Can Gamma Glutamyle Transferase Predict Unhealthy Metabolic Phenotype in Healthcare Workers in Azar Cohort Study?

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Abstract

Background: There is a close connection between serum gamma-glutamyltransferase (GGT), insulin resistance, and the increased number of the components of the metabolic syndrome (MetS). However, there are no studies evaluating the correlation between GGT and cardiometabolic phenotype. Thus, the main objective of the current study is to evaluate the relationship between GGT and cardiometabolic phenotypes among healthcare workers in Azar Cohort Study.

Method: In this cross-sectional study, anthropometric measurements, fasting blood sugar (FBS), triglyceride (TG), cholesterol, high lipoprotein density (HDL), GGT, and blood pressure of 1458 healthcare workers were evaluated. MetS was determined according to the report by the National Cholesterol Education Program Adult Treatment Panel III (ATP III). We classified participants into four cardiometabolic phenotypes. These phenotypes consist of metabolically-healthy lean (MHL) (no MetS and BMI < 25 kg/m^2), metabolically-unhealthy lean (MUHL) (MetS present and BMI < 25 kg/m^2), metabolically-healthy obese (MHO) (no MetS and BMI ≥25 kg/m^2), and metabolically-unhealthy obese (MUHO) (MetS present and BMI ≥ 25 kg/m^2).

Results: The first and third GGT tertiles have the highest prevalence of MHL (31%) and MHO (65.1%), respectively, which is statistically significant (P-value ≤ 0.001). In comparison with the lowest GGT tertile, the odds of MHO and MUHO increased by 2.84 (95% CI 2.01-4.01) and 9.12 (95%CI 5.54-15), respectively. However, the correlation between MUHL and GGT tertile does not show a similar trend. According to the ROC curve, the cutoff value of 18.5 U/l for GGT allowed us to distinguish between MHO and MUHO.

Conclusions: Based on the findings of the study, the GGT can be used as a biomarker to reveal the risk of MetS, and we believe that the GGT level can be used for the early detection of MHO at risk of MetS and for administering proper interventions.

1. Background

Gamma-glutamyltransferase (GGT) is a glycosylated protein produced by the epithelial cells of the intrahepatic bile ducts, and it is places on the external surface of the plasma membrane. GGT can be used as a marker for alcohol consumption status and hepatobiliary diseases, such as non-alcoholic fatty liver disease (NAFLD). GGT level is indirectly associated with increased oxidative stress and chronic inflammation, which is closely related to metabolic diseases [1, 2]. In addition, high ranges of GGT are correlated with cardiovascular diseases, atherosclerosis, type 2 diabetes, chronic kidney disease (CKD), and the metabolic syndrome (MetS) [1, 3].

MetS consists of a combination of metabolic risk factors, including high blood pressure, central obesity, hypertriglyceridemia, low high-density lipoprotein (HDL), cholesterol, and increased blood glucose. This syndrome is a major global public health problem since it increases the risk of heart disease, cancers, type 2 diabetes, and so on [4].

There is a close relationship between serum GGT, insulin resistance, and the increased number of components of MetS [5]. It has been reported that patients with MetS and high GGT are at a higher risk of cardiovascular disorders compared to individuals without MetS or patients with MetS and low GGT [6]. Moreover, recent studies have documented the relationship between GGT and mortality [7–9]. Strong evidence demonstrates that normal ranges of GGT values are associated with increased cardiovascular and all-cause mortality. This correlation was valid in both sexes of normal and obese subjects, with or without cardiovascular disease, and after adjusting for confounding factors [7, 8]. These findings imply that subjects with normal BMI or obese subjects may be metabolically healthy or unhealthy. Therefore, further studies are required to determine which biochemical parameters are associated with a healthier and less atherogenic metabolic health status in normal or obese individuals.

Although various studies have assessed the correlation between GGT and cardiometabolic risk factors in obesity, no studies have so far focused on differentiating between metabolically-healthy lean (MHL), metabolically-unhealthy lean (MUHL), metabolically-healthy obese (MHO), and metabolically-unhealthy obese (MUHO) states. Thus, it can be argued that GGT, as a simple cost-effective test, is not only important for the multi-marker approach in cardiovascular risk evaluation, but it can also be applicable for distinguishing between the metabolic subtypes (i.e., cardiometabolic phenotype) [10–12]. However, there are no studies focusing on the correlation between GGT and cardiometabolic phenotype. Thus, this study aimed to evaluate the relationship between GGT and cardiometabolic phenotypes among healthcare workers in Azar Cohort Study.

