The Open Biomarkers Journal
DOI: 10.2174/0118753183290270240319075030, 2024, 14, e18753183290270
ISSN: 1875-3183
1

RESEARCH ARTICLE **OPEN ACCESS**

Can Triglycerides-HDL-C Ratio, HOMA-IR, ApoB, Non-HDL Cholesterol, and Free Cholesterol be Laboratory-Associated Flags of Female Coronary Atherosclerosis Regardless of Being Diabetic?

Leonor Fernandes Teixeira[1], Nadielle Silva Bidu[2], Alysson Luiz Mendes da Silva[2], Gildásio Carvalho da Conceição[3], Daniele Brustolim[2], Roque Aras Junior[4] and Ricardo David Couto[2,5,*]

[1]*Department of Health Science, Medicine Course (Endocrinology), State University of Bahia/UNEB, Salvador, Bahia, Brazil*
[2]*Clinical Biochemistry Laboratory, Department of Clinical and Toxicological Analysis, Faculty of Pharmacy, Federal University of Bahia/UFBA, Salvador, Bahia, Brazil*
[3]*Associação de Pais e Amigos dos Excepcionais de Salvador (APAE-Salvador), Federal University of Bahia, Salvador, Bahia, Brazil*
[4]*Internal Medicine Department (Cardiology), Faculty of Medicine, Federal University of Bahia/UFBA, Salvador, Bahia, Brazil*
[5]*School of Medicine, Centro Universitário de Tecnologia e Ciências (UniFTC), Salvador, Brazil*

Abstract:

Aim: The study aimed to evaluate biomarkers, ratios, and indexes as flags of coronary obstructions in women with established coronary atherosclerotic disease regardless of diabetes.

Methods: A cross-sectional study was conducted on 42 confirmed atherosclerotic coronary female patients, stratified into diabetic or not and scheduled for angioplasty or coronary graft bypass surgery. Blood samples were collected immediately before coronary intervention for laboratory determinations, such as glycemia, HbA1c, insulin, HDL-C, PON-1, free cholesterol, LDL-C, Apo A-1, Apo B, and TG.

Results: In diabetic patients, insulin was positively correlated with triglycerides ($p < 0.0108$; $r = 0.2009$), apo B ($p < 0.0006$; $r = 0.3737$), non-HDL cholesterol ($p < 0.0084$; $r = 0.2156$), and free cholesterol ($p < 0.0084$; $r = 0.3251$). Applying a linear regression model, insulin from diabetic patients showed an association with glycemia, triglycerides, and HOMA-IR ($p < 0.001$, $R^2 = 0.9868$), but in non-diabetics, the association was only found between insulin and HOMA-IR ($p = 0.002$, $R^2 = 0.9031$). On the other hand, using triglycerides as a dependent variable, its association has been found in both groups, but only with HOMA-IR (diabetics: $p = 0.006$, $R^2 = 0.2504$; non-diabetics: $p = 0.014$, $R^2 = 0.4697$). Also, the TG/HDL-C ratio was higher than 2.5 in 90% of diabetics and 83.33% of non-diabetic patients.

Conclusion: The high prevalence of females with a TG/HDL-C ratio above 2.5, the association among insulin, HOMA-IR, and TG/HDL-C, and correlations with apoB, non-HDL-C, and free cholesterol, should be evaluated as flags of female precocious coronary atherosclerosis.

Keywords: TG/HDL-C, Insulin, HOMA-IR, Diabetes, Precocious atherosclerosis, Cholestrol.

*Address correspondence to this author at the Clinical Biochemistry Laboratory, Department of Clinical and Toxicological Analysis, Faculty of Pharmacy, Federal University of Bahia/UFBA, University Campus, Barão de Jeremoabo street, Ondina, Salvador, Bahia, Brazil; Postal Code: 40170-115; Tel/Fax: (+5571) 3283-6952/6900; E-mail: rdc@ufba.br

Cite as: Teixeira L, Bidu N, Mendes da Silva A, Carvalho da Conceição G, Brustolim D, Junior R, Couto R. Can Triglycerides-HDL-C Ratio, HOMA-IR, ApoB, Non-HDL Cholesterol, and Free Cholesterol be Laboratory-Associated Flags of Female Coronary Atherosclerosis Regardless of Being Diabetic?Open Biomark J, 2024; 14: e18753183290270. http://dx.doi.org/10.2174/0118753183290270240319075030

