EVALUATION OF SERUM γ-GLUTAMYL TRANSFERASE AND ITS ASSOCIATION WITH HIGH SENSITIVITY C-REACTIVE PROTEIN AND INSULIN LEVELS IN THE PATIENTS WITH METABOLIC SYNDROME

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Background. *Metabolic syndrome (MS), a collection of cardiovascular risk factors, is a major worldwide public health problem. The gathered data prove that serum gamma-glutamyl transferase (γGT) activity is a true marker of atherosclerotic cardiovascular disease (CVD) and is of a prognostic importance as well as the high-sensitivity C-reactive protein (hs-CRP).*

Objectives. *In the study, we sought to evaluate serum γGT activity, hs-CRP and insulin resistance in patients with MS.*

Methods. *The study involved 50 persons with metabolic syndrome and 50 healthy age and sex matched controls. Fasting serum samples of all participants were investigated for γGT, hs-CRP, insulin, blood glucose, lipid profile and liver function tests. Anthropometric measurements and BMI were also calculated*

Results. *In that case 50% showed significantly high γGT compared to the controls, 30% proved increased hs-CRP levels above >0.5 mmol/L, whereas 94% of the controls were within the reference range. 74% of cases revealed the presence of insulin resistance while 32% of the controls showed insulin resistance. High γGT levels were also observed in that case with deranged lipids levels and high BMI.*

Conclusions. *The study suggests that the patients with MS have a higher serum γGT activity. This study also proves that hs-CRP and HOMA-IR, which are independent risk factors of CVD, are also associated with MS. The correlation between γGT and the components of MS are also found significant compared to hs-CRP. Thus, γGT can be considered as an inexpensive and authentic predictor of MS, which can be a manifestation of CVD in near future.*

Key words: **metabolic syndrome; gamma-glutamyl transferase; high sensitivity C-reactive protein; HOMA-IR.**

Introduction

Metabolic syndrome (MS) is defined by a constellation of risk factors of cardiovascular disease (CVD), that include abdominal obesity, dyslipidemia, hypertension, and impaired glucose tolerance, which increase the risk of CVD and diabetes mellitus [1]. MS has been considered as one of the threatening non communicable public-health problem globally [2].

Serum gamma-glutamyl transferase (γGT) has long been considered a harbinger of hepatic dysfunction and alcohol intake [3]. Recently, accumulating epidemiology studies have revealed that γGT contributes in several pathophysiological processes, including oxidative stress and lipid peroxidation, which are important for pathogenesis and development of insulin resistance as well as MS [4, 5, 6]. In addition, when compared with other hepatic markers, γGT was the major predictor of type 2 diabetes [7,8,9]. γGT is a possible risk factor and a prognostic indicator of CVD. Further information is needed regarding the magnitude of the risk associated with γGT activity and individual cardiometabolic disorders. Such a relationship could help to decipher a high prevalence of MS.

Perhaps excessive energy consumption, which leads to obesity, is a more serious and frequent nutritional problem, but there can be a gradual and fairly predictable transition from simple obesity with no observable metabolic changes through insulin resistance. Insulin resistance arises from the inability of insulin to act normally in regulating nutrient metabolism in peripheral tissues. Increasing evidences of human population studies and animal research have established correlative as well as causative relations between chronic inflammation and insulin resistance [10]. Chronic, systemic, subclinical inflammation has also been identified as a driving force for insulin resistance. Since

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hs-CRP is a marker of systemic inflammation, it might explain the prevalence of insulin resistance in MS. Nevertheless, the relationship remains uncertain and has not been well researched yet. Therefore, the aim of this study was to examine the associations of serum γGT, hs-CRP and insulin resistance in the individuals with MS as well as its components.

Methods
Source of Data
This study was a hospital based cross sectional study, which comprised metabolic syndrome patients attending the outpatient and inpatient Departments of Medicine. The study was approved by the Local ethical committee of the institute and the informed consents were obtained from all subjects, who took part in the study.

Selection of Subjects
All subjects were diagnosed according to National Cholesterol Education Program, Adult Treatment Panel III criteria and it required the presence of 3 or more of the following [2]: a) fasting blood glucose ≥ 6.105 mmol/L; b) serum triglyceride ≥1.71 mmol/L or being on lipid lowering therapy; c) Serum HDL < 2.220 mmol/L in men and < 2.775 mmol/L in women or being on antilipidemic therapy; d) blood pressure ≥130 mmHg systolic and/or ≥85 mmHg diastolic or being on antihypertensive therapy; and e) waist circumference >102 cm in men and >88 cm in women. The subjects with following history were excluded. Alcohol intake more than 30 g/day (≈38 ml of 100% alcohol) and the patients with smoking history, Hepatitis B or C infection or other known liver diseases, liver enzymes exceeding the upper reference range in three times, use of hepatotoxic drugs, acute infectious/inflammatory conditions, familial hyperlipidemia, New York Heart Association class 3-4 heart failure.