2. Methods

This analysis was conducted using data obtained for the healthcare workers in Tabriz Cohort Study. The study is a part of large prospective epidemiological research studies in Iran (Persian Cohort Study) [13], which was conducted in 2020 as a prospective cohort study to determine the risk factors of non-communicable diseases (NCDs) among healthcare providers, official staff, and professors in Tabriz. The target population of our study includes 6,000 healthcare workers in hospitals, schools, and district healthcare networks under the supervision of Tabriz University of Medical Sciences (TBZMED). This study is included in Azar Cohort Study, which was conducted by the liver and gastrointestinal diseases Research center of Tabriz University of medical Sciences [14].

Applied baseline evaluation of recognized and novel risk factors of NCDs was in the form of face-to-face interviews or examinations.

We used the data for 1,458 participants of the Cohort Study in our research. Written informed consent was obtained from all participants. This study was approved by the Ethic Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1396.1263).

Participants of this study include fulltime and long-term contract employees aged between18 and 75 years, who are not pregnant or lactating, and who are not planning to retire within the next five years.

Patients who reported having been diagnosed with debilitating psychiatric disorders or physical illnesses by a health professional were excluded from this study.

2.1. Demographic Characteristics of the Participants

The questionnaires focused on demographic characteristics of the participants, i.e., age, gender, marital status, and educational level. Moreover, individual habits, such as smoking, drug use, hookah, and alcohol consumption, or being passive smokers were recorded for all the participants.

2.2. Anthropometric and Blood Pressure Measurements

The measured anthropometric data included weight, height, waist circumference, body mass index (ratio of weight in kilograms to height in meters squared), and blood pressure. The anthropometric measurements have been described in detail elsewhere [13]. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a mercury sphygmomanometer (Riester Exacta 1350 Sphygmomanometer, Germany) in sitting position after 10 minutes of rest. The averages of two measurements on one day with an interval of two minutes and twice in each arm was used in the statistical analysis.

2.3. Biochemical Factors

After an overnight fast of ≥ 12 hours, blood samples were drawn. Enzymatic methods were used to characterize GGT, fasting blood sugar (FBS), high-density lipoprotein (HDL), and triglyceride (TG).

2.4. Definition of MetS

The MetS criteria were defined based on the report by the National Cholesterol Education Program Adult Treatment Panel III (ATP III) [15]. Three or more of the following conditions must be met to confirm the diagnosis of MetS: TG ≥ 150 mg/dl (drug treatment for elevated triglycerides is an alternate indicator), waist circumference ≥ 102 cm in men and ≥ 88 cm in women, and HDL-C values of < 40 mg/dl in men and < 50 mg/dl in women. Increased systolic blood pressure (≥ 130 mmHg) and/or diastolic blood pressure (≥ 85 mmHg) or taking antihypertensive medication will represent hypertension. By definition, fasting glucose is considered elevated if it is ≥ 100 mg/dl, or if the individual is taking glucose-lowering medication.

In this study, we classified participants into four cardiometabolic phenotypes based on the BMI cutoff point (25 kg/m^2) and the presence of MetS. These phenotypes include MHL (No MetS and BMI < 25 kg/m^2), MUHL (MetS present and BMI < 25 kg/m^2), MHO (No MetS and BMI ≥ 25 kg/m^2), and MUHO (MetS present and BMI ≥ 25 kg/m^2).

2.5. Statistical Analysis

We used SPSS, version 11.5, Chicago, IL for data analysis. Continuous variables are demonstrated as mean ± standard deviation, while categorical variables are shown as numbers (percentages). Comparison among the four groups was performed using chi-square analysis and one-way ANOVA. We categorized

participants into the following serum GGT tertiles: Tertile 1: ≤14 U/l; Tertile 2: 15–23 U/l; and Tertile 3: ≥24 U/l. Multinomial logistic regression analysis was used for estimating the association between the cardiometabolic phenotype and the serum GGT tertile. Moreover, crude and adjusted odds ratios (OR) and their corresponding 95% confidence intervals (95% CI) were assessed. The effects of the confounding factors (i.e., age, gender, marital status, educational level, and current smoking status) were adjusted, and the MHL group was considered as the reference group. The diagnostic value of the GGT area under the curve was calculated by the receiver-operating characteristics (ROC) curves ([AUC] and 95% confidence interval [CI], sensitivity, and specificity). According to BMI classification, seven underweight participants were excluded. Eventually, 1,451 subjects were considered in the statistical analysis. P values < 0.05 were considered statistically significant.

