ORIGINAL PAPER

CRP/HDL–C and Monocyte/HDL-C ratios as Predictors of Metabolic Syndrome in Patients With Type 2 Diabetes Mellitus

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ABSTRACT

Background: Metabolic syndrome (MetS) denotes a cluster of co-occurring medical conditions associated with regulating hyperglycemia and acute cardiovascular events and complications. The escalating frequency of MetS among individuals afflicted with type 2 diabetes mellitus (T2DM) underscores its burgeoning significance as a critical public health concern and a complex clinical conundrum. Timely identification is imperative to avert the expedited progression of diabetic complications. **Objective:** To investigate the role of CRP/HDL-C and Monocyte/HDL ratios in predicting MetS in T2DM individuals. **Methods:** The study was designed as a two-year prospective study and included 80 T2DM patients divided into MetS and non-MetS groups based on MetS development over two years. The patients' serums were analyzed for complete blood count parameters, lipid profile, and C-reactive protein (CRP). Based on the laboratory test results, Monocyte/HDL-C and CRP/HDL-C ratios were calculated and analyzed. The receiver operating characteristic (ROC) curve and their corresponding areas under the curve (AUC) were used to determine prognostic accuracy. **Results:** Monocyte/HDL-C ratio and CRP/HDL-C ratio were significantly higher in MetS-T2DM2 than in nonMetS-T2DM (p=0.003 and p=0.029, respectively). The results of ROC curve analysis have shown that the CRP/HDL-C ratio (AUC of 0.695) and Monocytes/HDL-C ratio (AUC of 0.645) can serve as good predictors of MetS in T2DM patients. **Conclusion:** This study confirms the reliability of the Monocytes/HDL-C and CRP/HDL-C ratios as novel, simple, low-cost, and valuable predictors of MetS development in T2DM.

Keywords: Type 2 Diabetes Mellitus, Metabolic Syndrome, Monocytes/HDL-C-ratio, CRP/HDL-C -ratio.

1. BACKGROUND

Metabolic syndrome (MetS) is a group of conditions that raise the risk of coronary heart disease, diabetes, stroke, and other serious health problems. These conditions include abdominal obesity, hyperglycemia, hypertriglyceridemia, hypertension, and low high-density lipoprotein cholesterol levels (1).

In various parts of the world, the incidence of metabolic syndrome (MetS) has been estimated to range from 28 per 1000 people per year to more than 70 per 1000 people per year. Rapid economic development, the rise in popularity of the Western lifestyle, and a lack of physical activity have all contributed to the obesity and type 2 diabetes mellitus (T2DM) epidemics that

threaten to spread worldwide (2). Globally, the prevalence of MetS is rising at an alarming rate and is more common among T2DM patients. It was estimated that 70% to 80% of T2DM patients worldwide had MetS (3).

The synthesis of numerous studies within this encompassing review highlights MetS as an intricate interplay of disturbances. When interlinked with other pathologies, these disturbances give rise to profound alterations within the human body, particularly in individuals contending with T2DM. Furthermore, select inquiries suggest that even individuals newly diagnosed with diabetes can present indications of this syndrome. It exercises its impact not only on those who have recently entered the realm of diabetes but also on

individuals with an established history of diagnosis (4).

Researches into MetS among T2DM individuals demand significant attention, given the notable correlation between the existence of this syndrome and a marked elevation in both microvascular and macrovascular complications. These complications culminate in heightened morbidity and mortality rates, underscoring the importance of understanding and addressing this interplay (5).

Overweight/obesity, hypertension, and irregular metabolism of lipids and carbohydrates all contribute to the development of MetS as a group of risk factors. All aspects of MetS are recognized risk factors for atherosclerosis and cardiac disease. Simultaneously, T2DM is linked to a progression of the same pathological conditions leaving detrimental consequences on various organs, but primarily related to chronic low-grade inflammation affecting organ function (6, 7).