Sample size
After consulting a statistician, sample size was estimated to be 100, with 50 cases and 50 age and sex matched healthy controls.

Type of study: a cross sectional observational study.

Method of sample collection
The informed consents were taken from the patients and control subjects. The selected subject's blood samples were collected with all aseptic precautions. 5 ml of blood was collected from median cubital vein. The collected blood was allowed to clot for 30 minutes in a clean dry test tube and was subjected to centrifugation to separate the serum. The serum samples were stored in a Deep freezer at -80⁰C till they were studied.

The following parameters were considered appropriate for the study:

1. Serum insulin levels defined by chemiluminescence method and insulin resistance by homeostasis of model assessment of insulin resistance (HOMA-IR).
2. Serum γGT by colorimetric method.
3. hs-CRP by chemiluminescence method.
4. Renal and liver function tests by colorimetric method.
5. Lipid profile by enzymatic, colorimetric method.
6. Fasting blood sugar by hexokinase method.
7. Measurement of body mass index.
8. To measure waist circumference, top of right iliac crest was located. A measuring tape was placed in a horizontal plane around abdomen at level of iliac crest. Before reading the measurements, it was estimated that the tape was snug but did not compress the skin and was parallel to floor. The assessment was performed at the end of normal expiration.

Statistical analysis
Descriptive and inferential statistical analysis has been carried out during the study. The results on continuous measurements are presented on Mean±SD (Min-Max) and the results on categorical measurements are presented in Number (%). Statistical processing of the research results was performed by parametric analysis with the calculation of Student's t-test using the software package Microsoft EXCEL 5.0. Chi-square test was used to find the significance of study parameters on categorical scale between two or more groups. Pearson correlation between γGT and HOMA-IR and hs-CRP were performed to measure the strength between variables and relationships.

Results
The clinical characteristics of the study population are presented in Table 1. The current study is a case control study, in which the serum γGT, hs-CRP and insulin levels were determined in 50 metabolic syndrome subjects and were compared with 50 healthy age and sex matched controls. The results were tabulated and statistically analyzed.

The metabolic syndrome patients were diagnosed according to the National Cholesterol Education Program's Adult Treatment Panel III criteria (NCEP ATP III criteria). The study

Table 1. Clinical characteristics of the study population

Parameters	Controls	**Cases**	**P value**
None of the subjects	50	50	
Sex (male/female)	18/32	20/30	0.68
Age	50.2±9	51.4±9.7	<0.05*
BMI (kg/m^2)	21.5±3.5	29.6±3.9	<0.001**
Waist circumference (cm)	82.5±10.3	104±9.5	<0.001**

Note: the values expressed as mean ± SD. t-test was used for groups' comparison.
The differences in proportions were assessed by means of Chi-square test.
* Suggestive significance (P value P<0.05);
** Strongly significant (P value P≤0.001).

population belonged to age group ranging 40-70 years old, which was similar in the controls as well. The mean±SD of the cases and controls were 51.4±9. 7 years old and 50.2±9 years old respectively, which suggested that metabolic syndrome was prevalent in late middle ages. Waist circumference (WC) and body mass index (BMI) are the two important anthropometric measurements among the various definitions of metabolic syndrome. The study proved the mean±SD for WC in that case as 104±9.5 cm and in the controls as 82.5±10.3 cm. And the mean BMI in that case was 29.58±3.96 kg/m^2 and in the controls – 23.14±2.52 kg/m^2. Both these parameters were significantly higher in the cases with p≤0.001.

The biochemical characteristics of the study population are presented in Table 2. The mean concentration of fasting blood glucose in the controls was 4.1±0.93 mmol/L; in that case it was 6.5±2.1 mmol/L, which was significantly increased in the subjects with MS. Increased triacylglycerols and decreased HDL-cholesterol were potential markers of CVD.