3. Results

Table 1 presents the baseline characteristics of the participants according to their GGT tertiles. Among the three tertiles, the third tertile has a higher proportion of male, illiterate, and married participants. Moreover, the first and third GGT tertiles have the highest prevalence of MHL (31%) and MHO (65.1%), respectively, which is statistically significant (P-value ≤ 0.001). Furthermore, the mean values of WC, TG, cholesterol, HDL, FBS, SBP, DBP, and BMI show an accelerating trend from the first GGT tertile to the third GGT tertile (P-value ≤ 0.001).

Table 1
Baseline characteristics of participants according to GGT tertile (n = 1451)

GGT (IU/L)				
	Tertile 1 = ≤ 14 (n = 471)	**Tertile = 15–23 (n = 485)**	**Tertile = ≥ 24 (n = 495)**	P value
Gender n(%)				€<0.001
Male	99(21)	255(52.6)	371(74.9)	
Female	372(79)	230(47.4)	124(25.1)	
Education level n(%)				€<0.001
Illiterate	5(1.1)	14(2.9)	10(20)	
Primary school	14(3)	31(6.4)	40(8.1)	
High school	68(14.4)	77(15.9)	112(22.6)	
University	384(81.5)	363(74.8)	333(67.3)	
Marital status n(%)				€<0.001
Married	394(83.7)	420(86.6)	463(93.5)	
Not married	77(16.3)	65(13.4)	32(6.5)	
Cardiometabolic phenotype n (%)				€<0.001
*MHL	146(31)	115(23.7)	57(11.5)	
**MUHL	3(0.6)	7(1.4)	2(0.4)	
¶MHO	290(61.6)	294(60.6)	322(65.1)	
¶MUHO	32(6.8)	69(14.2)	114(23)	
Smoking status n(%)				€<0.001
Yes	13(2.7)	43(8.8)	46(9.3)	
No	456(96.9)	437(90.1)	434(87.7)	
Alcohol consumption n(%)				
Yes	1(0.2)	5(1)	3(0.6)	-

€P value :chi square test ;¥ P- value :one way Anova ; *MHL: metabolically healthy lean ;** MUHL: metabolically unhealthy lean ;¶MHO: Metabolically healthy obese ;¶¶MUHO: metabolically unhealthy obese

GGT (IU/L)				
No	470(99.6)	480(99)	492(99)	
Drug use n(%)				-
Yes	-	-	-	
No	-	-	-	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Age (year)	41.51 ± 6.16	42.83 ± 7.09	43.21 ± 6.74	¥<0.001
Waist circumference (cm)	92.08 ± 8.37	95.17 ± 8.9	98.75 ± 8.7	¥<0.001
Triglyceride (mg/dl)	96.12 ± 38.40	118.83 ± 50.85	147.90 ± 77.32	¥<0.001
Fasting blood sugar (mg/dl)	81.67 ± 15.93	86.34 ± 19.39	90.89 ± 23.39	¥<0.001
High density lipoprotein (mg/dl)	48.35 ± 11.01	45.45 ± 10.35	43.96 ± 9.85	¥<0.001
Cholesterol (mg/dl)	157.53 ± 33.98	166.95 ± 35.79	177.76 ± 37.91	¥<0.001
Systolic blood pressure (mm Hg)	105.13 ± 12.73	110.59 ± 13.69	116.44 ± 14.72	¥<0.001
Diastolic blood pressure (mm Hg)	73.06 ± 8.27	76.01 ± 8.77	79.27 ± 9.55	¥<0.001
Body mass index (kg/m^2)	26.73 ± 3.64	27.50 ± 3.91	29.06 ± 4.01	¥<0.001

€P value :chi square test ;¥ P- value :one way Anova ; *MHL: metabolically healthy lean ;** MUHL: metabolically unhealthy lean ;¶MHO: Metabolically healthy obese ;¶¶MUHO: metabolically unhealthy obese

The results in Table 2 indicate that the third tertile has the lowest proportion of females (P-value < 0.001) as a GGT dose-dependent variable in MHL, MHO, and MUHO classes of cardiometabolic phenotypes.