Received: November 08, 2023
Revised: March 03, 2024
Accepted: March 06, 2024
Published: March 28, 2024

1. INTRODUCTION

Diabetes is a syndrome characterized by high glycemic levels that promote significant pathophysiological metabolic changes [1]. Atherosclerotic Cardiovascular Disease (ASCVD), the main cause of morbidity and mortality in people with Diabetes Mellitus (DM), may promote or be favored by free cholesterol deposited into the vessels' walls. The high levels of glycemia and insulin resistance are associated with negative impacts on High-density Lipoprotein (HDL), reverse cholesterol transport, and antioxidant activity [2-5].

Insulin Resistance (IR) is an impaired biological response to insulin by tissue targets. IR promotes a lipid metabolism modulation resulting in dyslipidemia, characterized by increasing Triglycerides (TG), decreased High-density Lipoprotein Cholesterol (HDL-C), and synthesis of a larger proportion of small and dense Low-density Lipoprotein (LDL) particles (sdLDL) [3, 6]. These three conditions are independent risk factors for Cardiovascular Disease (CVD), with the risk being increased by two to fourfold in diabetic patients. Regarding the risk stratification, women are more susceptible than men (*i.e.*, three-fold in diabetic women and twice in diabetic men), as shown by the Framingham Heart Study, and the risk is 7.5 times higher in diabetics than in non-diabetic women [3, 7, 8].

The negative correlation between HDL-C levels and the incidence of CVD is already well established and evidenced in different epidemiological studies [9]. The estimation of cardiovascular risk through the use of surrogate markers, as the ratio of carried molecules by lipoproteins, has demonstrated an adequate way to predict risk since isolated markers sometimes do not effectively contemplate it [10]. High plasma TG levels have been reported to be associated with the increased risk of coronary heart disease because of direct TG-rich lipoprotein particles' atherogenic effect, especially on Intermediate-density Lipoproteins (IDLs). When high levels of TG are associated with low HDL-C, coronary atheromas are more extensive than those initiated exclusively by isolated high concentrations of Low-density Lipoprotein Cholesterol (LDL-C) [11]. Consequently, the TG/HDL-C ratio, an independent predictor of cardiovascular disease, has been considered to estimate cardiovascular risk because it is a non-invasive accurate means for coronary disease detection, predicting its presence and extension [12, 13].

The investigation and a better understanding of lipoprotein metabolism kinetics in pathological conditions, such as coronary artery disease, can contribute to the management of diabetic patients with atherosclerotic and cardiovascular unfavorable conditions. This article aimed to evaluate if the prevalence of a TG/HDL-C ratio above 2.5 and the association of insulin and HOMA-IR with TG/HDL-C, apoB, non-HDL, and free cholesterol correlations can be flags of coronary obstructions among other biomarkers in women with established coronary atherosclerosis regardless of diabetes.

2. MATERIALS AND METHODS

A cross-sectional study was carried out on 42 female patients, 41 to 75 years old, with cardiac catheterization confirmed coronary atherosclerotic disease, who had been scheduled for vascular angioplasty or coronary by-pass surgery at the Ana Nery Hospital, SESAB/UFBA, Salvador, Bahia, Brazil. The participants were selected by convenience sampling and were only included in the study if they signed a free, prior, and informed consent to participate. This study was approved by the Research Ethics Committee of the Ana Nery Hospital, letter no. 83/11, CEAA number 71148023.3.0000.0045 (November 28th, 2011).

Blood samples of each patient were collected before the interventional procedure. The samples were analyzed at the Clinical Biochemistry Laboratory, Faculty of Pharmacy, Federal University of Bahia (UFBA). The following biomarkers were measured: Total Cholesterol (TC), HDL-C, non-HDL-C (n-HDL-C), LDL-C, insulin, TG, Paraoxonase-1 (PON1), apolipoprotein A (apoA), apolipoprotein B (apoB), glycated hemoglobin (HbA1c), glycemia, and Free Cholesterol (FC). The HOMA-IR index (homeostasis model assessment – insulin resistance) has been calculated using the following formula: HOMA-IR = [glycemia (mmol/dL) * insulin]/22.5; HDL-C/ApoA, TG/HDL-C ratio, and index (log TG/HDL-C) have also been obtained.

