–14) and began only after the participants signed a Free and Informed Consent Form (Resolution 196/10 of October 1996–National Health Council–CNS). The procedures used during the experimental protocol followed the ethical standards of the Institutional Ethics Committee and the Helsinki Declaration of 1975, revised in 2008.

Subjects: data collection

The patients were 54 men and 43 women (aged from 36 to 88 years old) undergoing coronary arteriography. After signing the Free and Informed Consent, they answered a questionnaire on socioeconomic data, family history of CAD, smoking and alcohol habits, physical activity and use of statin. Blood pressure (BP), waist circumference (WC) and body mass index (BMI) were also evaluated.

Blood was obtained to determine glycaemia, triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c) and hs-CRP (high sensitivity C-reactive protein). The blood was drawn when the patient was already catheterized for the angiography procedure. The exams were performed after the protocol of the São Francisco Laboratory at the University

Hospital, University of Marilia, SP, Brazil and the results followed Lloyd-Jones *et al.*[11]

The indexes were calculated as follows: TC/HDL-c (CI-I) and LDL-c/HDL-c (CI-II) that advocates normal values respectively when less than 4.4 and 2.9. The estimate of LDL-c particle size (TG/HDL-c) should be higher than 2 mg/dL.[4]

Statistics

Our results were analyzed with the statistical program R version 2.15.2. Qualitative variables were obtained by calculating the absolute and relative frequencies. We used Pearson's chi-square test and Fisher's exact test or its extension for comparison of the categorical variables. A level of significance α of 5% was applied to all the conclusions obtained from the inferential analysis.

RESULTS

Values for IC-I and IC-II were considered altered when higher than, respectively 4.4 and 2.9. The estimate of LDL-c particle size was considered altered when smaller than 2 mg/dL.

There were statistically significant differences between subjects classified as normal and altered CI-I (Table 1) for family story of heart attack, LDL-c, TG and consequently for TC and HDL-c. It is also possible to observe that subjects with increased WC, sedentary, without using statin, with severe lesion in the catheterization report and with MS represented high percentages of altered CI-I.

Table 2 shows significant differences between the group with altered and normal values for CI-II only for family story of heart attack, total cholesterol levels, LDL-c and HDL-c. However, we can see that subjects with increased WC, BMI and hsCRP, with presence of MS, who do not exercise and do not use statin and with severe lesion in the catheterization report present high percentage of altered CI-II.

In Table 3 we can observe that significant differences only for the presence of hypertension, catheterization report (the most serious injuries predominated in individuals with altered TG/HDL-c) and to the levels of HDL-c and LDL-c. It is important to point that patients with increased WC and hsCRP levels and who have MS, do not exercise or use statin were classified as possessing sdLDL-c particle.

Subjects with smoking habits are more likely to exhibit altered values for CI-I, CI-II and sdLDL-c.

Table 1: Characteristics of the patients, according to TC/HDL-c (Castelli Index I)

		TC/HDL-c				
		altered		normal		p
Waist circunference	high	32	80.0%	39	73.6%	0.471[c]
	normal	8	20.0%	14	26.4%	
Physical activity practices	yes	9	21.4%	15	28.3%	0.444[c]
	no	33	78.6%	38	71.7%	
Use of statin	yes	15	39.5%	20	40.8%	0.899[c]
	no	23	60.5%	29	59.2%	
Hypertension	yes	33	78.6%	42	79.2%	0.936[c]
	no	9	21.4%	11	20.8%	
Smoking habit	yes	11	73.8%	12	22.6%	0.688[c]
	no	31	26.2%	41	77.4%	
Family history of heart attack	yes	21	50.0%	14	26.4%	0.018[c]
	no	21	50.0%	39	73.6%	
BMI	normal	12	28.6%	13	24.5%	0.897[c]
	overweight	19	45.2%	26	49.1%	
	obesity	11	26.2%	14	26.4%	
Catheterization report	nolesion	18	42.9%	23	43.4%	0.828[d]
	mild	4	9.5%	4	7.5%	
	moderate	3	7.1%	7	13.2%	
	severe	17	40.5%	19	35.8%	
Presence of plaques	none	18	42.9%	23	43.4%	0.538[c]
	unilateral	8	19.0%	14	26.4%	
	bilateral	11	26.2%	8	15.1%	
	multiple	5	11.9%	8	15.1%	
Procedure	clinical	30	71.4%	41	77.4%	0.738[c]
	surgical	6	14.3%	5	9.4%	
	angioplasty	6	14.3%	7	13.2%	
Total cholesterol	high	27	64.3%	9	17.0%	<0.001[c]
	normal	15	35.7%	44	83.0%	
HDL-c	low	31	73.8%	17	32.1%	<0.001[c]
	normal	11	26.2%	36	67.9%	
Glycemia	normal	18	42.9%	17	32.1%	0.359[c]
	Glucose intolerance	11	26.2%	21	39.6%	
	Diabetes	13	31.0%	15	28.3%	
LDL-c	high	32	78.0%	22	41.5%	<0.001[c]
	normal	9	22.0%	31	58.5%	
TG	high	23	54.8%	7	13.6%	<0.001[c]
	normal	19	45.2%	46	86.8%	
hsCRP (risk)	low	6	14.3%	9	17.0%	0.571[c]
	moderate	14	33.3%	22	41.5%	
	high	22	52.4%	22	41.5%	
Metabolic syndrome	yes	39	92.9%	45	84.9%	0.336[d]
	no	3	7.1%	8	15.1%	

[c]Pearson's chi-square test; [d]Extension of Fisher's exact test. *BMI: body mass index; †hsCRP: high sensibility C reactive protein.