Table 2
Demographic, anthropometric and biochemical factors according to GGT tertile stratified by cardiometabolic phenotype

	GGT (UL/l)			
	Tertile = ≤ 14 (n = 471)	**Tertile = 15–23 (n = 485)**	**Tertile = ≥ 24 (n = 495)**	**P value**
MHL				
Gender n(%)				€<0.001
Male	35(24)	83(72.2)	46(80.7)	
Female	111(76)	32(27.8)	11(19.3)	
	mean ± SD	**mean ± SD**	**mean ± SD**	
Age (year)	40.996.70	41.60 ± 6.78	41.28 ± 7.21	¥0.77
Waist circumference (cm)	85.09 ± 5.70	87.25 ± 5.82	86.84 ± 5.30	¥0.02
Triglyceride (mg/dl)	86.09 ± 32.16	107.10 ± 47.13	106.08 ± 38.56	¥0.007
Fasting blood sugar (mg/dl)	80.78 ± 9.52	84.06 ± 12.53	85.42 ± 18.26	¥<0.001
High density lipoprotein (mg/dl)	49.58 ± 10.99	47.15 ± 10.75	45.65 ± 8.99	¥0.03
Cholesterol (mg/dl)	152.14 ± 33.87	163.30 ± 32.47	165.50 ± 34.91	¥0.006
Systolic blood pressure (mm Hg)	101.23 ± 11.20	108.11 ± 13.06	109.98 ± 13.41	¥<0.001
Diastolic blood pressure (mm Hg)	70.26 ± 7.19	74.01 ± 7.16	74.74 ± 7.85	¥<0.001
MUHL				
Gender n(%)				€0.33
Male	1(33.3)	4(57.1)	0(0)	
Female	2(66.7)	3(42.9)	2(100)	
	mean ± SD	**mean ± SD**	**mean ± SD**	
Age (year)	50.33 ± 7.37	42 ± 5.47	44 ± 2.82	¥0.16
Waist circumference (cm)	90.06 ± 2.0	90.91 ± 6.44	92.5 ± 0.70	¥0.11

€P value :chi square test ; ¥ P- value :one way ANOVA ; *MHL: metabolically healthy lean ;** MUHL: metabolically unhealthy lean ;¶MHO: Metabolically healthy obese ;¶¶MUHO: metabolically unhealthy obese

		GGT (UL/l)		
Triglyceride (mg/dl)	182 ± 86.48	194.14 ± 34	112 ± 67.88	¥0.95
Fasting blood sugar (mg/dl)	75 ± 2.64	83.42 ± 12.84	124 ± 65.05	¥0.46
High density lipoprotein (mg/dl)	41 ± 6	39.29 ± 5.64	46 ± 0.0	¥0.34
Cholesterol (mg/dl)	161 ± 14.17	167.42 ± 37.19	160.5 ± 55.86	¥0.88
Systolic blood pressure (mm Hg)	114.33 ± 6.02	119.95 ± 18.03	97.5 ± 3.53	¥0.23
Diastolic blood pressure (mm Hg)	85.33 ± 0.57	78.85 ± 15.38	67.50 ± 3.53	¥0.34
MHO				
Gender n(%)				€<0.001
Male	58(20)	142(48.3)	241(74.8)	
Female	232(80)	152(51.7)	81(25.2)	
	mean ± SD	**mean ± SD**	**mean ± SD**	
Age (year)	41.73 ± 5.85	42.84 ± 7.23	42.99 ± 6.62	¥0.04
Waist circumference (cm)	94.81 ± 7.47	97.05 ± 8.21	98.62 ± 7.11	¥0.002
Triglyceride (mg/dl)	95.15 ± 31.72	110.69 ± 41.62	134.66 ± 64.37	¥<0.001
Fasting blood sugar (mg/dl)	81.89 ± 18.70	83.82 ± 11.52	86.02 ± 11.13	¥<0.001
High density lipoprotein (mg/dl)	48.65 ± 11.11	46.02 ± 10.34	45.15 ± 9.96	¥<0.001
Cholesterol (mg/dl)	159.63 ± 33.45	166.58 ± 36.60	178.74 ± 37.47	¥<0.001
Systolic blood pressure (mm Hg)	106.18 ± 12.71	109.65 ± 12.97	114.90 ± 14.21	¥<0.001
Diastolic blood pressure (mm Hg)	73.78 ± 8.25	75.67 ± 8.78	78.43 ± 9.45	¥<0.001
MUHO				
Gender n(%)				€<0.001
Male	5(15.6)	26(37.7)	84(73.7)	
Female	27(84.4)	43(62.3)	30(26.3)	