Concerning irregularities in lipid metabolism inherent for T2DM and MetS, obesity in both groups of patients is accompanied by an increase in low-density lipid (LDL) and a decrease in high-density lipid (HDL), affecting a primary endothelial structure for the development of atherosclerotic changes (8).

Because MetS is a multifactorial disease highly related to an activated inflammatory state, a stem for interrelations between different aspects of MS might be found in the inflammation. Obesity per se brings a certain level of inflammation that could be expressed as a surge of C-reactive protein (CRP) produced by the hepatocytes, while a base of that CRP-evidenced inflammatory process may be hidden in the interleukin 6 (IL-6) as one of the triggers but not being the only one. The root of those processes originates from the adipocytes, and it is related to tumor necrosis factor-alpha (TNF-alpha) when TNF-alpha superimposes the development of insulin insensitivity as a key hallmark of MetS (9, 10). Due to their pleiotropic roles concerning other cellular components of the immune system, TNF-Alpha, and IL-6 are positively modulated directly by other parts of the immune system, such as monocytes (11).

Alongside an established relationship between mentioned inflammatory hallmarks in MetS and T2DM, such as CRP, certain combinations for deriving their indices might be used. CRP/HDL-C was previously used in research related to metabolic syndrome expressing a role of predictor for the development of MetS, while Monocytes/HDL as a systematic inflammatory marker is associated with T2DM complications but with apparently much higher value in T2DM patients than in healthy populations (12, 13).

2. OBJECTIVE

This study aimed to investigate the role of CRP/HDL-C and Monocyte/HDL-C ratio in predicting MetS in T2DM patients.

3. MATERIAL AND METHODS

Study design

Ninety-six individuals of both sexes with a confirmed diagnosis of T2DM without MetS were initially included in the prospective two-year study. Individuals were selected randomly in Family Medicine Centers and Endocrinology Consultation Centers in Sarajevo Canton Health Centers. After

24 months of observation, 80 patients met the research criteria, and their data were taken for statistical analysis.

At the end of the study, individuals with T2DM who met the research criteria (n=80) were divided into two groups:

a) MetS-T2DM group - individuals who did not develop MetS during the study (n=31)

b) nonMetS-T2DM group - individuals who developed MetS during the research (n=49).

At the commencement and conclusion of the study period, comprehensive data were collected from all T2DM patients, including their medical history, medication usage interview, waist circumference, and blood pressure (BP) measurement.

Individuals with the following disorders or conditions were excluded from the study: any chronic diseases such as heart and kidney diseases, thyroid diseases, liver diseases, serious infections, and malignancy) diagnosed within six months before and during the study period or taking any drugs known to cause disturbance of lipid metabolism and inflammatory cells.

Informed consent was obtained from all individuals, and the study received approval from the Ethical Committee of the Faculty of Medicine at the University of Sarajevo. The research adhered to the principles outlined in the Declaration of Helsinki concerning the rights of patients participating in biomedical research (Revision 2013).

Definition of MetS

The presence of MetS was determined based on the presence of at least 3 of 5 diagnostic criteria according to the recommendations of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) (14):

- Central obesity (waist circumference): men >102 cm, women >88 cm
- Triglycerides ≥1.7 mmol/L
- HDL cholesterol: men ≤ 1.03 mmol/L, women ≤ 1.29 mmol/L
- Arterial pressure: ≥ 139 / ≥89 mm Hg
- Postprandial glucose: ≥ 6.1 mmol/L

Laboratory evaluation

After taking the medical history and physical examination, blood was taken for laboratory tests by puncture of the cubital vein. At the beginning of the study and after 24 months, the individuals were subjected to the following laboratory tests using standard methods: complete blood count, fasting blood glucose, triglycerides, HDL-cholesterol. C-reactive protein was determined from a serum sample by immunoturbidimetric method, which was amplified by particles on a Cobas 6000 Roche/Hitachi analyzer.

The Monocyte/HDL-C ratio was obtained by dividing monocyte count (109/L) by HDL-C (mmol/L) (15).

