ORIGINAL ARTICLE

Serum Liver Enzymes in Metabolic Syndrome and Nonmetabolic Syndrome Patients: A Case–Control Study

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Abstract

Background: Metabolic syndrome (Met-S) is a major threat to human health all over the world due to a rise in obesity and sedentary lifestyle. It is associated with many cardiovascular risk factors, including insulin resistance, obesity, atherogenic dyslipidemia, and hypertension. This study was conducted to determine the correlation of serum liver enzymes, especially serum gamma-glutamyl transferase (GGT), in Met-S and non-Met-S patients.

Objectives: To determine the correlation of serum liver enzymes, especially serum GGT, in Met-S and non-Met-S patients.

Materials and Methods: An observational case–control study was carried out on a total of 100 patients—50 cases of Met-S as defined by the International Diabetes Federation (IDF) 2005 and 50 age- and gender-matched controls (non-Met-S patients) aged >18 years—at a tertiary care hospital of Western India. Patients' history taking, general anthropometric, and systemic examination were done. Liver function tests [serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), GGT, alkaline phosphatase (ALP)], C-reactive protein (CRP), and ultrasonography (USG) for visualizing liver involvement were done.

Results: The maximum number of patients with Met-S were >50 years of age, with male predominance (78%) and a high prevalence of diabetes, hypertension, and central obesity among them as major components of Met-S. Liver function tests such as GGT, SGPT, SGOT, and CRP were significantly raised in Met-S patients compared to non-Met-S patients. The majority of the Met-S patients with deranged liver function tests had fatty liver on USG abdomen.

Conclusion: This study showed a significant association between elevated levels of GGT, SGPT, SGOT, CRP, and fatty liver in Met-S patients compared to non-Met-S patients.

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Introduction

The term metabolic syndrome (Met-S) is also known as "syndrome X" and insulin resistance syndrome.[1] It refers to the co-occurrence of several known cardiovascular risk factors, including insulin resistance, obesity, atherogenic dyslipidemia, and hypertension.[2] Globally, Met-S is a major threat to human health all over the world.[3,4]

The worldwide prevalence of Met-S is on the rise, with the overall global prevalence estimated to be 20–25% of the adult population. A study conducted in 11 large urban cities of India during 2006–2010 reported the prevalence of Met-S as high as 35%.[5]

In 2005, the International Diabetes Federation (IDF) published new criteria for Met-S, which includes central obesity—waist circumference in male ≥90 cm and female ≥80 cm—plus two or more of the following: hypertriglyceridemia ≥150 mg/dL, with or without medications; low high-density lipoprotein (HDL) cholesterol <40 mg/dL in male and <50 mg/dL in female, with or without medications; hypertension ≥130/85 mm Hg, with or without medications; and fasting plasma glucose ≥100 mg/dL, with or without medications.[6]

Associated findings included fatty liver (especially in concurrent obesity) progressing to nonalcoholic fatty liver diseases (NAFLD), acanthosis nigricans, xanthoma and xanthelasma, arcus senilis, polycystic ovarian syndrome (PCOS) in females, elevated uric acid levels, etc.

Metabolic syndrome patients have simple fatty infiltration of the liver, steatohepatitis with necroinflammatory changes (NAFLD), and a variable degree of fibrosis, which may progress to liver cirrhosis. These changes of NAFLD due to Met-S lead to alteration of liver histology, morphology, and cellular dysfunction, which causes elevation of liver enzymes like gamma-glutamyl transferase (GGT), serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), and alkaline phosphatase (ALP). It is an independent risk factor for the mortality and morbidity of cardiovascular disease (CVD), along with diabetes mellitus, stroke, and hypertension in recent epidemiological and clinical studies due to its atherogenic property.[7]

According to certain studies, higher liver enzymes, especially GGT, occur due to low-grade hepatic inflammation induced by hepatic steatosis. Alternatively, excess fat in the liver could enhance oxidative stress, leading to overconsumption of glutathione with a compensatory increase in liver enzyme synthesis, along with high C-reactive protein (CRP) level, which reflects hepatic inflammation due to fatty liver.[8] Raised liver enzymes are relatively sensitive and easily obtained markers of fatty liver and reflect chronic ectopic fat deposition in the liver with Met-S association.