€P value :chi square test ; ¥ P- value :one way ANOVA ; *MHL: metabolically healthy lean ;** MUHL: metabolically unhealthy lean ;¶MHO: Metabolically healthy obese ;¶¶MUHO: metabolically unhealthy obese

	GGT (UL/l)			
	mean ± SD	**mean ± SD**	**mean ± SD**	
Age (year)	41.06 ± 5.82	44.90 ± 6.80	44.81 ± 6.61	¥0.01
Waist circumference (cm)	99.57 ± 5.61	100.81 ± 7.57	105.18 ± 8.12	¥0.009
Triglyceride (mg/dl)	142.56 ± 57.20	165.40 ± 61.74	206.84 ± 93.17	¥0.05
Fasting blood sugar (mg/dl)	84.31 ± 12.14	101.15 ± 39.57	106.79 ± 38.46	¥<0.001
High density lipoprotein (mg/dl)	40.78 ± 7.00	40.78 ± 8.59	39.71 ± 8.85	¥0.65
Cholesterol (mg/dl)	162.75 ± 38.58	174.55 ± 37.09	181.41 ± 39.59	¥<0.001
Systolic blood pressure (mm Hg)	112.84 ± 14.20	117.71 ± 14.79	124.33 ± 13.68	¥<0.001
Diastolic blood pressure (mm Hg)	78.37 ± 8.70	80.43 ± 8.97	84.08 ± 8.75	¥0.001

€P value :chi square test ; ¥ P- value :one way ANOVA ; *MHL: metabolically healthy lean ;** MUHL: metabolically unhealthy lean ;¶MHO: Metabolically healthy obese ;¶¶MUHO: metabolically unhealthy obese

Interestingly, the mean values of WC, TG, FBS, cholesterol, DBP, and SBP are increasing in MHL, MHO, and MUHO groups, which represents a dose-response manner matching to the GGT tertile (P-value < 0.05). Additionally, there is a similar trend in the mean values of SBP and DBP, increasing significantly with increasing GGT tertile (P-value < 0.05), whereas WC, FBS, and cholesterol do not follow this trend. Table 3 shows the association between serum GGT and cardiometabolic phenotype.

Table 3
Odds ratios and 95% confidence intervals for cardiometabolic phenotype according to serum Gamma-glutamyltransferase tertiles

	GGT (UL/L)		
	Tertile = ≤ 14 (n = 471)	**Tertile = 15–23 (n = 485)**	**Tertile = ≥ 24 (n = 495)**
	OR(95% CI)	OR(95% CI)	OR(95% CI)
MUHL	Reference	2.96(0.74–11.70)	1.70(0.27–10.48)
MHO	Reference	1.28(0.96–1.72)	2. 84(2.01–4.01)
MUHO	Reference	2.73(1.68–4.44)	9.12(5.54-15.00)
MUHL			
Model 1	Reference	3.63(0.87–15.18)	2.55(0.36–17.82)
Model2	Reference	3.61(0.86–15.14)	2.45(0.35–17.20)
Model3	Reference	2.87(0.65–12.54)	2.27(0.32–16.06)
MHO			
Model1	Reference	1.55(1.13–2.12)	3.92(2.66–5.79)
Model2	Reference	1.56(1.14–2.15)	3.90(2.63–5.78)
Model 3	Reference	1.54(1.12–2.12)	3.93(2.65–5.83)
MUHO			
Model 1	Reference	3.40(2.04–5.66)	13.85(7.95–24.15)
Model2	Reference	3.43(2.06–5.71)	13.78(7.90-24.08)
Model3	Reference	3.53(2.11–5.90)	14.29(8.15–25.08)

MHL was considered as a reference group; Model 1: adjusted for age and gender ; Model 2 adjusted for age, gender; Model 3 adjusted for age, gender, education level, marital status, smoking status

We performed a multinomial regression analysis, showing that compared to the lowest GGT tertile, the odds of MHO and MUHO increased by 2.84 (95% CI 2.01–4.01) and 9.12 (95%CI 5.54-15) respectively. The significant correlation was still valid after adjusting for different confounding factors (i.e., age, gender, marital status, education level, smoking, and alcohol consumption). The observed odds ratio for MUHO was 3.53 in Model 3 (adjusting for age, gender, marital status, education level, smoking, and alcohol consumption), which is the highest. This value was 2.11–5.90 in the second GGT tertile, while it was 14.29 (8.15–25.08) in the third GGT tertile. In contrast, the correlation between MUHL and the GGT tertile has no similar trend.

