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Original Article

THE ROLE OF TRIGLYCERIDE TO HDL CHOLESTEROL RATIO IN SERA AS A CLINICAL SURROGATE MARKER FOR CARDIOVASCULAR RISK AND INSULIN RESISTANCE IN PATIENTS WITH METABOLIC SYNDROME

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Summary

The study aimed to investigate the triglycerides to HDL-cholesterol ratio (Tg/HDL) and the interaction of this ratio with insulin resistance (IR) and insulin secretion indices, with the levels of interleukin - 1(IL-1), interleukin-6 (Il-6), and tumour necrotic factor- α (TNF-α) in sera among patients with metabolic syndrome (MS). A prospective, cross-sectional, comparative study was conducted on 45 patients with MS without data for hyperglycemia and 21 metabolically healthy non-obese controls. The levels of fasting and postprandial glucose, immunoreactive insulin (IRI), total cholesterol, triglycerides (Tg), IL-1, IL-6, and TNF-α were measured in all the participants. We calculated the LDL cholesterol levels, Tg/HDL ratio, homeostatic model of insulin resistance (HOMA-IR), and the homeostatic model of β-cell function (HOMA-b). Patients with MS had higher BMI (38.73±1.84 vs. 24.32±2.71 kg/m2; $p<0.05$) and waist circumference (115.56 ±4.7 vs. 81.1±8.4cm; $p<0.05$) than non-obese controls. The same patients had higher LDL cholesterol levels (3.42±0.3 vs. 2.63±0.66 mmol/l; $p<0.05$) and Tg (1.59±0.22 vs. 1.08±0.31mmol/l; $p<0.05$), as well as lower levels of HDL-cholesterol (1.03±0.09 vs. 1.27 ± 0.24mmol/l; $p<0.05$) compared to the controls. The Tg/HDL ratio was 2.03±0.87 among the patients with MS and 0.88±0.27 in controls; $p<0.05$. The plasma levels of basal IRI (19.32±3.22 mIU/l vs. 9.13±0.73mIU/l; $p<0.05$), HOMA-IR (4.02 vs. 1.97; $p<0.05$) and HOMA-b (258.77±57.76 vs. 183.31±17.52; $p<0.05$) were significantly higher in the MS group. The same patients with MS had higher concentrations of IL-1 (18.37±4.28pg/ml vs. 7.12±1.74pg/ml; $p<0.05$), IL-6 (1.01±0.3pg/ml vs. 0.1±0.3pg/ml; $p<0.05$) and TNF-α (2.13±1.43 pg/ml vs. 1.82±0.94pg/ml; $p=0.24$) too. Positive correlations between the levels of IL- 1 and Tg/HDL ratio ($r= 0.46$; $p=0.008$), IL-1 and HOMA-%B ($r=0.47$; $p=0.005$) were found. The Tg/HDL ratio is a potential, cheap and available surrogate marker for screening for cardiovascular risk and insulin resistance in patients with MS in clinical practice.

Keywords: metabolic syndrome, insulin resistance, atherogenic index, cytokines.

Introduction

Metabolic syndrome (MS) is considered a combination of risk factors for developing cardiovascular diseases and diabetes mellitus type 2 (DMT2). Insulin resistance (IR) is at the core of the modern MS concept. All expert

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groups which developed the criteria for clinically defining MS [1,2,3] regard visceral obesity as the main component. Its combination with arterial hypertension, dyslipidemia, and hyperglycemia accelerates the progression of atherosclerosis. Malfunctions in secretion and metabolic effects of adipocytokines [interleukin-1(IL-1), interleukin-6(IL-6), tumor-necrotic factor-α(TNF-α)] were found to be associated with visceral obesity [4]. They systematically affect the central nervous system, cardiovascular system, pancreas, liver and affect vessel and tissue inflammation, coagulation, and fibrinolysis [5]. They also play a role in regulating carbohydrate metabolism, insulin sensitivity, and the showcase of IR [6,7].

Laboratory finds of atherogenic dyslipidemia in MS include hypertriglyceridemia, lowered serum levels of HDL-cholesterol and apolipoprotein A1- (ApoA-1), increased fractions of small dense LDL-cholesterol particles, and apolipoprotein B (ApoB) in plasma. Levels of small dense LDL-cholesterol fractions are considered the most substantial predictive factor for cardiovascular diseases [8]. However, direct measurement of those is technically challenging and is not a standard routine laboratory testing.