DISCUSSION

Several factors may influence the occurrence of cardiovascular disease (CAD) as smoking, obesity, physical inactivity, high levels of total cholesterol and low levels of HDL-c, high blood pressure and insulin resistance. These factors account for 61% of CAD deaths and more than 75% of deaths resulting from ischemic and hypertensive heart diseases.[11-13]

There is a consensus in the literature that the management of hyperlipidemia should be done in order to prevent CAD but many doubts about the association of the lipids have yet to be solved. As pointed before, CI-I and CI-II and the ratio TG/HDL-c may assist in vascular risk assessment since they are important predictors of acute myocardial infarction. The presence of sdLDL-c is related to the development of atherogenesis due to its low affinity for LDL-c receptors and greater susceptibility to peroxidation.[4,5,7,8,14,15]

Our results show that, in general, for abnormal values of the three ratios cited above, there was a positive association with increased levels of serum lipids and that there are high percentages of subjects with increased WC, BMI and hsCRP and also the presence of MS, physical inactivity and family story of heart disease. Most patients with severe lesions in the arteries presented altered CI-II and sdLDL-c. Vieira *et al.*[15] found similar results. Piotrowicz *et al.*[13] also found high percentages of obesity, high LDL-c values and family history in patients with cardiovascular risk.

The increase in BMI and WC is related to CAD due to the production of inflammatory mediators such as interleukin-6, adiponectin, inhibi-

Table 2: Characteristics of the patients, according to LDLc/HDL-c (Castelli Index II)

		LDL-c/HDL-c				
		altered		normal		p
Waist circunference	high	22	78.6%	48	75.0%	0.712[c]
	normal	6	21.4%	16	25.0%	
Physical activity practices	yes	9	30.0%	15	23.4%	0.496[c]
	no	21	70.0%	49	76.6%	
Use of statin	yes	10	35.7%	24	41.4%	0.615[c]
	no	18	64.3%	34	58.6%	
Hypertension	yes	23	76.7%	51	79.7%	0.739[c]
	no	7	23.3%	13	20.3%	
Smoking habit	yes	9	70.0%	14	21.9%	0.393[c]
	no	21	30.0%	50	78.1%	
Family history of heart attack	yes	15	50.0%	19	29.7%	0.056[c]
	no	15	50.0%	45	70.3%	
BMI	normal	9	30.0%	16	25.0%	0.683[c]
	overweight	15	50.0%	30	46.9%	
	obesity	6	20.0%	18	28.1%	
Catheterization report	nolesion	11	36.7%	29	45.3%	0.209[d]
	mild	4	13.3%	4	6.3%	
	moderate	1	3.3%	9	14.1%	
	severe	14	46.7%	22	34.4%	
Presence of plaques	none	11	36.7%	29	45.3%	0.735[c]
	unilateral	7	23.3%	15	23.4%	
	bilateral	8	26.7%	11	17.2%	
	multiple	4	13.3%	9	14.1%	
Procedure	clinical	20	66.7%	50	78.1%	0.410[d]
	surgical	4	13.3%	7	10.9%	
	angioplasty	6	20.0%	7	10.9%	
Total cholesterol	high	21	70.0%	15	23.4%	<0.001[c]
	normal	9	30.0%	49	76.6%	
HDL-c	low	22	73.3%	25	39.1%	0.002[c]
	normal	8	26.7%	39	60.9%	
Glycemia	normal	14	46.7%	21	32.8%	0.402[c]
	Glucose intolerance	8	26.7%	24	37.5%	
	Diabetes	8	26.7%	19	29.7%	
LDL-c	high	26	86.7%	28	43.8%	<0.001[c]
	normal	4	13.3%	36	56.3%	
TG	high	13	43.3%	16	25.0%	0.073[c]
	normal	17	56.7%	48	75.0%	
hsCRP (risk)	low	3	10.0%	12	18.8%	0.552[c]
	moderate	12	40.0%	24	37.5%	
	high	15	50.0%	28	43.8%	
Metabolic syndrome	yes	27	90.0%	56	87.5%	>0.999[d]
	no	3	10.0%	8	12.5%	

[c]Pearson's chi-square test; [d]Extension of Fisher's exact test. *BMI: body mass index; †hsCRP: high sensibility C reactive protein.