The patients were stratified into two groups: diabetics and non-diabetics. The LDL-C was calculated with Friedewald's formula: LDL-C = cholesterol total – HDL-C – (TG/5) [14]. Body Mass Index (BMI) was calculated as body weight/$(height)^2$, and BMI classification was considered following the World Health Organization (WHO) criteria [15]. The following cutoffs for lipid parameters were used: (a) isolated hypercholesterolemia: serum LDL-cholesterol levels ≥ 160 mg/dL; (b) isolated hypertriglyceridemia: serum triglyceride levels ≥ 150 mg/dL; (c) isolated HDL-C low levels: HDL-cholesterol levels < 50 mg/dL (female level); (d) high TG/HDL-C ratio: TG/HDL-C > 2.5; and (f) HOMA-IR ≥ 2.5 [16-19]. TG/HDL-C values greater than 2.5 in women were considered a risk factor for cardiovascular disease [17].

To achieve a minimum test power of 80%, capable of identifying maximum absolute differences of 7.14 units between the medians, using a paraoxonase reference standard deviation of 10% (for high values compatible with CAD), 42 females were selected to participate in the study. The critical level chosen for significance was 0.05 (5%) for a 95% confidence interval (GraphPad StatMate 2.0).

The data descriptive analysis was performed by using centrality and dispersion estimates to obtain summary measures. After that, a normality test D'Agostino-Pearson was performed, followed by Pearson's linear correlation to determine the association between insulin and the other biomarkers determined. The outlier detection was done by using Grubb's test. To compare biochemistry parameters between diabetics and non-diabetic patients, the two-sample t-test was used, and a linear regression was

performed to obtain possible associations among insulin and glycemia, TG, and HOMA-IR; and TG and glycemia and HOMA-IR. Also, a linear correlation was made of TG/HDL-C ratio and log TG/HDL-C index with insulin and HOMA-IR. Data analysis was considered significant when the obtained differences showed critical levels (p) less than 5% ($p < 0.05$) for a 95% confidence interval. For the statistical tests, the Stata 14.2 software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP), GraphPad InStat v.3.05, and GraphPad Prism 5.01 software (GraphPad Software, Inc., CA, USA) were used.

3. RESULTS

42 coronary atherosclerotic female patients with a mean age of 59.64 (± 8.05) were conveniently included in the study. 30 (71.43%) of the patients were diabetic (diabetes mellitus type 2), and 12 (28.57%) were non-diabetics. None of the patients showed low weight or class III obesity (BMI ≥ 40.0 kg/m2). Table 1 shows the patient's demographics and clinical and behavioral characteristics.

Table 2 shows the glycemia, insulin levels, and Insulin Resistance index (HOMA-IR) of the participating patients.

The general prevalence of isolated hypercholesterolemia, hypertriglyceridemia, and low HDL-C levels is shown in Table 3.

Insulin was found to be positively correlated with triglycerides, apoB, non-HDL cholesterol, and free cholesterol (non-esterified cholesterol) in diabetics (Table 4). Insulin was not significantly correlated with the other biomarkers tested in the diabetics and with all other biomarkers in the non-diabetics.

In a linear regression model with insulin as a dependent variable, the levels of glycemia, triglycerides, and HOMA-IR in diabetics were found to be associated ($p < 0.001$, $R^2 = 0.9868$); however, in non-diabetics, the association was only found between insulin and HOMA-IR ($p = 0.002$, $R^2 = 0.9031$). On the other hand, using triglycerides as a dependent variable, its association was observed only with HOMA-IR in both groups, *i.e.*, diabetics ($p = 0.006$, $R^2 = 0.2504$) and non-diabetics ($p = 0.014$, $R^2 = 0.4697$). The model was selected based on the best coefficient of determination (R^2).

ApoB: apolipoprotein B; n-HDL-C: Cholesterol non-HDL. r: Pearson correlation test, significant at $p < 0.05$ for a 95% confidence interval.

Table 1. Demographic, clinical, and behavioral characteristics of the females with and without diabetes included in the study.