The TG/HDL cholesterol ratio is identified as a surrogate predictive marker for atherosclerosis. Calculating it as an atherogenic index is simple and easy.

Several direct and indirect methods for determining IR can be used in patients with MS and at high cardiovascular risk [9]. The hyperinsulinemic-euglycemic clamp technique is regarded as the gold standard. Unfortunately, this method is complicated and requires much time, so it is inappropriate for epidemiological studies and clinical practice. Because of this, indirect indices have been developed for determining IR as the homeostatic model for insulin resistance [Homeostasis Model Assessment (HOMA)- HOMA- IR] [10]. However, the lack of a standardized methodology for studying endogenous insulin is a limiting factor for using this model in clinical practice [11].

Some studies define the increased ratio of TG/HDL as a good indicator of liver IR [12,13] and as a predictor for the development of DMT2 [14]. Unfortunately, there is not much data available regarding the clinical administration of the TG/HDL ratio as an IR assessment index.

We aimed to investigate the triglycerides to HDL-cholesterol ratio (Tg/HDL) and interaction of this ratio with insulin resistance and insulin secretion indices, with the levels of interleukin -1(IL-1), interleukin-6 (Il-6), and tumour necrotic factor- α (TNF-α) in sera in the patients with metabolic syndrome (MS).

Methods and Patients

A prospective, cross-sectional, comparative, case-control study was conducted on 45 patients (men and women) with MS**.** The participants in the study were selected from patients hospitalized at the Clinic of Endocrinology of Dr. Georgi Stranski University Hospital – Pleven, after their signing informed consent forms for participation in the study. Their results, obtained from investigations, were compared to those of 21 healthy non-obese controls (9 men and 12 women). The diagnosis MS was accepted according to the one in the primary medical documentation with less than 3 out of 5 positive diagnostic criteria of IDF (International Diabetes Federation) from 2010. Data for smoking habits, arterial hypertension, family history for cardiovascular diseases, and diabetes was collected by interviewing the participants. Height and weight were measured, and BMI was calculated for each patient. Their waist measurements were taken using standard methods. Arterial blood pressure was measured according to the recommendations of Thomas [20]. The patients with systolic blood pressure ≥130mmHg or/and diastolic blood pressure ≥ 85mmHg, or/and taking antihypertensive drugs were considered hypertensive.

Blood samples in a fasting state were collected in the morning by venipuncture. The lab tests were performed at the clinical laboratory of the University Hospital, whose activities are regulated by the National System for Laboratory Control. The plasma triglycerides, total cholesterol, and HDL-cholesterol levels were examined using an enzyme-colorimetric method (automatic analyzer BA 400; BioSystems S.A, Spain). The values of LDL cholesterol were calculated by Friedewald's formula. Carbohydrate metabolism was evaluated by oral glucose tolerating test (OGTT) with 75 grams of glucose. Blood glucose was measured in

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venous plasma at 0, 60, and 120 minutes of the OGTT by applying the glucose oxidase method (KABE Labortechnik, Denmark; Beckman Glucose Analyzer, USA). The insulin levels were also monitored at 0, 60, and 120 minutes by enzyme-linked immunosorbent assay ELISA (Stat Fax 2100; Awareness Technology, USA). Two indirect methods were used for insulin-resistance assessment: 1) Homeostatic Model Assessment for Insulin Resistance (HOMA-IR); HOMA IR = fasting insulin (mIU/l) × fasting plasma glucose (mmol/l)/ 22.5, with reference range for HOMA-IR- from 0.7 to 2.4 [21]; 2) Tg/HDL ratio [Tg/HDL ratio= plasma triglycerides (mmol/l)/ levels of HDL- cholesterol in plasma (mmol/l)].

The HOMA-b model for assessment of β-cells function was used. HOMA-%b was calculated using the following formula: 20 x fasting serum insulin (mIU/l) /fasting plasma glucose (mmol/l)-3.5 [21]. Adipocytokines - Il-1, IL-6, and TNF-α (Gen-Probe Diaclone SAS, France) were determined by ELISA (Stat Fax 2100; Awareness Technology, USA).