CRP/HDL-C ratio was calculated by dividing the serum concentration of CRP(mg/L) by HDL-C measured in mmol/L (16).

Statistical analysis

All statistical analyses were conducted using SPSS software version 19.0 (SPSS, Inc., Chicago, Illinois). The distribution of variables was assessed using both the Kolmogorov-Smirnov and Shapiro-Wilk tests. While continuous variables with a non-normal distribution were expressed as the median (interquartile range), continuous variables with a normal distribution were given with the results as mean ±standard devia-
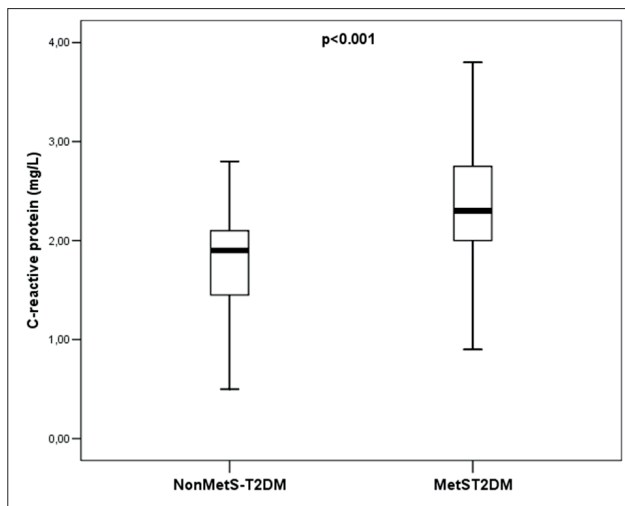
Figure 1. C-reactive protein in nonMetS-T2DM and MetS-T2DM patients; T2DM - type 2 diabetes mellitus; MetS – metabolic syndrome
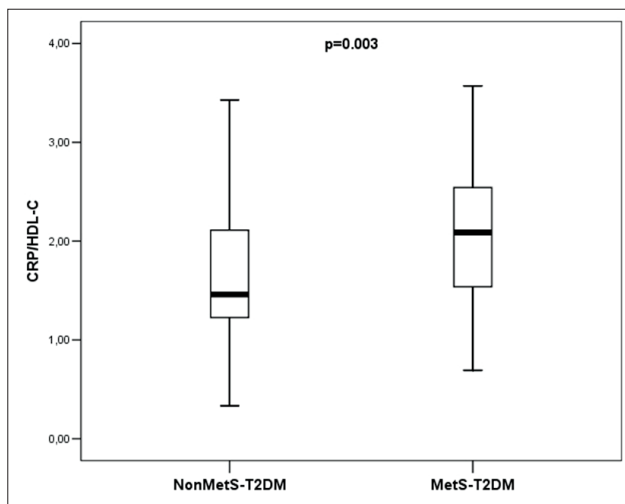

Figure 2. CRP/HDL-C ratio in nonMetS-T2DM and MetS-T2DM patients; T2DM - type 2 diabetes mellitus; MetS – metabolic syndrome

tion. To compare continuous variables with a normal distribution, we employed a two-sample t-test, while for those with a non-normal distribution, the Mann-Whitney U test was utilized. To predict MetS in individuals with T2DM, we used Receiver Operating Characteristic (ROC) analysis to determine the optimal cut-off point with sensitivity and specificity considerations. Additionally, we calculated the areas under the ROC curve (AUC) for each predictor. Statistical significance was defined as $p < 0.05$.

4. RESULTS

CRP concentration in nonMetS-T2DM patients was 1.90 (1.42-2.10) mg/L, while in MetS-T2DM patients it was 2.30 (2.0-2.77). The determined difference in CRP concentration between the examined groups was significant (p<0.001) (Figure 1).