Characteristics	Total	Diabetics	Non-diabetics
	n = 42	n = 30	n = 12
Age (years), mean (± SD)	59.64 (± 8.05)	59.66 (± 7.92)	59.58 (± 8.73)
Body mass index (BMI) (n, %)	-	-	-
Adequate weight[a]	13 (30.95)	9 (30.01)	4 (33.33)
Overweight[b]	13 (30.95)	7 (23.33)	6 (50.00)
Class I obesity[c]	12 (28.58)	10 (33.33)	2 (16.67)
Class II obesity[d]	4 (9.52)	4 (13.33)	0
Smoker (n, %)	-	-	-
Yes	16 (38.10)	11 (36.67)	5 (41.67)
No	26 (61.90)	19 (63.33)	7 (58.33)
Previous AMI[1] (n, %)	-	-	-
Yes	22 (52.38)	16 (53.33)	6 (50)
No	20 (47.62)	14 (46.67)	6 (50)

Note: [1]Before cardiac surgery. [a]BMI 18.5 to 24.9 kg/m^2; [b]BMI 25.0 to 29.9 kg/m^2; [c]BMI 30.0 to 34.9 kg/m^2; [d]BMI 35.0 to 39.9 kg/m^2 [15]. AMI: acute myocardial infarction; BMI: body mass index; n: frequency. All patients used simvastatin as a dyslipidemia treatment, and some of them were using insulin (NPH or regular®) as an antidiabetic drug.

Table 2. Glucose insulin levels and Insulin Resistance index (HOMA-IR) of the participating patients.

Parameters	Diabetics	Non-diabetics
Glycemia (mg/dL), (mean, CI)	137.57 (115.61 – 159.53)	127.8 (85.77 – 169.82)
Insulin (µU/mL), (mean, CI)	9.15 (1.49 – 16.8)	7.64 (1.91 – 13.37)
HOMA-IR (mean, CI)	2.78 (0.20 – 5.35)	2.14 (0.17 – 4.10)
TG/HDL-C ratio	5.03 (4.35 – 5.69)	4.69 (2.22 – 7.15)

Note: CI: confidence interval; IR: insulin resistance. Parameters did not differ significantly (one-sample t-test and Kolmogorov-Smirnov, $p>0.05$). HOMA-IR significance was set at $p = 0.0779$ (insulin resistance cutoff: HOMA-IR ≥ 2.5) [17]. TG/HDL-C ratio higher than 2.5 was 90% prevalent in diabetics and 83.33% in non-diabetics. Diabetic patients were using insulin (NPH or regular®) as an antidiabetic drug.

Table 3. Dyslipidemia parameters and calculated ratios between the studied patient groups.

Classification	Diabetics (n = 30)			Non-diabetics (n = 12)		
	Total n (%)	Previous AMI (n)		Total n (%)	Previous AMI (n)	
		Yes	No		Yes	No
Isolated:	-	-	-	-	-	-
Hypercholesterolemia	2 (6.9)	0	2	0	0	0
Hypertriglyceridemia	9 (31.03)	4	5	2 (18.18)	2	0
HDL-C low levels	25 (86.21)	11	14	10 (90.91)	5	5
LDL-C high levels	1 (3.45)	0	1	0	0	0

Note: AMI: acute myocardial infarction. Sample stratification: diabetics n = 30, non-diabetics n = 12. Isolated hypercholesterolemia: serum LDL-cholesterol levels ≥ 160 mg/dL; isolated hypertriglyceridemia: serum triglyceride levels ≥ 150 mg/dL; isolated HDL-C low levels: HDL-cholesterol levels < 50 mg/dL (female cut-off level) [16, 17, 18]. The non-diabetic patients did not show high levels of total cholesterol and LDL-C.

Table 4. Positive linear correlation of insulin among other biomarkers in diabetic patients.

Variables	Insulin in Diabetic Patients	
	p	*r*
Triglycerides	0.0108	0.2009
ApoB	0.0006	0.3737
n-HDL-C	0.0084	0.2156
Free cholesterol	0.0084	0.3251

4. DISCUSSION

In this study, the relatively young age of patients with coronary diseases stood out, showing the large occurrence of premature atherosclerosis in young women. Premature atherosclerosis is defined as an ischemic cardiovascular event that occurs before 65 years of age in women and 55 years of age in men [18]. The women's natural cardiovascular protection is conferred mostly by estrogen action. However, during the climacteric, a biological phase that starts around 40 years, the ovarian function decreases, reducing estrogen synthesis and influencing cardiovascular protection [19-21]. We noticed a significant percentage of women with previous episodes of acute myocardial infarction among diabetics, which not only corroborates this condition of premature atherosclerosis, but also shows evidence of a more advanced stage.