The prevalence of Met-S has progressively increased globally over several decades due to risk factors like sedentary lifestyle, addiction to smoking and alcoholism, mental stress, and obesity. According to IDF and National Cholesterol Education Program (NCEP), the prevalence of Met-S is estimated at >30% in the United States; however, by using adult treatment panel (ATP) criteria, prevalence is estimated at about 22%.[9–11]

It is of paramount importance to study the serum liver enzymes in metabolic and non-Met-S patients to treat it at early stages and prevent its further progression, which will help reduce the morbidity and mortality due to cardiovascular, cerebrovascular, and liver disease (fatty liver) in patients with Met-S.

Materials and Methods

This observational case–control study was carried out on 50 metabolic and 50 non-Met-S patients of >18 years of age who were visiting the medical outpatient department (OPD) of Sir Sayajirao General Hospital or were admitted in general medicine wards. Study was carried out over 1 year, from January to December 2021.

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Patients having Met-S as defined by International Diabetes Federation criteria were included in the study. IDF criteria include central obesity with two or more of hypertriglyceridemia, low HDL, hypertension, and diabetes mellitus.[6] Age- and gender-matched non-Met-S patients visiting medical OPD or admitted in medicine wards of the hospital were included randomly as control. These controls (non-Met-S patients) were included randomly from medical OPD or wards and therefore they had none or few of the components of Met-S but not fulfilling all criteria of Met-S.

Exclusion criteria included chronic alcohol consumption, viral hepatitis, pregnant women, ischemic heart disease, cardiac failure, and other cardiovascular events, severely immunocompromised patients, subjects with history of abdominal or cardiac surgery, malignancy, thyroid disease, severe renal insufficiency, drugs like antiepileptics, oral contraceptive pills, erythromycin, cimetidine, acute infections, and inflammatory disorders.

A detailed history and clinical examination were done as per predesigned and pretested proforma.

Patients were subjected to detailed anthropometric examination and laboratory investigations like liver function test (SGPT, SGOT, GGT, ALP), renal function tests. Ultrasonography (USG) of abdomen for visualization of liver involvement for fatty changes for both metabolic and non-Met-S patients was done.

Results

More numbers of males (78%) had Met-S compared to females (22%) as per Table 1.

Maximum numbers of patients were in the 51–60 years of age-group with a mean age of 58 years as shown in Table 1. It was inferred that the majority of the patients manifest Met-S later in life. In our study, all case and control patients were age- and gender-matched.

Table 1: Gender and age-wise distribution in metabolic and non-Met-S patients

	Met-S, n = 50, n (%)	*Non-Met-S, n = 50, n (%)*
Gender		
Female	11 (22)	16 (32)
Male	39 (78)	34 (68)
Age (years)		
31–40	3 (6)	4 (8)
41–50	7 (14)	7 (14)
51–60	19 (38)	20 (40)
61–70	16 (32)	14 (28)
>71	5 (10)	5 (10)

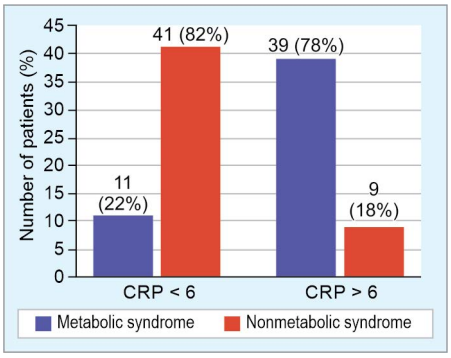

Fig. 1: Association of serum CRP value in both metabolic and non-Met-S patients

Table 2: Comparison of components of Met-S between patients with and without Met-S

Components of Met-S	*Met-S (n = 50)*	*Non-Met-S (n = 50)*	*p-value*
Raised blood pressure (hypertension)	48 (96%)	10 (20%)	<0.0001†
Central obesity	50 (100%)	17 (34%)	<0.0001†
Fasting plasma glucose (≥100 mg/dL)	50 (100%)	31 (62%)	<0.0001†
Hypertriglyceridemia	34 (68%)	3 (6%)	<0.0001†
Low HDL	12 (24%)	6 (12%)	0.118‡