In this study, mean Triglycerides in metabolic syndrome cases was 1.86±0.96 mmol/L and in the controls, it was 1.41±0.8 mmol/L, which was significantly higher. HDL-cholesterol levels in cases were found to be 0.73±0.2mmol/L and 0.96±0.3mmol/L in the controls. The lower HDL-cholesterol levels in that case was found to be significant with p<0.005.

The mean±SD of γGT in that case was 60.96±45.64 U/L and in the controls 29.78±18.01U/L with a P value <0.001**. The mean±SD of serum insulin in that case was 29.34±26.94 µIU/ml and in the controls 11.97±5.98 µIU/ml with P value ≤0.01**. The mean±SD of hs-CRP in that case was 76.2±47.6 mmol/L and in the controls 27.6± 11.4 mmol/L with P value ≤0.001**. The mean±SD of HOMA-IR in that case was 9.44±4.39 and in the controls 2.32±1.48 with P value ≤0.001**.

The comparison of γGT, insulin, hs-CRP, HOMA-IR is presented in Table 3. Pearson correlation was completed to analyse the relationship between γGT, hs-CRP and HOMA-IR in MS cases are as presented in Table 4. γGT

Table 2. Biochemical characteristics of the study population

Variables	**Controls**	**Cases**	**P value**
Glucose (mmol/L)	4.1±0.93	6.5±2.1	<0.01*
Total cholesterol (mmol/L)	3.8±1.16	4.3±1.38	<0.05*
Triglycerides (mmol/L)	1.41±0.8	1.86±0.96	<0.05*
HDL cholesterol (mmol/L)	0.96±0.3	0.73±0.2	<0.05*
Serum albumin (mmol/L)	36.7±8.2	31.8±7.4	<0.01**
Aspartate aminotransferase (U/L)	19.8±7.9	24.26±15	0.06
Alanine aminotransferase (U/L)	17±9.7	22.38±12.1	<0.01**
Alkaline phosphatase (U/L)	71.4±25.6	83.5±33.9	<0.05*
Serum phosphate (mmol/L)	1.1±0.2	0.9±0.2	<0.01**
Serum creatinine (µmol/L)	61.9±26.5	53.5±0.3	<0.01**

Notes: the values expressed as mean SD. T-test was used for groups comparison.
* Suggestive significance (P value <0.05);
* Moderately significant (P value <0.01);
** Strongly significant (P value ≤0.001).

Table 3. Comparison of γ-GT, insulin, hs-CRP, HOMA-IR in both study groups

Parameters	Controls	Cases	P value
γ-GT (U/L)	29.78±18.01	60.96±45.64	<0.001**
Insulin (µIU/ml)	11.97±5.98	29.34±26.94	<0.01*
hs-CRP (mmol/L)	27.6±11.4	76.2±47.6	<0.001**
HOMA-IR	2.32±1.48	9.44±4.39	<0.01*

Notes: values expressed as mean±SD.
Z-test was used for groups comparison *. Suggestive significance (P value <0.05).
* Moderately significant (P value <0.01);
** Strongly significant (P value ≤0.001).

Table 4. Pearson correlation of γ-GT, HOMA-IR, hs-CRP in metabolic syndrome

Parameters	Metabolic syndrome (n=50)	
	r value	P value
γGT vs HOMA-IR	0.26	0.060+
γGT vs hs-CRP	0.252	0.078+
hs-CRP vs HOMA-IR	0.207	0.15

Notes: + suggestive significance.

showed a positive correlation with HOMA IR and hs-CRP which was of suggestive significance.

Discussion

MS comprises a group of atherogenic factors [11]. Besides, the gathered data have reported of many biochemical and anthropometric parameters associated with MS, together with parameters of obesity and products released by adipose tissue, plasma insulin levels, liver enzymes, and CRP [12, 13].

Many epidemiology studies have proved that circulating serum γGT levels may be associated with the evolvement and clinical progression of CVD, even after adjusting for confounding factor like alcohol consumption [14, 15]. Although high levels of γGT have been speculated to be directly atherogenic [16], just like several other biomarkers for MS, a direct causation of atherosclerosis remains to be elucidated. As presented in Table 3, a higher γGT along with insulin resistance levels in MS involves a potentially greater risk for subsequent development of type 2 diabetes.

The increasing evidences have proved that the circulating γGT, which is primarily synthesized from liver, is a key target organ for development of MS. A number of studies have also shown that the serum level of γGT directly correlates with an increased risk of MS [17]. This was evidenced by significant correlations between γGT levels and all MetS components, independently of age and gender, except for blood pressure values [18]. Hardly any studies have proved increased γGT activity in hypertensives, which could be associated with the relation between γGT and MS [19, 20].