Other comorbidities, such as being overweight and obesity, also impact atherosclerosis prematurity. Approximately 70% of patients have a BMI over 25 kg/m^2, evidencing overweight and obesity as factors that increase the risk of cardiovascular disease. Obesity and diabetes mellitus, along with metabolic syndrome, are interrelated conditions, with many pathophysiological mechanisms that, in succession, lead to cardiovascular complications [22].

As all patients used simvastatin, the prevalence of isolated high LDL-C levels was low. However, triglyceride levels, which are not affected by that statin, were higher in both groups of patients in the study, being more prevalent in diabetic patients. The dyslipidemia profile was found appropriate for diabetic patients, and interestingly, these alterations were observed just before the onset of diabetes (pre-diabetes patients), being associated with insulin resistance [23].

The higher the insulin concentration, the greater the concentrations of lipoprotein biomarkers conferring cardiovascular risk. Deficiency of adequate cellular insulin signaling, due to absence or resistance, initiates a sequence of enzymatic abnormalities, involving the activity of the enzymes lipoprotein lipase and Cholesteryl Ester Transfer Protein (CETP) in diabetic patients. In the case of the lipoprotein lipase, the enlarged activity promotes an increase in the triglycerides levels [24, 25], and in the case of CETP, the biosynthesis of large and triglycerides-rich VLDL begins, resulting in a more atherogenic small and dense apoB richer LDL [26, 27]. Responsible for the exchange of esterified cholesterol and triglycerides from HDL to LDL in diabetic patients, CETP interferes with the metabolic pathways of free and esterified cholesterol [28].

Insulin Resistance score (HOMA-IR) is considered an independent risk factor of cardiovascular disease in diabetes patients [29]. Considering the cutoff of 2.5 [17], we observed diabetic patients to have a higher risk of developing another cardiovascular episode. Besides, Pivatto *et al.* [30] identified HOMA-IR as the main predictive factor in metabolic syndrome development. So, a more careful follow-up should be conducted for these patients.

Lipid ratios are better predictors of coronary artery disease compared to decreasing lipids evaluation, reflecting the interaction between atherogenic and protector lipid fractions [17, 31]. Particularly, the TG/HDL-C ratio is related to insulin resistance, atherogenesis, evidence of more dense and atherogenic LDL particles (type B lipid profile), arterial stiffness, and acute cardiovascular event in diabetes patients, being an important cardiovascular

risk predictor [12, 28, 31, 32]. In our study, in both groups, we found an elevated prevalence of a high TG/HDL-C ratio with a median higher than 2.5, indicating a lipid profile more atherogenic inclusive in the non-diabetic group. The TG/HDL-C ratio evidenced a higher probability of other cardiovascular episodes.

TG/HDL-C ratio is also an indicator of Insulin Resistance (IR), the main risk factor for the development of diabetes mellitus [12, 24, 33]. So, the ratio may be used as a predictor of incident diabetes mellitus [34]. As we found an elevated TG/HDL-C ratio above the cut-off among non-diabetic patients, the risk of developing diabetes mellitus was higher.

The positive linear correlation between insulin and free cholesterol indicates possible metabolic errors in diabetic patients' lipid enzyme activity, which may increase cardiovascular metabolic risk [26]. In the normal cell signaling response to insulin, degradation of apoB is stimulated [27], although in cases of diabetes, with unsatisfactory insulin response, apoB degradation does not occur as expected. As apoB is constitutive of lipoproteins and inclusive of atherogenic fractions (non-HDL lipoproteins), the high levels are associated with the elevation of cardiovascular risk [30, 35, 36], which explains the obtained correlation between apoB and insulin. The slow apoB degradation is a result of the lipoprotein lipase's decreased activity, which also stimulates VLDL synthesis, promoting an increase in atherogenic lipid fractions and cardiovascular risk [27].

In the diabetic panorama, insulin resistance also involves, as a consequence of the reduction in the ABCA1 activity, decreased HDL protection against atherosclerosis and modified Lecithin-Cholesterol Acyltransferase (LCAT) activity, which esterifies free cholesterol into HDL particles [28, 37, 38]. The alteration of all enzymatic and transfer protein activities observed in diabetic patients results in lipid metabolism and lipoprotein remodeling modifications originating in highly atherogenic lipoprotein particles [27].