Table 3: Characteristics of the patients, according to TG/HDL-c

		TG/HDL-c				
		altered		normal		p
Waist circunference	high	52	80.0%	19	67.9%	0.206[c]
	normal	13	20.0%	9	32.1%	
Physical activity practices	yes	16	23.9%	8	28.6%	0.631[c]
	no	51	76.1%	20	71.4%	
Use of statin	yes	25	42.4%	10	35.7%	0.554[c]
	no	34	57.6%	18	64.3%	
Hypertension	yes	57	85.1%	18	64.3%	0.023[c]
	no	10	14.9%	10	35.7%	
Smoking habit	yes	19	71.6%	4	14.3%	0.144[c]
	no	48	28.4%	24	85.7%	
Family history of heart attack	yes	26	38.8%	9	32.1%	0.539[c]
	no	41	61.2%	19	67.9%	
BMI	normal	15	22.4%	10	35.7%	0.298[c]
	overweight	32	47.8%	13	46.4%	
	obesity	20	29.9%	5	17.9%	
Catheterization report	nolesion	26	38.8%	15	53.6%	0.001[d]
	mild	2	3.0%	6	21.4%	
	moderate	7	10.4%	3	10.7%	
	severe	32	47.8%	4	14.3%	
Presence of plaques	none	26	38.8%	15	53.6%	0.249[c]
	unilateral	15	22.4%	7	25.0%	
	bilateral	14	20.9%	5	17.9%	
	multiple	12	17.9%	1	3.6%	
Procedure	clinical	47	70.1%	24	85.7%	0.215[d]
	surgical	10	14.9%	1	3.6%	
	angioplasty	10	14.9%	3	10.7%	
Total cholesterol	high	28	41.8%	8	28.6%	0.226[c]
	normal	39	58.2%	20	71.4%	
HDL-c	low	42	62.7%	6	21.4%	<0.001[c]
	normal	25	37.3%	22	78.6%	
Glycemia	normal	22	32.8%	13	46.4%	0.457[c]
	Glucose intolerance	24	35.8%	8	28.6%	
	Diabetes	21	31.3%	7	25.0%	
LDL-c	high	38	57.6%	16	57.1%	0.969[c]
	normal	28	42.4%	12	42.9%	
TG	high	30	44.8%	0	0.0%	<0.001[c]
	normal	37	55.2%	28	100.0%	
hsCRP (risk)	low	8	11.9%	7	25.0%	0.023[c]
	moderate	22	32.8%	14	50.0%	
	high	37	55.2%	7	25.0%	
Metabolic syndrome	yes	62	92.5%	22	78.6%	0.077[d]
	no	5	7.5%	6	21.4%	

[c]Pearson's chi-square test; [d]Extension of Fisher's exact test. *BMI: body mass index; †hsCRP: high sensibility C reactive protein.

tor of plasminogen activator -1 and tumor necrosis factor α. The imbalance in the release of these chemical mediators associated with physical inactivity changes several factors associated with CAD favoring the development of a low intensity inflammatory process that results in a local immune response characterized by increased production of inflammatory biomarkers as hsCRP and production of free radicals that damage the vascular endothelium. Authors have shown that high levels of hsCRP, regardless of the lipid profile, increase the risk of acute myocardial infarction.[2,16,17]

This protein is produced by the liver and regulated by cytokines IL-1, IL -6 and TNF-α. It may also be produced by adipocytes and increases

in response to active infection or acute inflammation. Moderate increases are associated with chronic inflammatory conditions such as atherosclerosis.[2,3,18-20]

Our results also show that the group with altered TG/HDL-c has higher percentages of subjects with higher values of TC and LDL-c and decreased HDL-c levels. It is also possible to observe that this group presented the higher percentages of arterial severe lesions and higher number of plaques. HDL-c and TG levels and sdLDL-c may be considered independent risk factors for CAD.[4] Vieira *et al.*[15] and Yadav *et al.*[21] showed that triglyceride levels represent a predictor of sdLDL-c, while increased levels of HDL-c are predictive for larger LDL-c particle. Mogarekar, Kulkari[22] suggest that the quality of sdLDL-c is more important than only LDL-c levels. Manabe *et al.*[23] and Nishikido *et al.*[24] found percentages significantly higher of patients with CAD associated with sdLDLc. The sdLDL-c (diameter less than 25.5 nm) is associated with three times higher rate of myocardial infarction.[1-9] Even observing high percentages of individuals possessing dyslipidemia, more than 80% of the patients related lipid lowering treatment.

The use of the ratios proposed by CI-I, CI-II and the estimate of LDL-c particle size may represent simple parameters for estimating cardiovascular risks without worrying with the use and interpretation of logarithms that can become unfeasible in clinical practice. They may also be effective to evaluate the effectiveness of therapies that have been used by the doctor. Besides, they allow the minimization of the high costs that would be required by using specialized techniques and the need of qualified team for performing the logarithms and scores proposed by numerous studies in the literature.

CONCLUSION

It is extremely important to have a complete metabolic profile from patients with heart disease diagnosis in order to work on secondary prevention. Our results show that Castelli Index and the ratio TG/HDL-c are positively associated to modifications in the lipid profile, BMI, WC and hsCRP levels as well as the physical inactivity and the presence of MS. Improvement of these risk factors may provide a better life expectance for the patients.

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CONFLICT OF INTEREST

All authors declare no conflict of interests and no funding supports.

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