The CRP/HDL-C ratio value in nonMetS-T2DM patients was 1.46 (1.19-2.11), while in MetS-T2DM patients, it was 2.08 (1.53-2.56). The determined difference in the value of CRP/HDL-C between the examined groups was significant (p=0.003) (Figure 2).
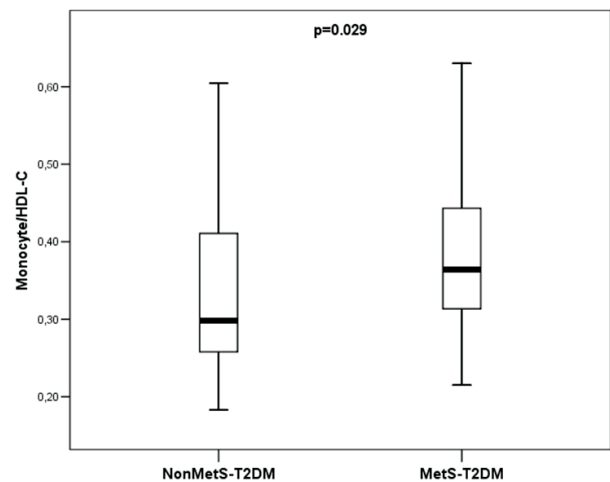

Figure 3. Monocyte/HDL-C ratio nonMetS-T2DM and MetS-T2DM patients; T2DM - type 2 diabetes mellitus; MetS – metabolic syndrome

The Monocyte/HDL-C ratio value in nonMetS-T2DM patients was 0.29 (0.25-0.41), while in MetS-T2DM patients it was 0.36 (0.31-0.44). The determined difference in Monocytes/HDL-C between the examined groups was significant (p=0.029) (Figure 3). The ROC curve for CRP produced an AUC of 0.738 (p<0.001) with a sensitivity of 52.0% and specificity of 81.2% for the cutoff point of 2.25. The ROC curve for CRP/HDL-C produced an AUC of 0.695 (p=0.003) with a sensitivity of 68.7% and specificity of 68.7% for the cutoff

Age (years)	48.58±4.53
Gender (male/female)	40 (50.0%) / 40 (50.0%)
Duration of diabetes (years)	5.0 (4.0-7.0)
DM with METS after 24 months	49 (61.2%)
SP (mmHg)	130.0 (130.0-140.0)
DP (mmHg)	90.0 (80.0-100.0)
CRP (mg/L)	2.07±0.68
Monocytes (109/L)	0.40±0.08
HDL-C (mmol/L)	1.2 (1.0-1.4)
Monocytes/HDL-C	0.34 (0.28-0.43)
CRP/HDL-C	1.75 (1.41-2.33)

Table 1. Baseline characteristics of T2DM patients

Variable	AUC	95% CI	p	Cut off point	Sensitivity (%)	Specificity (%)
CRP	0.738	0.630-0.845	<0.001	2.25	52.0	81.2
CRP/HDL-C	0.695	0.575-0.815	0.003	1.7	68.7	68.7
Monocytes/HDL-C	0.645	0.516-0.774	0.029	0.32	72.9	56.2

Table 2. Optimal Cut-off values, the area under the curve (AUC), sensitivity, and specificity of CRP, CRP/HDL-C ratio, and Monocytes/HDL-C ratio in the prediction of MetS in T2DM patients

point of 1.7. The ROC curve for Monocytes/HDL-C produced an AUC of 0.645 (p=0.029) with a sensitivity of 72.9% and specificity of 56.2% for the cutoff point of 0.32 (Table 2.).

5. DISCUSSION

Current lifestyles involving excess energy intake and a sedentary lifestyle with low physical activity have led to an epidemic of obesity-related diseases. These are primarily cardiovascular diseases, the leading cause of death in the world, T2DM, the prevalence of which has increased dramatically in

the Western world in recent decades, and MetS. These chronic diseases create a tremendous economic burden on the health system of every country, increase morbidity and mortality, and reduce the quality of life of individuals.

This study aimed to determine whether novel indices in patients with T2DM can predict the development of MetS. This is the first research considering the abovementioned indices regarding MetS development in T2DM patients. Misinterpretation of early valuable laboratory status in T2DM patients represents a massive problem for contemporary medical practice but is mainly related to predisposing factors to MetS development (14).