CONCLUSION

Our study has evidenced an elevated prevalence of female patients with a high TG/HDL-C ratio and the association between insulin and HOMA-IR regardless of whether they are diabetic or not. The findings of a high prevalence of TG/HDL-C ratio higher than 2.5 and the association of insulin and HOMA-IR with apoB, non-HDL-C, and free cholesterol, should be better evaluated to be used as flags of female precocious coronary atherosclerosis independent of being diabetic. With the use of simvastatin, the prevalence of high levels of isolated LDL-C has been found to be low, with HDL functionality being improved. The use of statins has been found to limit lipoprotein modifications and cardiovascular risk scenarios. Future appropriately designed studies are needed to support the use of surrogate biomarkers in specific at-risk populations in order to achieve a positive clinical outcome.

LIST OF ABBREVIATIONS

DM	=	Diabetes Mellitus
HDL	=	High-density Lipoprotein
HDL-C	=	High-density Lipoprotein Cholesterol
IR	=	Insulin Resistance
ASCVD	=	Atherosclerotic Cardiovascular Disease
CVD	=	Cardiovascular Disease
LDL	=	Low-density Lipoprotein
BMI	=	Body Mass Index
TC	=	Total Cholesterol
CETP	=	Cholesteryl Ester Transfer Protein

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Research Ethics Committee of the Ana Nery Hospital, letter no. 83/11, with CEAA number 71148023.3.0000.0045 (November 28th, 2011).

HUMAN AND ANIMAL RIGHTS

No animals were used that are the basis of this study. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

The participants were selected by convenience sampling and were only included in the study after they signed a free, prior, and informed consent to participate.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

FUNDING

This work was supported by the National Council of Scientific and Technological Development (CNPq – Brazil) and financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES – finance code 001).

CONFLICT OF INTEREST

Dr. Ricardo David Couto is the Associate Editorial Advisory Board member of The Open Biomarkers Journal.

ACKNOWLEDGEMENTS

The authors thank the technical staff for all scientific support and the Coordination of Improvement of Higher Education Personnel – CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil) for the students' fellowships.

REFERENCES

[1] IDF Diabetes Atlas. (10th ed..), Brussels, Belgium: International Diabetes Federation 2021.

[2] American Diabetes Association. Cardiovascular disease and risk management: Standards of medical care in diabetes- 2020. Diabetes Care 2020; 43(S1): S111-34. http://dx.doi.org/10.2337/dc20-S010 PMID: 31862753

[3] Taskinen MR. Quantitative and qualitative lipoprotein abnormalities in diabetes mellitus.Diabetes. American Diabetes Association 1992; pp. 12-7. http://dx.doi.org/10.2337/diab.41.2.S12

[4] Couto RD, Dallan LAO, Lisboa LAF, Mesquita CH, Vinagre CGC, Maranhão RC. Deposition of free cholesterol in the blood vessels of patients with coronary artery disease: A possible novel mechanism for atherogenesis. Lipids 2007; 42(5): 411-8. http://dx.doi.org/10.1007/s11745-007-3041-9 PMID: 17443358

[5] Santos APC, Vieira MS, Deus DF, *et al*. Atherogenic indices and HDL particle size as laboratory parameters to evaluate cardiovascular risk in the presence of dyslipidemia. J Biophys Chem 2014; 5: 24-32. http://dx.doi.org/10.4236/jbpc.2014.52004

[6] Freeman AM, Pennings N. Insulin resistance. StatPearls. Treasure Island (FL): StatPearls Publishing 2021.

[7] Siqueira AFA, Almeida-Pititto B, Ferreira SRG. Cardiovascular disease in diabetes mellitus: Classical and non-classical risk factors. Arq Bras Endocrinol Metabol 2007; 51(2): 257-67. http://dx.doi.org/10.1590/S0004-27302007000200014 PMID: 17505632

[8] Smanio PEP, Carvalho AC, Tebexreni AS, *et al*. Coronary artery disease in asymptomatic type 2 diabetic women: comparative study between exercise stress testing, cardiopulmonary testing and myocardial perfusion scintigraphy with dipyridamole in identifying ischemia. Arq Bras Cardiol 2007; 89(5): 290-7. http://dx.doi.org/10.1590/S0066-782X2007001700003 PMID: 18066448