All statistical analyses were performed using STATGRAPHICS Centurion XV.I. Data are presented as their mean values and standard deviations (means ± SD) or individual data and median values. Comparisons between the groups were made using the independent sample t-test for parametric comparison of the two means, the Kolmogorov-Smirnov test for a non-parametric comparison, and the Mann-Whitney tests for the test median of two groups. Two-sided P values <0.05 were considered to indicate statistically significant differences. The Pearson (r) correlation for measuring the strengths of association between two variables was also done.

Results

In the study group, 62.5% of the patients with MS had a family history of cardiovascular disease vs. 45.5% of the subjects from the control group. There was a positive family history for DMT2 in 53.13% of the MS group and 50% of the controls.

The clinical characteristics and lipid profiles of the patients with MS and the control group are shown in Table 1.

The average age of the participants with MS (40.07±4.24 years) was higher than that of the control group (31.14±6.92 years). Statistically higher BMI, waist circumference, systolic and diastolic blood pressure were found in the

Table 1. Clinical characteristics and lipid profile in patients with metabolic syndrome and in controls

Index	MS (n_1=45)	Controls (n_2=21)	Significance (p< 0.05)
Age (years)	40.07±4.24	31.14±6.92	**<0.05**
BMI (kg/м²)	38.73±1.84	24.32±2.71	**<0.05**
Waist circumference (cm)	115.56±4.78	81.1±8.4	**<0.05**
Arterial hypertension % (number of patients)	77.7(35)	42.9 (9)	
Systolic blood pressure (mmHg)	130.68±15.69	116.67±15.52	**<0.05**
Diastolic blood pressure (mmHg)	86.33±7.93	76.19±9.6	**<0.05**
Fasting glucose (mmol/l)	5.25 ± 0.24	4.89±0.47	**0.06**
Total cholesterol (mmol/l)	4.51±0.23	4.47±0.52	**<0.05**
HDL-cholesterol (mmol/l)	1.03±0.09	1.26±0.24	**<0.05**
LDL-cholesterol (mmol/l)	3.42±0.30	2.58±0.62	**<0.05**
Triglycerides (mmol/l)	1.59±0.22	1.06±0.33	**<0.05**
Triglycerides/total cholesterol	**2.03±0.87**	**0.88±0.27**	**<0.05**

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Table 2. Indices of carbohydrate metabolism (blood glucose, basal insulin levels, HOMA-IR, and HOMA-%B) in patients with MS and controls

Index	MS (n_1=45)	Controls (n_2=21)	Significance (p< 0.05)
Glucose 0 min (mmo/l)	5.25±0.8	4.9±0.47	**0.06**
Glucose 60min (mmol/l)	8.13±2.25	6.67±1.56	**<0.05**
Glucose 120min (mmol/l)	6.1±1.8	5.13±1.23	**<0.05**
Insulin, fasting (mIU/l)	19.32±3.22	9.13±0.74	**<0.05**
HOMA-IR	4.62±0.8	1.97±0.16	**<0.05**
HOMA-%B	**258.77±57.76**	**183.31±107.92**	**<0.05**

Table 3. The levels of investigated cytokines (IL-1, IL-6 and TNF-α) in patients with MS and controls

Index	MS (n_1=45)	Controls (n_2=21)	Significance (p< 0.05)
IL-1 (pg/ml)	9.13±0.74	4.33±1.46	**<0.05**
IL-6 (pg/ml)	1.97±0.16	0.51±0.3	**<0.05**
TNF-α (pg/ml)	**2.49±1.17**	**1.12±0.58**	**0.24**

MS patients. These patients had significantly higher plasma levels of total cholesterol, LDL-cholesterol, triglycerides, and lower cholesterol levels compared with the controls. The Tg/HDL ratio in MS group patients was 2.03±0.87 vs. 0.88±0.27 in the controls (p<0.05).

The blood glucose levels, endogenous insulin during OGTT, HOMA IR, and HOMA B in the MS group and the controls are shown in Table 2.

There were significant differences in glucose levels at 60 and 120 min during the OGTT between the two groups. Higher basal insulin levels (17.08±9.18 mIU/l vs. 8.8±1.64 mIU/l; p<0.05), manifested insulin resistance, calculated via HOMA-IR (3.82±2.27 vs. 1.92±0.41; p<0.05) and higher β-cells function (245.19±125.97 vs. 128.09±28.63; p<0.05) were detected in the MS patients. The levels of investigated cytokines (IL-1, IL-6andTNF-α) in the MS patients and the controls are shown in Table 3.