It is postulated that insulin insensitivity may be the root of the problem in MetS and T2DM because hyperinsulinemia production of beta cell dysfunction stepping towards deprivation of insulin production because of a high demand according to the fundamental physiological rule (17).

Discovering novel disease mechanisms in pathophysiology, T2DM and MetS are intertwined with some links accompanying some standard stem as it could be found in non-alcoholic fatty liver disease (NAFLD) and similar diseases caused by metabolic dysfunction (18).

Considering the involvement of standard blood tests as part of regular lab check-ups, their importance is the usage of them in a purpose for deriving inflammatory indices with the role of biomarkers and further unlocking a secret solution for prompt diagnosing MetS progression in T2DM.

Our main finding was cost-effective biomarkers included in laboratory check-ups, and it turned out that CPR, CRP/HDL-C, and Monocytes/HDL-C, by sensitivity and specificity, represent trusted inflammatory biomarkers for predicting MetS development in T2DM patients.

Considering analyzed inflammatory indices in the sense of T2DM and MetS, some of our results correspond with previous research regarding the inflammatory indices that had been researched in T2DM or MetS. Jia et al. found that Monocytes/HDL-C ratio was statistically significantly greater in T2DM patients with ultrasound-verified fatty liver than in T2DM patients without fatty liver among 1,501 patients (19).

Due to T2DM patients with diabetic nephropathy, Monocytes/HDL-C ratio is a statistically significant biomarker due to its increase in T2DM patients with kidney dysfunction (20).

A study about the involvement of the Monocytes/HDL-C ratio as a biomarker in carotid artery plaque formation found that the Monocytes/HDL-C ratio positively correlated with body mass index (BMI) as a hallmark in diagnosing obesity and Hb1Ac, therefore representing potential links between T2DM and MetS (21).

Wang et al. analyzed the role of the Monocytes/HDL-C ratio for MetS patients in a cross-sectional study, concluding that this ratio is directly related to an increased risk of MetS development compared to a healthy population without an increased level of this ratio (22).

Previously, the Monocyte/HDL-C ratio was proven to predict clinical severity in already diagnosed patients with MetS (23).

Due to its known inflammatory role, CRP has many relations but also occurs in dyslipidemia. Korea National Health and Nutrition Examination Survey conducted by Jeon et al.

(24) found that CRP levels are associated with an increased risk of dyslipidemia, T2DM, and MetS in the general population. Concerning the widespread role of inflammation in disease progress, Dongway et al. (25) analyzed CRP in T2DM patients and a healthy group finding a strong positive correlation between LDL and BMI with CRP.

Jiala et al. researched a prediction of MetS, concluding that an increased CRP/HDL-C ratio is equivalent to the ratio between triglycerides and HDL-C in predicting MetS, supporting its validity as a biomarker (26).

In terms of searching for a standard molecular stem of all aforementioned predictors and their components (CRP, HDL-C, and monocytes), HDL-C has a direct role in the development of monocytes being a preventer of monocyte pro-inflammatory action and makes an inverse relation to monocyte count, while monocytes are the primary source of TNF-alpha, further supporting the inflammatory state by raising the CRP level (27, 28).

Although HDL-C represents a link between those components from indices, its involvement in the inflammatory process can have a relation with an antioxidant enzyme paraoxonase-1 (Pon-1) playing a protective role against a capacity loss of HDL-C and the depleting cluster of differentiation such as CD11b (29).

CD11b is a very underappreciated marker for obesity status. Its role regulates obesity-induced insulin resistance via limiting alternative activation and proliferation of adipose tissue macrophages – which corresponds to the MetS characteristics (30).

Alongside its presence in obesity, CD11b is highly expressed in MetS patients and corresponds to a hyperglycemia state directly related to a glucose level. Additionally, Pon-1 anti-inflammatory effects are proven in acute and chronic inflammation, directly corresponding to HDL levels (31, 32).