[9] Semenkovich CF. Insulin resistance and atherosclerosis. J Clin Invest 2006; 116(7): 1813-22. http://dx.doi.org/10.1172/JCI29024 PMID: 16823479

[10] Brites FD, Bonavita CD, De Geitere C, *et al*. Alterations in the main steps of reverse cholesterol transport in male patients with primary hypertriglyceridemia and low HDL-cholesterol levels. Atherosclerosis 2000; 152(1): 181-92. http://dx.doi.org/10.1016/S0021-9150(99)00452-9 PMID: 10996354

[11] Bitzur R, Cohen H, Kamari Y, Shaish A, Harats D. Triglycerides and HDL cholesterol. Diabetes Care 2009; 32(S2): S373-7. http://dx.doi.org/10.2337/dc09-S343 PMID: 19875584

[12] Duarte BBG, Gínez ZI, Duarte GR, Rasgado TE, Vivanco RG, Fuentes PR. The multidisciplinary research group of diabetes, triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) index as a reference criterion of risk for metabolic syndrome (MetS) and low insulin sensitivity in apparently healthy subjects. Gac Med Mex 2017; 153: 140-5.

[13] Luz PL, Favarato D, Junior JRF-N, Lemos P, Chagas ACP. High ratio of triglycerides to HDL-cholesterol predicts extensive coronary disease. Clinics 2008; 63(4): 427-32. http://dx.doi.org/10.1590/S1807-59322008000400003 PMID: 18719750

[14] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18(6): 499-502. http://dx.doi.org/10.1093/clinchem/18.6.499 PMID: 4337382

[15] World Health Organization. Physical status: The use of and interpretation of anthropometry, report of a WHO expert committee. 1995. Available from: https://www.who.int/publications/i/item/9241208546

[16] Ganguli D, Das N, Saha I, *et al*. Association between inflammatory markers and cardiovascular risk factors in women from Kolkata, W.B, India. Arq Bras Cardiol 2011; 96(1): 38-46. http://dx.doi.org/10.1590/S0066-782X2010005000165 PMID: 21180893

[17] Almeida AF, Sena MHLG, Gomes TS, *et al*. TG/HDL-c ratio, anthropometric and biochemical indicators of cardiovascular risk in chronic renal patients undergoing conservative treatment. Nutr Clín Diet Hosp 2017; 37: 10-6. http://dx.doi.org/10.12873/374fortes

[18] Xavier HT, Izar MC, Faria Neto JR, *et al*. V brazilian guideline on dyslipidemia and prevention of atherosclerosis. Arq Bras Cardiol 2013; 101(4): 01-22. http://dx.doi.org/10.5935/abc.2013S010 PMID: 24217493

[19] Cho SK, Huh JH, Yoo JS, Kim JW, Lee KJ. HOMA-estimated insulin resistance as an independent prognostic factor in patients with acute pancreatitis. Sci Rep 2019; 9(1): 14894. http://dx.doi.org/10.1038/s41598-019-51466-5 PMID: 31624312

[20] I brazilian guideline on cardiovascular prevention, brazilian archives of cardiology. 2013. Available from: www.arquivosonline.com.br (Accessed on: July 26, 2021).

[21] S.A. Standards technical manuals series sexual rights reproductive rights-notebook. 2008. Available from: http://www.saude.gov.br/editora (Accessed on: June 17, 2021).

[22] Collins P, Webb CM, de Villiers TJ, Stevenson JC, Panay N, Baber RJ. Cardiovascular risk assessment in women – An update. Climacteric 2016; 19(4): 329-36. http://dx.doi.org/10.1080/13697137.2016.1198574 PMID: 27327421

[23] Kannel WB, Hjortland MC, McNamara PM, Gordon T. Menopause and risk of cardiovascular disease: The Framingham study. Ann Intern Med 1976; 85(4): 447-52. http://dx.doi.org/10.7326/0003-4819-85-4-447 PMID: 970770

[24] Zheng D, Li H, Ai F, *et al*. Association between the triglyceride to high-density lipoprotein cholesterol ratio and the risk of type 2 diabetes mellitus among Chinese elderly: The Beijing longitudinal study of aging. BMJ Open Diabetes Res Care 2020; 8(1): e000811. http://dx.doi.org/10.1136/bmjdrc-2019-000811 PMID: 32205325