†Fisher's exact test; ‡Chi-squared test

Table 3: Comparison of liver function test parameters between patients with and without Met-S

Liver function test	*Met-S (n = 50)*	*Non-Met-S (n = 50)*	*Total*	*p-value*	*Odds ratio (95% CI)*
GGT(U/L)					
Normal (7–35 U/L)	1 (2%)	13 (26%)	14 (14%)	0.0008†	1
Deranged	49 (98%)	37 (74%)	86 (86%)		11.88 (1.969–71.689)
SGPT(U/L)					
Normal (≤40 U/L)	12 (24%)	33 (66%)	45 (45%)	<0.0001‡	1
Raised	38 (76%)	17 (34%)	55 (55%)		5.896 (2.471–14.07)
SGOT(U/L)					
Normal (≤45 U/L)	7 (14%)	28 (56%)	35 (35%)	<0.0001‡	1
Raised	43 (86%)	22 (44%)	65 (65%)		7.347 (2.803–19.256)
ALP(U/L)					
Normal (≤110 U/L)	2 (4%)	9 (18%)	11 (11%)	0.051†	1
Raised	48 (96%)	41 (82%)	89 (89%)		4.441 (0.977–20.176)

†Fisher's exact test; ‡Chi-squared test

Table 4: Association of CRP with GGT (U/L) in Met-S patients

CRP	*GGT ≤35 (n = 1)*	*GGT = 36–50 (n = 12)*	*GGT >50 (n = 37)*	*Total*	*p-value*
≤6	0 (0%)	6 (54.54%)	5 (45.45%)	11 (22%)	0.03
>6	1 (2.56%)	6 (15.38%)	32 (82.05%)	39 (78%)	
Total	1 (100%)	12 (100%)	37 (100%)	50 (100%)	

Table 5: Comparison of USG abdomen between patients with and without Met-S

USG abdomen	*Met-S (n = 50)*	*Non-Met-S (n = 50)*	*Total*	*p-value*
Normal liver parenchyma	8 (16%)	46 (92%)	54 (54%)	<0.0001[†]
Fatty liver	42 (84%)	4 (8%)	46 (46%)	
Total	50 (100%)	50 (100%)	100 (100%)	

[†] Fisher's exact test

Table 2 shows distribution of components of Met-S among the study population. Controls (non-Met-S patients) were taken randomly from the OPD of the institute, so few of them had central obesity, raised blood pressure, raised blood sugar level, or dyslipidemia. On comparing these components of Met-S in patients with metabolic and non-Met-S, each individual component was more commonly seen in patients with Met-S (*p*-value < 0.05).

Among Met-S group patients, 98% had raised GGT, 76% had raised SGPT, 86% had raised SGOT, and 96% had raised ALP level. When comparing this with age- and gender-matched patients of non-Met-S, this was statistically significant (*p*-value < 0.05) (Table 3).

As per Figure 1, 78% (39) patients of Met-S had higher CRP value of >6 while only 22% (11) patients of non-Met-S had higher CRP value of >6 (*p*-value < 0.05).

Among 39 patients of Met-S with CRP value of >6, 32 patients had GGT level >50 U/L also. This shows strong correlation between CRP and GGT in patients of Met-S. It suggests the majority of patients with Met-S had high CRP and high GGT level with significant *p*-value of 0.03 among them (Table 4).

As per Table 5, 84% (42) patients of Met-S patients and 8% (4) patients of non-Met-S patients had fatty liver in USG. This shows strong association of Met-S and fatty liver changes in USG (*p*-value < 0.0001).

Discussion

In our study, we found that 38% of patients with Met-S were of 51–60 years age. Krishnamoorthy et al. study observed that there was a steady increase in the burden across the age-groups from 13% in the 18–29 years group to 50% in the 50–59 years group. Prasad et al. study showed significantly higher rates of Met-S in older age-groups.[12]

In this study, male patients with Met-S were more than female patients with Met-S. However, Prasad et al. observed an age-standardized prevalence rate of Met-S of 33.5% overall, with 24.9% males and 42.3% females. The study done by Prasad et al. was a community-based study, and the present study was a hospital-based study. Kapoor et al. found gender discrimination in access to healthcare, with an overall sex ratio of 1.69 male to 1 female outpatient visit in a large referral public hospital of Delhi, India.[13] Gender discrimination in access to healthcare, along with reluctance of female patients to enroll in the study, may be the reason for a greater number of male patients with Met-S than females in this study compared to other studies.

