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Association of gamma--glutamyltranspeptidase and uric acid with anthropometric indices and metabolic risk factors in women with excessive body weight — a preliminary study

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ABSTRACT

Introduction. Obesity is strongly associated with insulin resistance, known to be related to elevated gamma-glutamyltranspeptidase activity (GGTP) and uric acid (UA) level. However, the mechanism of this relationship has not yet been clarified. We investigated the relationship of GGTP and UA with anthropometry and components of metabolic syndrome in overweight and obese young women.

Materials and methods. GGTP, UA, fasting glucose, fasting insulin, HOMA and lipids were determined in blood samples obtained from overweight (n = 24; BMI = 25–30 kg/m^2) and obese (n = 28; BMI > 30 kg/m^2) women aged 25–40 yrs and age-matched healthy controls (n = 38; BMI < 25 kg/m^2).

Results. GGTP and UA were elevated over the upper reference values only in 19.2% and 11.5% of women from the study group, but median GGTP and UA were significantly higher in obese and overweight women compared to controls. In the whole study group, and in obese women, GGTP activity was more associated with WC, WHR and WtHR which was not found for UA. The correlations between GGTP and HOMA-IR and fasting insulin were significant for women with excessive body weight and obese women only, whereas the correlations between UA and parameters of insulin resistance in the whole study group and in obesity did not reach statistical significance. Moreover, we found significant differences in GGTP activity between women with and without insulin resistance in both the study group and obese women ($p < 0.0001$; $p < 0.01$). In the whole study group, and in obese women only, GGTP positively correlated with TC, LDL-C, TG, TC/HDL-C ratio, SBP and DBP, whereas in overweight women it only correlated with SBP. We also found that women in higher GGTP quartiles had higher concentrations of TC, LDL-C and TC/HDL-C ratio ($p < 0.03$; $p < 0.05$; $p < 0.05$ for quartile trend respectively).

Conclusions. GGTP activity and uric acid concentration are higher in overweight and obese women, although only GGTP activity seems to be related to anthropometric parameters, insulin resistance and atherogenic indices, essential components of metabolic syndrome in young women. GGTP activity may be a surrogate marker of insulin resistance and metabolic syndrome.

Key words: gamma-glutamyltranspeptidase, uric acid, metabolic syndrome, insulin resistance, overweight and obese women

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Introduction

Overweight and obesity are risk factors for cardiovascular and metabolic diseases widely present in the modern world. Metabolic syndrome is a cluster of risk factors for cardiovascular disease related to insulin resistance. It is well known that insulin resistance is associated with a fatty liver and that a fatty liver is associated with elevated gamma-glutamyltranspetidase (GGTP) activity [1, 2]. Serum GGTP has been proposed as a marker of insulin resistance (IR) and is associated with a marked increase in the risk of cardiovascular disease. On the other hand in overweight and obesity, hyperinsulinaemia secondary to insulin resistance may enhance the reabsorption of uric acid and thus contribute to the association of hyperuricaemia with hypertension. Recent studies in humans suggest that elevated uric acid predicts the development of hyperinsulinaemia and obesity [1, 3–5]. The aim of this study was to investigate the association between gamma-glutamyltranspeptidase, uric acid, and the anthropometry and components of metabolic syndrome in overweight and obese young women.

Material and methods

The study group included 52 young women with abnormal body mass aged 20–45 years, recruited from patients of the Department of Internal Diseases, E. Warminski City Hospital in Bydgoszcz. Of the women, 24 were overweight (25 kg/m^2 ≥ BMI < 30 kg/m^2) and 28 were obese (BMI ≥ 30 kg/m^2). The control group (BMI < 25 kg/m^2) consisted of 38 age-matched women (20–45 yrs) recruited on a voluntary basis. All women included in the study had not taken any contraceptives, anti-inflammatory or other medicines known to affect lipid or carbohydrate metabolism. In each subject, body weight, height, waist circumference and blood pressure were measured and waist to hip ratio (WHR), waist to height ratio (WtHR), and BMI were calculated. Insulin sensitivity was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR). Cutoff values for elevated HOMA-IR ≥ 2.75 were accepted based on the results of our own study. The diagnosis of MS was based on the definitions of the International Diabetes Federation (IDF 2005). This was defined as central obesity, measured by ethnic-specific waist circumferences, plus two of the following components: hypertriglyceridaemia (TG ≥ 150 mg/dL), HDL-cholesterol < 50 mg/dL, high blood pressure (≥ 130/85 mm Hg) and raised fasting glucose ≥ 100 mg/dL. We used the European waist circumference cutoffs (≥ 80 cm in women) to define central obesity.

Written informed consent from each participant was obtained and the study was approved by the Bioethics Committee at Collegium Medicum, Nicolaus Copernicus University.