[25] Young KA, Maturu A, Lorenzo C, *et al*. The triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio as a predictor of insulin resistance, β-cell function, and diabetes in Hispanics and African Americans. J Diabetes Complications 2019; 33(2): 118-22. http://dx.doi.org/10.1016/j.jdiacomp.2018.10.018 PMID: 30522790

[26] Tan KCB. Reverse cholesterol transport in type 2 diabetes mellitus. Diabetes Obes Metab 2009; 11(6): 534-43. http://dx.doi.org/10.1111/j.1463-1326.2008.01012.x PMID: 19175378

[27] Oliveira CP, Maranhão RC, Bertato MP, Wajchenberg BL, Lerario AC. Removal from the plasma of the free and esterified forms of cholesterol and transfer of lipids to HDL in type 2 diabetes mellitus patients. Lipids Health Dis 2012; 11(1): 65. http://dx.doi.org/10.1186/1476-511X-11-65 PMID: 22676273

[28] Solano MP, Goldberg RB. Management of dyslipidemia in diabetes. Cardiol Rev 2006; 14(3): 125-35. http://dx.doi.org/10.1097/01.crd.0000188034.76283.5e PMID: 16628021

[29] Barter PJ, Rye KA. Cholesteryl ester transfer protein inhibition as a strategy to reduce cardiovascular risk. J Lipid Res 2012; 53(9): 1755-66. http://dx.doi.org/10.1194/jlr.R024075 PMID: 22550134

[30] Pivatto I, Bustos P, Amigo H, Acosta AM, Arteaga A. Association between proinsulin, insulin, proinsulin/insulin ratio, and insulin resistance status with the metabolic syndrome. Arq Bras Endocrinol Metab 2007; 51(3): 1128-33.

[31] He Y, Ronsein GE, Tang C, *et al*. Diabetes impairs cellular cholesterol efflux from ABCA1 to small HDL particles. Circ Res 2020; 127(9): 1198-210. http://dx.doi.org/10.1161/CIRCRESAHA.120.317178 PMID: 32819213

[32] Sprandel MCO, Hueb WA, Segre A, Ramires JAF, Kalil-Filho R, Maranhão RC. Alterations in lipid transfers to HDL associated with the presence of coronary artery disease in patients with type

2 diabetes mellitus. Cardiovasc Diabetol 2015; 14(1): 107. http://dx.doi.org/10.1186/s12933-015-0270-8 PMID: 26268997

[33] Di Bonito P, Moio N, Scilla C, *et al*. Usefulness of the high triglyceride-to-HDL cholesterol ratio to identify cardiometabolic risk factors and preclinical signs of organ damage in outpatient children. Diabetes Care 2012; 35(1): 158-62. http://dx.doi.org/10.2337/dc11-1456 PMID: 22040842

[34] Marotta T, Russo BF, Ferrara LA. Triglyceride-to-HDL-cholesterol ratio and metabolic syndrome as contributors to cardiovascular risk in overweight patients. Obesity 2010; 18(8): 1608-13. http://dx.doi.org/10.1038/oby.2009.446 PMID: 20019684

[35] Bonora E, Formentini G, Calcaterra F, *et al*. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: Prospective data from the verona diabetes complications study. Diabetes Care 2002; 25(7): 1135-41.

[36] Williams K, Sniderman AD, Sattar N, D'Agostino R Jr, Wagenknecht LE, Haffner SM. Comparison of the associations of apolipoprotein b and low-density lipoprotein cholesterol with other cardiovascular risk factors in the insulin resistance atherosclerosis study (IRAS). Circulation 2003; 108(19): 2312-6. http://dx.doi.org/10.1161/01.CIR.0000097113.11419.9E PMID: 14581403

[37] Barter PJ, Ballantyne CM, Carmena R, *et al*. Apo B *versus* cholesterol in estimating cardiovascular risk and in guiding therapy: Report of the thirty-person/ten-country panel. J Intern Med 2006; 259(3): 247-58. http://dx.doi.org/10.1111/j.1365-2796.2006.01616.x PMID: 16476102

[38] Walldius G, Jungner I. Apolipoprotein B and apolipoprotein A-I: Risk indicators of coronary heart disease and targets for lipid-modifying therapy. J Intern Med 2004; 255(2): 188-205. http://dx.doi.org/10.1046/j.1365-2796.2003.01276.x PMID: 14746556