Among the patients of Met-S, all 50 (100%) of them had central obesity with raised fasting plasma glucose level, 48 (96%) had raised blood pressure, 34 (68%) had hypertriglyceridemia, and 12 (24%) had low HDL level. Biadgo et al. estimated the prevalence of Met-S among diabetic patients using NCEP-ATP III and IDF criteria and found the most prevalent component of Met-S was elevated triglyceride (56.6% in NCEP-ATP III and 62.3% in IDF criteria), followed by abdominal obesity (61%) in IDF and elevated blood pressure (55.4%) in NCEP-ATP III criteria.[14]

In our study, 49 (98%) out of 50 patients with Met-S had raised GGT (>35 U/mL) level, compared to 37 (74%) out of 50 non-Met-S patients who had raised GGT level. Apart from that, SGPT was raised in 38 (76%) of Met-S patients and 17 (34%) of non-Met-S patients. SGOT level was raised in 43 (86%) patients with Met-S and 22 (44%) patients with non-Met-S. All the above values signify that liver function test parameters have a strong correlation with Met-S patients in comparison to non-Met-S patients. Wang et al. revealed that liver function tests, especially GGT level, showed a significantly positive correlation in Met-S patients as an early predictive marker of Met-S, CVD, heart failure, and all-cause mortality.[15] Rantala et al. revealed a highly significant relationship between GGT and the components of the Met-S even after adjustment for age, body mass index, and alcohol consumption.[16] GGT level is associated with the development of CVD risk factors, including diabetes, hypertension, and the Met-S.[17]

In our study, 78% of Met-S cases had higher CRP value of >6 compared to non-Met-S controls. This was suggestive of an inflammatory condition of the liver due to ectopic fat deposition in the liver. Rutter et al. suggested that CRP level was significantly positive in Met-S patients compared to non-Met-S patients.[18]

Krishnamoorthy et al. and Akbaraly et al. observed that circulating GGT and transaminase activities are elevated in patients with Met-S. GGT plays an important role in glutathione homeostasis, which is an antioxidant defense mechanism for the cell. Elevated GGT levels could be a marker of oxidative stress, subclinical inflammation, and proatherogenic molecules in patients with Met-S. Ultimately, this leads to increased levels of CRP in them.[5,19] Similar correlation between CRP and GGT was also noted in our study, with significant *p*-value of 0.03. In our study, 82.05% of Met-S patients had GGT value of >50 U/L with CRP levels of >6, while 45.45% of Met-S patients had GGT value of >50 U/L with CRP levels of <6. It showed strong positive correlation between CRP and GGT in Met-S patients.

We found a strong correlation between USG changes of fatty liver in patients with Met-S (84%) compared to non-Met-S patients (8%). Goyal et al. found fatty liver in 73% of cases of Met-S and in 38% of controls. It shows a strong correlation between fatty liver and Met-S.[20]

The positive correlation between GGT and CRP is suggestive of likely inflammation, atherosclerosis, and fatty liver, and it is a risk factor for high cardiovascular morbidity and mortality in upcoming years in patients with Met-S.

Our study findings are limited primarily by the small sample size. Other than that, the long-term outcome on the patients was not studied. Moreover, the study individuals were taken only from one center and hence may not represent the whole population.

Conclusion

Most of the patients with Met-S had deranged liver enzymes (GGT, SGPT, SGOT, ALP) and fatty changes of liver in USG. The majority of Met-S patients had raised CRP level due to low-grade hepatic inflammation and atherogenic property in view of increased oxidative stress and reduced glutathione reductase level, which causes more damage to liver cells and alteration of its function. It is a risk factor for high cardiovascular and cerebrovascular morbidity and mortality in future.

We can prevent cardiovascular and cerebrovascular morbidity and mortality by identifying components of Met-S in the population at an early age and preventing further progression of Met-S in them. We can reduce the prevalence of Met-S by educating people about all high-risk factors causing the disease as primordial prevention, along with regular medication and checkup of the particular disease, and educating them on how to prevent further complications.

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