The association between the serum γGT and hs-CRP (Table 2), which is, as put forward by Ortega et al. [21], the low-grade inflammation in liver caused by hepatic steatosis in MS, could have caused increase in γGT levels. hs-CRP, an acute-phase reactant of hepatic origin and a sensitive marker for systemic inflammation, predicts the occurrence of diabetes, metabolic syndrome and atherosclerotic diseases in healthy subjects [23]. It has been hypothesized that increased γGT levels might occur before elevation in CRP, and the related oxidative stress would give rise to a subsequent inflammatory response [24]. Also, fatty infiltration in liver might have enhanced oxidative stress, leading to glutathione metabolism with compensatory increase in γGT secretion. As γGT activity reflects oxidative stress and inflammation, the increased levels can actively predict the incidence of MS [17].

Many studies have proved the association between the increased γGT and insulin resistance, as well as the subsequent development of type 2 DM [14, 19]. The increase of γGT levels in serum might be as a result of secondary hepatic inflammation [22].

Conclusions

This study suggests that increased gamma-glutamyl transferase activity could be considered as harbinger of low-grade systematic

inflammation and oxidative stress through mediation of glutathione transport. Current study contributes to the increasing number of evidences that gamma-glutamyl transferase estimation in metabolic syndrome, which is simple and inexpensive, could be considered among the strongest serum predictors of insulin resistance, imminent type 2 diabetes and cardiovascular events.

Conflict of interest
The authors declare no conflict of interest.

ВЗАЄМОЗВ'ЯЗОК МІЖ ПОКАЗНИКАМИ ГАММА-ГЛЮТАМІЛТРАСФЕРАЗИ, ВИСОКОЧУТЛИВОГО С-РЕАКТИВНОГО БІЛКА ТА РІВНЯ ІНСУЛІНУ У ПАЦІЄНТІВ З МЕТАБОЛІЧНИМ СИНДРОМОМ

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Вступ. *Метаболічний синдром (МС), як сукупність факторів ризику розвитку серцево-судинних захворювань (ССЗ), є важливою проблемою охорони здоров'я. Отримані дані свідчать про те, що активність сироваткової гамма-глютамілтрансферази (ГГТ), у якості маркера атеросклеротичного процесу при ССЗ, має прогностичне значення, як і показники високочутливого С-реактивного білка (вч-СРБ).*

Мета. *Дослідити активність сироваткової ГГТ, вч-СРБ та інсулінорезистентність у пацієнтів з метаболічним синдромом.*

Методи. *Дослідження включало 50 пацієнтів з МС та 50 здорових осіб. Зразки сироватки були взяті у всіх учасників натщесерце для дослідження активності ГГТ, рівня вч-СРБ, інсуліну, глюкози в крові, оцінки ліпідного профілю та проведення печінкових проб. Також були розраховані антропометричні показники та індекс маси тіла (ІМТ).*

Результати. *У 50% досліджуваних з метаболічним синдромом активність ГГТ була достовірно вищою відносно контрольної групи, у 30% діагностовано підвищений рівень вч-СРБ (вище >0,5 ммоль/л), тоді як показники 94% осіб контрольної групи знаходилися в діапазоні норми. У 74% випадків виявлено наявність інсулінорезистентності у пацієнтів з метаболічним синдромом, тоді як у контрольній групі цей показник склав 32%. Висока активність ГГТ також спостерігалася при порушеннях ліпідного профілю та високому ІМТ.*

Висновок. *Отримані нами дані свідчать, що у пацієнтів з метаболічним синдромом активність сироваткової гамма-глютамілтрансферази достовірно вища, порівняно з контрольною групою. Також нами встановлено, що показники високочутливого С-реактивного білка та рівень інсулінорезистентності, які є незалежними факторами ризику серцево-судинних захворювань, також асоціюються з метаболічним синдромом. Встановлено кореляційні зв'язки між активністю гамма-глютамілтрансферази та високочутливого С-реактивного білка.*

Таким чином, показники сироваткової гамма-глютамілтрансферази можна розглядати як економічно доступний та достовірний предиктор метаболічного синдрому, що може передувати появі серцево-судинних захворювань у найближчому майбутньому.

КЛЮЧОВІ СЛОВА: **метаболічний синдром; гамма-глютамілтрансфераза; високочутливий С-реактивний білок; індекс HOMA-IR (Homeostasis Model Assessment of Insulin Resistance).**

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