We performed ROC analysis to differentiate between MHO and MUHO. The cutoff value of 18.5 U/l for GGT allowed us to distinguish MHO from MUHO with a sensitivity of 72.6% and a specificity of 50.7%. GGT had acceptable diagnostic accuracy (AUC 0.634 [95% CI: 0.59–0.67]) (Fig. 1). The depicted ROC curve for MHL and MUHL and the related findings are not reported here because they are not significant. This can be due to the small sample size of the MUHL.

4. Discussion

Our main findings with regard to the three cardiometabolic phenotype classes (i.e., MHL, MHO, and MUHO) are as follows. The frequency of females decreased as a dose-dependent variable of GGT tertile, which means that the lowest frequency was observed in the third GGT tertile. In MHL, MHO, and MUHO groups, significant changes in the mean WC, TG, cholesterol, FBS, DBP, SBP, and low HDL can be seen by increasing the GGT levels. The odds of MHO and MUHO increased according to the GGT tertile. The highest odds occurred in the third GGT tertile. This significant correlation was more pronounced after adjusting for confounding factors.

Our results confirm the findings of an earlier study, showing a positive correlation between serum GGT and MetS after adjusting for demographics, BMI, alcohol consumption, and smoking [16–21]. Xue et al. noted that risk of MetS increased 4.37 folds in the highest GGT quartiles after adjusting for confounding factors [18]. In another cross-sectional study, Lee et al. adjusted for age and drinking status, and obtained comparable results with an odds ratio of 2.97 in the highest GGT quartile [19]. Although the results of these studies show that GGT increases the risk of MetS, other studies show an increase in the risk of MetS even with a normal range of GGT [22, 23].

In most cases, the findings related to the association between MetS and GGT levels were adjusted for BMI. Recent studies show a subset of overweight and obese individuals who have been documented to have normal metabolic profiles [24]. According to some reports, “metabolically-normal” individuals with elevated body size may have a similar risk of chronic disease to normal-weight individuals and individuals without metabolic abnormalities [25]. In contrast, approximately 24% of normal-weight U.S. adults (BMI < 25.0 kg/m^2) are considered metabolically abnormal [26], which places them at a high risk for chronic diseases, and as compared to the MHNW individuals, those are generally associated with elevated BMI. Understanding the effect of body size in individuals, which puts them at a higher risk for the metabolic syndrome, can have implications for public health and clinical practice. To the best of the authors’ knowledge, there is no published studies on the association between cardiometabolic phenotype and GGT levels, except for one study with a small sample size (n = 140), which investigated the correlation between the GGT levels and MHO and at-risk obese individuals in young non-diabetic obese women [27]. While some metabolically-healthy normal-weight and obese participants have an increased risk of unhealthy phenotype, others may have considerably stable and desirable metabolic profiles, which is a matter of concern [28].

Accordingly, it is important to determine reliable biomarkers to distinguish healthy subjects at risk for transition to an unhealthy metabolic condition. GGT is an accessible marker in basic blood tests which can easily be measured and interpreted. Therefore, in this study, we examine the association between the cardiometabolic phenotype and the GGT levels. In this regard, our findings indicated the highest prevalence of MHO and MUHL in the third GGT tertile (highest level); however, a number of MHL individuals are also in the third GGT tertile. This indicates that these metabolically-healthy subjects may be at risk of a transition to a metabolically-unhealthy condition.

These findings are similar to those of Mankowska-Cyl et al., who noted that the elevated GGT was more prevalent in at-risk obese women than MHO women [27].

