Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Original Research Article

Assessment of Serum -glutamyl Transferase and High Sensitivity C-reactive Protein and Insulin Levels in Metabolic Syndrome Patients: A Cross-sectional Observational Study

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Received :12-08-2021. Revised:22-08-2021. Accepted:18-09-2021

Abstract

Aim: Evaluation of serum γ-glutamyl transferase and its association with high sensitivity C - reactive protein and insulin levels in the patients with metabolic syndrome.

Material and methods: This cross sectional observational study was carried out in the Department of Medicine Nalanda Medical College and Hospital, Patna, Bihar, India for 1 year. 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.

Results: 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/m2 and in the controls – 23.14±2.52 kg/m2. 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 triacylglycerol's 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

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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**.
Conclusion: 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.
Keywords: oxidative stress, HOMA- IR, glutathione transport

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 comunicable 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.[4-6] In addition, when compared with other hepatic markers, γGT was the major predictor of type 2 diabetes.[7-9] 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, sub- clinical inflammation has also been identified as a driving force for insulin resistance. Since 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.

Material and methods

This cross sectional observational study was carried out in the Department of Medicine Nalanda Medical College and Hospital, Patna, Bihar, India for 1 year.

Methodology

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]: fasting blood glucose ≥ 6.105 mmol/L; serum triglyceride ≥1.71 mmol/L or being on lipid

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

lowering therapy; c) Serum HDL < 2.220 mmol/L in men and < 2.775 mmol/L in women or being on antilipidemic therapy; 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.
After consulting a statistician, sample size was estimated to be 120, with 60 cases and 60 age and gender matched healthy controls.

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.

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 60 metabolic syndrome subjects and were compared with 60 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 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/m2 and in the controls – 23.14±2.52 kg/m2. 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 triacylglycerol's 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**.

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

Table 1: Clinical characteristics of the study population

Parameters	Controls	**Cases**	**P value**
None of the subjects	60	60	
Sex (male/female)	23/37	25/35	0.61
Age	50.2±9	51.4±9.7	<0.05*
BMI (kg/m2)	21.5±3.5	29.6±3.9	<0.001**
Waist circumference (cm)	82.5±10.3	104±9.5	<0.001**

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**

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*

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

Parameters	**Metabolic syndrome (n=60)**	
	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

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]

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

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.[21,22] 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]

Conclusion

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.

Reference

1. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: A joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; International atherosclerosis society; and international association for the study of obesity. Circulation. 2009;120:1640-5.
2. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta- analysis. J Am Coll Cardiol. 2010;56:1113-32.
3. Nemesánszky E, Lott JA. Gamma-glutamyl transferase and its isoenzymes: Progress and problems. Clin Chem. 1985;31:797-803.
4. André P, Balkau B, Vol S, Charles MA, Eschwège E, DESIR Study Group, et al. Gamma-glutamyl transferase activity and development of the metabolic syndrome (International

diabetes federation definition) in middle-aged men and women: Data from the epidemiological study on the insulin resistance syndrome (DESIR) cohort. Diabetes Care. 2007;30:2355-61.

5. Targher G. Elevated serum gamma-glutamyl transferase activity is associated with increased risk of mortality, incident type 2 diabetes, cardio- vascular events, chronic kidney disease and cancer - A narrative review. Clin Chem Lab Med. 2010;48:147- 57.
6. Turgut O, Tandogan I. Gamma-glutamyl transferase to determine cardiovascular risk: Shifting the paradigm forward. J Atheroscler Thromb. 2011;18:177-81.
7. Cho NH, Jang HC, Choi SH, Kim HR, Lee HK, Chan JC, et al. Abnormal liver function test predicts type 2 diabetes: A community-based prospective study. Diabetes Care. 2007;30:2566-8.
8. Ford ES, Schulze MB, Bergmann MM, Thamer C, Joost HG, Boeing H, et al. Liver enzymes and incident diabetes: Findings from the European prospective investigation into cancer and nutrition (EPIC)- potsdam study. Diabetes Care. 2008;31:1138-43.
9. Sato KK, Hayashi T, Nakamura Y, Harita N, Yoneda T, Endo G, et al. Liver enzymes compared with alcohol consumption in predicting the risk of type 2 diabetes: The Kansai healthcare study. Diabetes Care. 2008;31:1230-6.
10. Xu H, Barnes GT, Yang Q, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 2003; 112: 1821-30.
11. Grundy SM, Cleeman JI, Daniels SR, Dona- to KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: An American heart association/National heart, lung, and blood institute scientific statement: Executive summary. Crit Pathw Cardiol. 2005;4:198-203
12. Tracy RP. Inflammation, the metabolic syndrome and cardiovascular risk. Int J Clin Pract Suppl. 2003;134:10-7.
13. González AS, Guerrero DB, Soto MB, Díaz SP, Martinez-Olmos M, Vidal O, et al. Metabolic syndrome, insulin resistance and the inflammation markers C-reactive protein and ferritin. Eur J Clin Nutr. 2006;60:802-9.
14. Wei D, Chen T, Gao Y, Tian H. Serum gamma-glutamyl transferase and ferritin are related to insulin resistance: A Population- based study. Clin Lab. 2015;61:1157-61.
15. Emdin M, Passino C, Michelassi C, Donato L, Pompella A, Paolicchi A, et al. Additive prognostic value of gamma-glutamyl transferase in coronary artery disease. Int J Cardiol. 2009;136:80-5.
16. Du G, Song Z, Zhang Q. Gamma-glutamyl transferase is associated with cardiovascular and all-cause mortality: A meta-analysis of prospective cohort studies. Prev Med. 2013;57:31-7.
17. Kunutsor SK, Apekey TA, Seddoh D. Gamma glutamyl transferase and metabolic syndrome risk: A systematic review and dose response meta-analysis. Int J Clin Pract. 2015;69:136-44.
18. Relationship between serum gamma-glutamyltransferase activity and cardiometabolic risk factors in metabolic syndrome. J Family Med Prim Care. 2018;7(2):430-434.
19. Liu CF, Gu YT, Wang HY, Fang NY. Gamma-glutamyl transferase level and risk of hypertension: A systematic review and meta- analysis. PLoS One. 2012;7:e48878
20. Stranges S, Trevisan M, Dorn JM, Dmochowski J, Donahue RP. Body fat distribution, liver enzymes, and risk of hypertension: Evidence from the western New York study. Hypertension. 2005;46:1186-93
21. Ortega E, Koska J, Salbe AD, Tataran- ni PA, Bunt JC. Related articles, links serum gamma-glutamyl transpeptidase is a determinant of insulin resistance independently of adiposity in Pima Indian children. J Clin Endocrinol Metab 2006;91:1419-22.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

22. Aksakal E, Tanboga IH, Kurt M, Kaygın MA, Kaya A, Isik T, et al. The relation of serum gamma-glutamyl transferase levels with coronary lesion complexity and long-term outcome in patients with stable coronary artery disease. Atherosclerosis 2012;221:596-601
23. Ridker PM, Wilson PW, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardio- vascular risk? Circulation 2004; 109: 2818-2825.
24. Lee DH, Jacobs DR Jr. Association between serum gamma glutamyl transferase and C-reactive protein. Atherosclerosis 2005; 178: 327-330.