From all women included in the study, fasting blood was drawn in the early morning (7.00–9.00 am). Serum was obtained within less than one hour to avoid proteolysis and stored deep-frozen (–80°C) in small aliquots until assayed, but for no longer than eight months.

Serum was assayed for gamma-glutamyltranspeptidase, uric acid, HDL-C, triglycerides (TG), total cholesterol (TC), glucose, (ARCHITECT ci8200, Abbott Diagnostics) and insulin (AxSYM, Abbott Diagnostics). LDL-C, TG: HDL-C (the index of LDL particle size and surrogate for IR) and TC: HDL-C values were calculated. The clinical cut-points for GGTP and uric acid were accepted as > 39 U/L and > 6 mg/dL, reflecting elevated as over the respective upper reference values. The women's height [cm], weight [kg], waist and hip circumferences [cm], and blood pressure [mm Hg] were measured using standard methods. Waist circumference was measured in the horizontal plane midway between the superior iliac crest and the lower margin of the last rib. Hip circumference was taken around the pelvis at the point of maximal protrusion of the buttocks. Body mass index (BMI) was calculated. Waist circumference and waist-to-hip ratio (WHR) served as a measure of regional fat distribution. Systolic (SBP) and diastolic blood pressures (DBP) were measured twice according to the standard procedures, in a seated position after at least 5 mins rest, by trained personnel using an automatic blood pressure monitor M6 Comfort (HEM-7223-E, OMRON, Poland). Three consecutive readings were taken, and the average was recorded. Insulin resistance was calculated by the homeostasis model assessment (HOMA) method, using fasting blood glucose and insulin concentrations (HOMA-IR = fasting blood glucose mmol/L × fasting insulin μU/ml/22.5).

Statistical methods

All data is presented as mean ± standard deviation (Gaussian distribution of results) or median and 25th and 75th percentile (non-Gaussian distribution). The Student T-test and U-Mann-Whitney test were used to compare differences. Comparisons of mean values between groups were done by ANOVA or Kruskal-Wallis test. Pearson's or Spearman correlation test were used and multiple regression analysis was performed. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using Statistica 8.0 for Windows (StatSoft).

Results

Mean age was similar in the study group and the control group. The baseline characteristics of participants are shown in Table 1.

Table 1. Anthropometric parameters in study and control groups

	Study group Me (Q1–Q3)		Control group Me (Q1–Q3) n = 38	p <
	Obese n =28	Overweight n = 24		
Waist [cm]	108 (100–119)	88 (85–90)	71 (69–74)	0.0001
WHR	0.88 (0.85–0.92)	0.82 (0.80–0.86)	0.76 (0.73–0.80)	0.0001
BMI [kg/m^2]	35.3 (32.3–38.4)	27.6 (26.3–28.5)	21.4 (19.6–22.4)	0.0001

WHR — waist to hip ratio; BMI — body mass index
Data is presented as median (Q1–Q3); statistical significance was taken as $p < 0.05$

Elevated activity of GGTP > 39U/L was found in only 19.2% of the study group, where eight women were obese and only two overweight, while an elevated concentration of UA > 6 mg/dl was found in 11.5% (two women overweight and four obese) (Tab. 2). None of the control women had increased GGTP or UA values.

Median GGTP and UA values were significantly higher in obese (21 U/L; 4.8 mg/dL, $p < 0.00007$; $p < 0.00005$, respectively) and overweight (14 U/L; 4.4 mg/dL, $p < 0.01$; $p < 0.005$, respectively) compared to controls (10 U/L and 3.8 mg/dL) (Tab. 3).

Table 2. Prevalence of elevated values of GGTP and UA in the study group

	Number of subjects	Percentage
GGTP > 39 U/L	10/52	19.2%
UA > 6 mg/dL	6/52	11.5%

GGTP — gamma-glutamyltranspeptidase; UA — uric acid

Furthermore, we found significant differences in GGTP activity and serum uric acid concentration between overweight and obese women ($p < 0.005$; $p < 0.05$) (Fig.1). GGTP activity was also higher in women with metabolic syndrome (23 U/L vs 12 U/L; $p < 0.000001$).

In the whole study group, and in obese women, GGTP activity was more associated with anthropometric predictors of metabolic syndrome risk factors such as WC, WHR and WHtR (Tab. 4).