In particular, most of the anti-inflammatory effects of HDL-C are related to its component apolipoprotein A-1 (apoA-1) due to their interconnectivity besides phospholipids inside the HDL-C molecule. Regarding the role in MetS pathophysiology, the serum quantity of apoA-1 is significantly lower in MetS patients than in a group of healthy patients, according to research made by Yi et al. (33).

Besides criteria for MetS diagnosis due to obesity, it was found that apoA-1 transgenic mice excreted a protective effect against obesity compared to wild-type mice when both groups were fed high-fat diets (34).

In obese patients corresponding to one of the criteria mentioned above for MetS, macrophages originating from adipose cells are converted to pro-inflammatory M1-like macrophages and secrete many pro-inflammatory cytokines, such as TNF-alpha, causing failure in insulin signaling as a step towards MetS. The processes are mainly attributed to adipocyte death via NF-κB-mediated inflammation (35).

Inflammatory status is followed by a microinflammation (expressed through Nf-κB high activity being characteristically increased due to the chronic-low inflammation of adipose tissue) with an upregulation of TNF-alpha (playing a vital role in the endothelial cell damage), interleukin 16 (IL-6), interleukin 18 (IL-18) and the vascular endothelial growth factor (although implicated in the diabetic retinopathy) (36).

MetS and T2DM are diseases related to dysregulated in-

sulin and glucose metabolism that may consequently lead to vasoconstriction due to an activation of the renin-angiotensin-aldosterone system and an upregulated production of endothelin-1 in the endothelial cells but simultaneously appreciating that an additional obliteration of the blood vessels lumen might be caused by the atherosclerotic changes due to the inflammatory processes and hypertension using a turbulent blood flow (37).

Therefore, high glucose causes an upregulation of the transforming growth factor beta (TGF Beta), leading to a higher activity of the protein kinase C (PKC) and a surplus of its upstream products, such as 1,2-diacylglycerol (DAG) – which is a cofactor for PKC activation (38).

Some mediator products, such as DAG, influence the pathophysiology of MetS because its high activity mediates insulin resistance as a cornerstone of MetS pathogenesis (39).

MetS is a state that brings many consequences and comorbidities, but some of them can firstly leave changes on cellular structures such as platelets and endothelial cells, making a huge potential financial cost in terms of further treatment, such as a hypercoagulable state.

In the spirit of the hypercoagulable state mentioned above, platelets reactivity, as s key rmediator of the hypercoagulable state, is directly proportional to the hyperglycemia manifesting in several ways taking a serious role in the context of the TNF Alpha and MetS. High glucose increases CD40L (belonging to the TNF receptor family and structurally similar to the TNF Alpha) and thrombospondin-1 in the platelets. As a result of platelet hyperactivity, platelet microvesicles form concomitant with the formation of endothelial cell microvesicles as one of the critical steps toward the hypercoagulable state (40).

Furthermore, Agouni et al. (41) found out that microvesicles originated from platelets, besides endothelial and erythrocytes microvesicles, of MetS patients contributed to the development of endothelial dysfunction and atherosclerotic changes through a mechanism of nitric oxide (NO) production defect and superoxide anion production making a predisposition for further protein tyrosine nitration.

In interpreting the study's results, the limitation should be acknowledged. By searching the literature, we could find only partial results to compare with our results - most studies were focussed exclusively on a single disease without causative relation.

6. CONCLUSION

This is the first study that considered the predictive role of novel indices derived from inflammatory parameters and lipograms in the pathogenesis of MetS patients with T2DM. Along with CPR, CRP/HDL-C and the Monocytes/HDL-C responded as reliable biomarkers for the prediction of MetS development in T2DM patients because the cost-effective, easily accessible aforementioned markers were determined to have a practical predictive value in patients with T2DM. Timely adjusted therapy to prevent MetS in T2DM with its clinical signs is a crucial step for preventive measures. Previous research is directed towards avoiding T2DM in MetS patients, but this paper gives a new perspective that T2DM patients develop MetS due to the unregulated proinflammatory status as it is possible to be foreseen from CBC results.

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