Furthermore, by evaluating the metabolic syndrome components (WC, DBP, SBP, TG, FBS, and low HDL), we observed a dose-response manner, which was increasing per GGT tertile. These findings indicate that higher GGT levels may represent metabolic modifications, and they can function as a clinical guide for different cardiometabolic phenotype classes. ROC was described to assess the distinguishing function of GGT among different cardiometabolic phenotype classes, which demonstrates a cutoff value of 18.5 UL/l for GGT, and it may indicate the transition of an MHO individual to the MUHO class.

The detailed mechanism of this relationship was not completely clarified. However, some possible descriptions can be suggested, e.g., serum GGT levels have been stated as one of the oxidative stress markers [29, 30]. Elevated serum GGT activity leads to the shift of extra glutathione into cells and glutathione metabolism, which causes oxidative stress [18]. It has been documented that oxidative stress plays a predominant role in the pathogenesis of the metabolic syndrome [19, 20].

Furthermore, gamma-glutamyltransferase plays a pro-inflammatory role in mediating the interconversion of leukotrine-C4 (LT-C4) into leukotriene -D4, where LT-C4 is a glutathione-containing inflammatory mediator [31]. Thus, by studying the predefined and novel cardiovascular risk factors, a correlation can be found between serum GGT and the increased risk of MetS in MUHL and MHO individuals.

The main limitation of this study was that the causal inferences between serum GGT and cardio metabolic phenotype could not be investigated because of the cross-sectional nature of its background. The low number of MUHL participants was another limitation of this study. The major strength of the present study was that it was the first work to study the association between GGT and cardiometabolic phenotype in healthcare workers. The advantage of serum GGT is in the availability of this marker in routine clinical practice and its standardized measurement methods. It can be helpful to distinguish the transition from MHO to MUHO, which may lead to an early and more accurate identification of MHO subjects who are at a risk of transition to MUHL, while it can also facilitate better preventive strategies. Using the data of a cohort study with a large sample size is another strength of this study.

5. Conclusions

We demonstrated that the prevalence of MHO and MUHO might increase by increasing GGT. Moreover, we determined a cutoff value for GGT to assess the MHO subjects who are at a risk of transition to MUHO condition. Thus, GGT may be used as a biomarker to reflect the risk of the metabolic syndrome, and we suggest that the GGT level can be used for the early detection of at-risk MHO individuals and for administering proper interventions.

Abbreviations List

-Metabolic syndrome:MetS

- Gamma Glutamyle Transferase:GGT

-Body Mass Index:BMI

-National Cholesterol Education Program Adult Treatment Panel III report: NCEP ATP III

-Metabolically Healthy Lean: MHL

-Metabolically Unhealthy Lean: MUHL

-Metabolically Healthy Obese: MHO

-Metabolically Unhealthy Obese: MUHO

- Non-Alcoholic Fatty Liver Disease: NAFLD

- Employees' Health Cohort Study of Tabriz: EHCSTR

- Systolic Blood Pressure: SBP

- Diastolic Blood Pressure: DBP

-Waist circumference :WC

Declarations

Ethics approval and consent to participate

This study was approved by the ethic committee of Tabriz University of medical sciences (IR.TBZMED.REC.1396.1263).

Availability of data and materials

The data that support the findings of this study are available from [Vice Chancellor for Research] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [Vice Chancellor for Research]