The results of Spearman's correlations between GGTP and UA and parameters of insulin resistance in the study group and obese women are presented in Table 5. The correlations between GGTP and HOMA-IR and fasting insulin were significant for women with excessive body weight and in obese women (r = 0.57,

Table 3. Median GGTP activity and UA concentration in relation to BMI

	Study group Me (Q1–Q3)		Control group III Me (Q1–Q3)	p I vs. III	p II vs. III
	Obese I	Overweight II			
GGTP [U/L]	21 (15–34)	14 (10–18)	10 (9–13)	0.00007	0.01
UA [mg/dL]	4.8 (4.4–5.3)	4.4 (3.8–4.8)	3.8 (3.3–4.3)	0.00005	0.005

GGTP — gamma-glutamyltranspeptidase; UA — uric acid; BMI — body mass index
Data is presented as median (Q1–Q3). Statistical significance was taken as $p < 0.05$

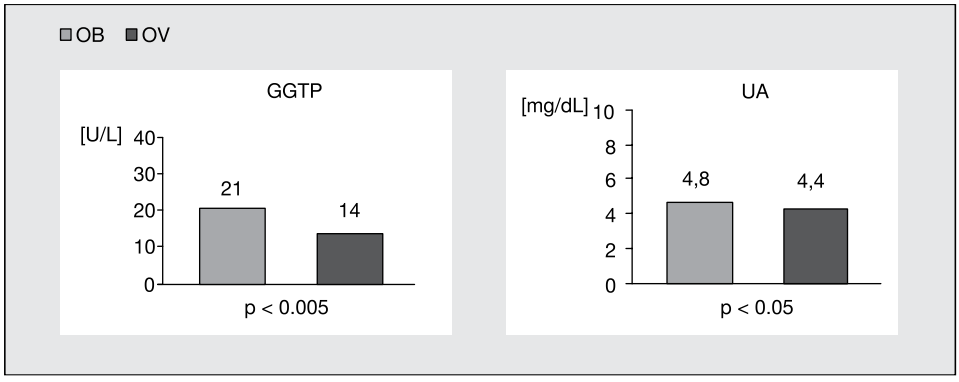

Figure 1. Gamma-glutamyltranspeptidase (GGTP) and uric acid (UA) in obese (OB) and overweight (OV) women

Table 4. Association between GGTP activity and UA level with anthropometric parameters

	Study group		
	WC	**WHR**	**WHtR**
GGTP [U/L]	r = 0.51 p < 0.000001	r = 0.31 p < 0.001	r =0.50 p < 0.000001
UA [mg/mL]	r = 0.20 p < 0.06	ns	ns
Obese women			
GGTP [U/L]	r = 0.31 p < 0.01	r = 0.29 p < 0.02	r = 0.34 p < 0.007
UA [mg/mL]	ns	ns	ns
Overweight women			
GGTP [U/L]	r = 0.42 p < 0.01	ns	ns
UA [mg/mL]	ns	ns	ns

GGTP — gamma-glutamyltranspeptidase; UA — uric acid; WC — waist circumference; WHR — waist to hip ratio; WHtR — waist to height ratio; ns — non-significant

Table 5. GGTP activity and UA concentration in relation to HOMA-IR and insulin in the study group and in obese women

Study group		
	HOMA-IR	**Insulin**
GGTP [UL]	r = 0.57 p < 0.00002	r = 0.56 p < 0.00003
UA [mg/mL]	ns	ns
Obese women		
	HOMA-IR	**Insulin**
GGTP [U/L]	r = 0.52 p < 0.004	r = 0.55 p < 0.002
UA [mg/mL]	r = 0.33 p < 0.08	r = 0.36 p < 0.06

GGTP — gamma-glutamyltranspeptidase; UA — uric acid; HOMA-IR — homeostasis model assessment of insulin resistance

Statistically significant correlations ($p < 0.05$)

$p < 0.00002$; $r = 0.56$, $p < 0.00003$ and $r = 0.52$, $p < 0.004$; $r = 0.55$, $p < 0.002$ respectively). The correlations between UA and parameters of insulin resistance in the whole study group did not reach statistical significance, although serum uric acid concentration showed a tendency to higher values with insulin resistance in obese women.

Moreover, we found significant differences in the activity of GGTP between women with and without insulin resistance in the whole study group ($p < 0.0001$). Similarly, GGTP activity was significantly lower in obese women without insulin resistance ($p < 0.01$) (Tab. 6).

In the whole study group, and in obese women only, GGTP positively correlated with TC, LDL-C, TG, and atherogenic indices such as TC/HDL, SBP and DBP, whereas in overweight women it correlated only with SBP.

Finally, we analysed the relation of lipids with serum GGTP in obese women (Tab. 7). Median TC, LDL-C concentration and TC/HDL ratios were significantly higher in the IV quartile compared to the I quartile and we observed also trends to increasing concentrations of TG and TG/HDL ratio in relation to GGTP activity. We have presented only the results for obese women, but in the whole study group these relations were significantly higher and stronger.