Patients with MS had significantly higher concentrations of IL-1 (18.37±4.28pg/ml vs. 7.12±1.74pg/ml; p<0.05), IL-6 (1.01±0.3pg/ml vs. 0.1±0.3pg/ml; p<0.05) and TNF-α (2.13±1.43 pg/ml vs. 1.82±0.94pg/ml; p=0.24). The TNF-α levels did not reveal any statistically significant difference between the study group and the controls. In the MS group, a positive correlation was demonstrated between the level of IL-1 and the TG/HDL ratio (r= 0.46; p=0.008), IL-1 and HOMA-%B (r=0.47; p=0.005).

Discussion

The studies on plasma triglycerides, total cholesterol, HDL, and LDL cholesterol are established as routine biochemical methods for assessing atherosclerotic risk in patients at increased cardiovascular risk. To improve the screening and identification of at-risk individuals, numerous atherogenic indices have also been created: risk atherogenic indices of Castelli I and Castelli II, the ratio of Tg/CDL-cholesterol, and the plasma atherogenic index). In their studies, Da Luz et al. [18] established levels of the Tg/HDL ratio above 2.0 as risk factors and those above 4.0 as the most potent prognostic marker among plasma lipids and atherogenic coronary disease indices. The results of our study showed statistically higher values of the tested atherogenic index Tg/HDL cholesterol among MS patients compared to the controls. A positive correlation was also found

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between increased Tg/CDL-cholesterol ratio and increased mortality and cardiovascular incidents in women [22].

In the MS patients we studied, the TG/HDL ratio was also above 2.0 and corresponded with the increased plasma levels of total cholesterol, LDL cholesterol, and triglycerides. In a study of metabolic-atherogenic parameters among 52 women with MS, Koleva et al. also established statistically higher levels of the Tg/HDL cholesterol index (1.75±1.11) compared to 22 metabolically healthy overweight or obese women (0.83±0.36) [23]. Our results differed from those from a descriptive study among 500 participants with and without MS in the Pleven region. The researchers found no differences in the TG/HDL cholesterol ratio in the two groups (2.77 vs. 2.6). It should be noted that the average age of the patients with MS surveyed was higher (49.3±6.4 years) than the age of those we surveyed (40.07±4.24years) [24].

In patients with visceral obesity, the presence of dyslipidemia is often combined with IR. On the other hand, the presence of fatty infiltration of the liver and muscles is a factor for IR development. A study among 258 obese without diabetes mellitus found that serum triglycerides, the Tg/HDL ratio, and insulin concentrations were the best biochemical markers for identifying IR [25]. For the Tg/HDL cholesterol index, a value above 1.8 is considered as an IR indicator. Our results match those of McLaughlin. Depending on ethnicity and gender, different studies show different IR-predictive values of the Tg/HDL ratio. For white non-Hispanics and Mexicans, the ratio was over 3.0 [26], and for male African-Americans, it was over 2.5 [27].

In our study, correlational links between the Tg/HDL ratio and HOMA-IR were not found. A likely explanation for these results is that the TG/HDL ratio is an interrupted variable, describing the probability of IR development. The original calculation of IR is achieved by calculating HOMA-IR [28]. It is known that, together with leptin, IL-1modulates lipid metabolism through its ability to suppress the activity of the lipoprotein lipase enzyme [29]. In our MS patients, we found higher serum IL-1 levels and a positive correlation between IL-1 levels and the TG/HDL ratio.

As expected, the levels of IL-6 among the MS patients we studied were also higher than the healthy controls because between 25-30% of its circulating levels are excreted from fat tissue [30].

As a confirmation of data from a clinical study of Kang among 51 women [31] and in the MS patients we studied, significantly higher concentrations of TNF-α were reported. It is assumed that adipocytes and macrophages located in fat stores serve as a source of TNF-α. The concentration of TNF-α increases with obesity and is closely related to IR in peripheral tissues and serum levels of IL-1 and IL-6 [32].

Conclusion

In conclusion, the results of our study point to a higher TG/HDL cholesterol index among MS patients and correspond to increased levels of HOMA-IR and IL-1 levels in them. Follow-up studies are needed, among a larger group of MS patients, to determine the influence of age and gender on the Tg/HDL-cholesterol ratio. In addition to the well-established clinical laboratory parameters for identifying patients with MS and IR, the Tg/HDL- cholesterol index is an inexpensive and easy additional indicator, which can be used in routine practice for screening people at increased cardiovascular risk.

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