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

-The conception or design of the work: MHS,ARO

-The acquisition, analysis:NG,EF

OR interpretation of data:EF

Drafted the work or substantively revised:EF,NF,SZ

all authors have read and approved the manuscript

Consent for publication

Not Applicable

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Figures

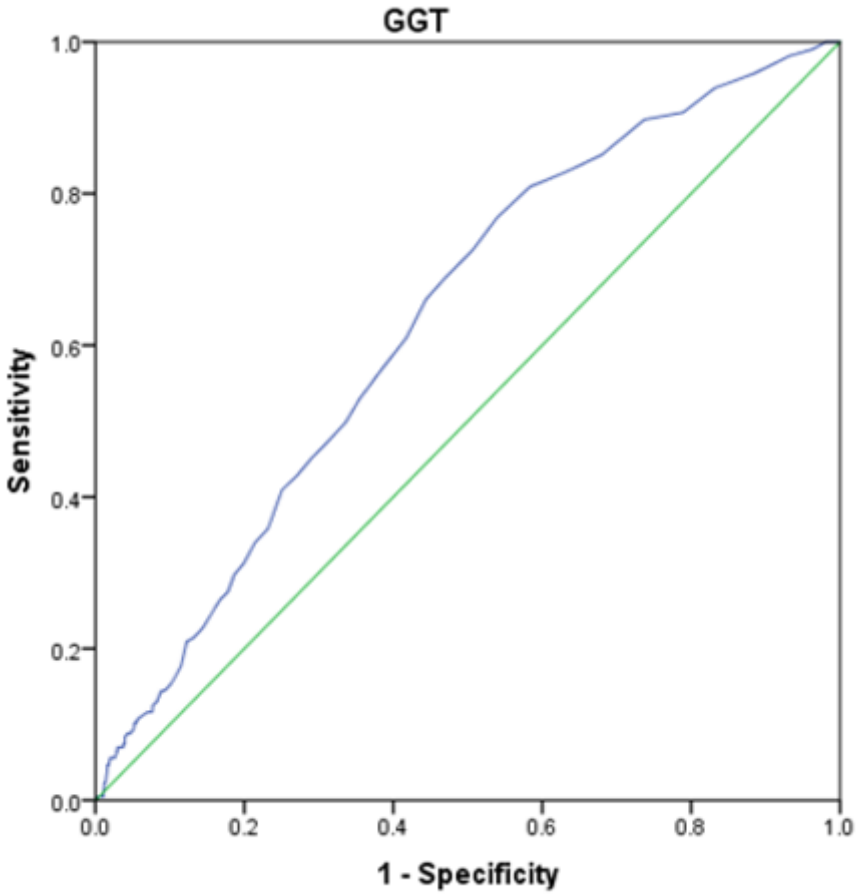
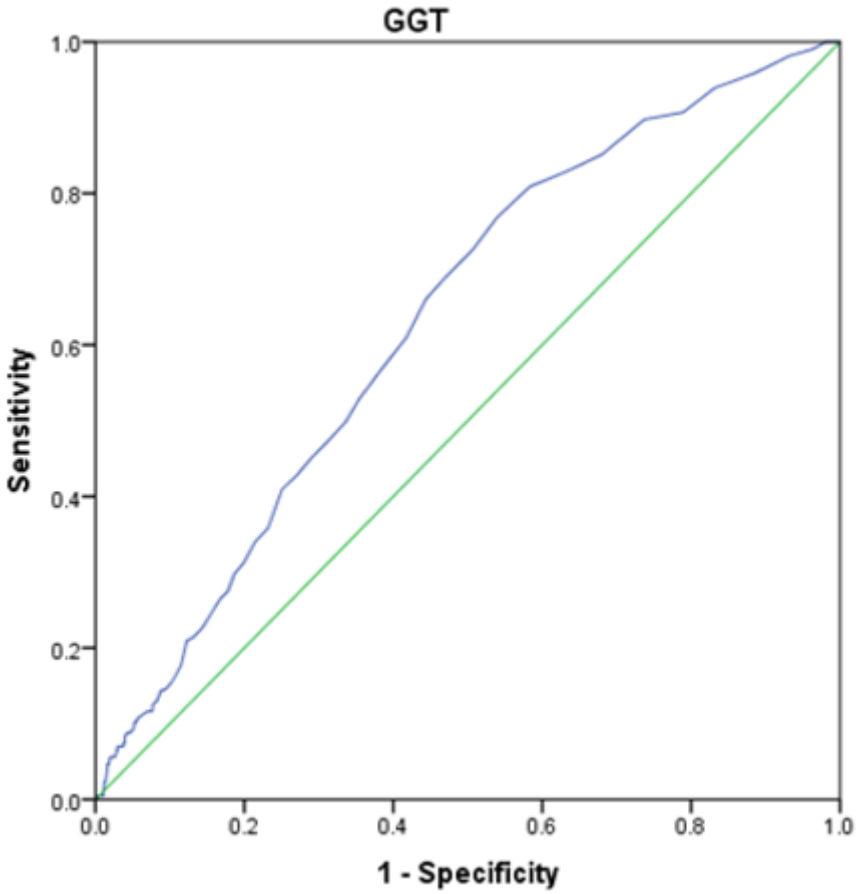


Figure 1

Figure 1. Receiver-operating characteristics curve of Gamma-glutamyl transferase for meatbolically healthy obese and metabolically unhealthy obese Area under the curve 0.634. GGT: Gamma-glutamyltransferase



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