Discussion

Obese subjects are more likely to develop glucose intolerance and diabetes, in part owing to the ability of adipose tissue to secrete adipokines, chemokines and enzymes into the bloodstream, having a major impact on energy homeostasis and progression from obesity to atherosclerotic diseases, in particular leading to induction of insulin resistance [6]. Obesity is strongly associated with IR and metabolic syndrome [1, 7], which are known to be associated with an elevated gamma-glutamyltranspeptidase (GGTP) level [1, 4, 8]. However, the mechanism of the relationship between insulin resistance and GGT elevation has not yet been clarified. Our observational study confirms the increasing prevalence of elevated GGTP activity (19.2%) and UA level (11.5%) in women with excessive body mass. According to Botton et al., as early as 8–17 years

Table 6. GGTP activity and UA concentration in relation to insulin resistance in the study group and in obese women

	Study group with IR HOMA ≥ 2.75 n = 22	**Study group without IR HOMA < 2.75 n = 30**	**p**
GGTP [U/L]	**20** (16–27)	**14** (10–20)	0.0001
UA [mg/mL]	**4.5** (3.7–5.3)	**4.4** (4.1–4.8)	ns
	Obese with IR n= 15 HOMA ≥ 2.75	**Obese without IR n = 13 HOMA < 2.75**	**p**
GGTP [U/L]	**27** (19–46)	**16** (12–21)	0.01
UA [mg/mL]	**5.1** (4.2–5.8)	**4.6** (4.4–5.1)	ns

GGTP — gamma-glutamyltranspeptidase; UA — uric acid; HOMA — homeostasis model assessment; ns — non-significant
Statistically significant correlations ($p < 0.05$)

Table 7. Association between GGTP in quartiles and lipids in obese women

	GGTP Q I (8–15 U/L)	**Q II (16–21)**	**Q III (22–34)**	**Q IV (> 35 U/L)**	**p Q I vs. Q IV**
TC	**139** (96–179)	**158** (150–165)	**222** (172–254)	**199** (174–209)	0.03
TG	**89** (69–94)	**90** (58–100)	**121** (109–158)	**115** (85–122)	0.09
HDL-C	**44** (39–50)	**48** (45–54)	**47** (42–49)	**42** (38–50)	ns
LDL-C	**76** (45–112)	**92** (85–98)	**135** (98–169)	**121** (112–138)	0.05
TG/HDL-C	**1.8** (1.3–2.1)	**1.9** (1.1–2.2)	**2.8** (2.2–3.6)	**2.6** (2.2–3.1)	0.07
TC/HDL-C	**3.3** (2.6–4.3)	**3.4** (2.8–3.4)	**4.7** (4.2–5.1)	**4.8** (4.1–5.2)	0.03

GGTP — gamma-glutamyltranspeptidase; UA — uric acid; TC — total cholesterol; TG — triglycerides; HDL-C — high-density lipoprotein-cholesterol; LDL-C — low-density lipoprotein-cholesterol
Data is presented as median (Q1-Q3); statistical significance was taken as $p < 0.05$

old, for the IOTF definition of obesity, GGTP increased from 9.4 UI/L in normal weight boys to 11.7 UI/L in overweight or obese boys ($p = 0.0002$). In girls, GGTP increased from 8.2 UI/L in normal weight to 9.4 UI/L in overweight or obese ($p = 0.02$) girls [9]. Similarly, Pacifico et al. showed that UA concentrations were significantly higher in obese children compared to controls; moreover, they correlated with the most established cardiovascular risk factor (carotid intima-media thickness — IMT) [10].

We defined two groups of women according to an increase in BMI: women with overweight and obese women. Our results indicate that median GGTP and UA values were significantly higher in obese compared to controls. Many prospective studies have shown that the activity of GGTP is positively associated with BMI [11–13] and central body fat distribution — measured as the percentage of body fat adjusted for BMI [14]. Therefore, obesity, and particularly abdominal obesity, may be associated with plasma concentration of hepatic markers even at a weak degree of obesity in adults, as in children.

We found significant differences in the activity of GGTP between women with and without metabolic syndrome (23 U/L vs. 12 U/L; $p < 0.000001$). Similar results were obtained by Lee et al.: activity of GGTP in women with MS and without MS was 23 vs. 19 IU/L; $p = 0.01$, respectively [15]. Other population-based studies have shown an association between raised GGTP activity and metabolic syndrome [2, 16, 17].

In epidemiological studies, BMI has been used extensively to assess relative weight and obesity status and their relation to several health outcomes, including hepatic enzymes, whereas anthropometric measures of central adiposity, such as waist circumference, WHR, and abdominal height, widely used to assess the relationship between body fat distribution and metabolic and cardiovascular diseases, have been scarcely considered in their association with liver enzyme activity [1, 15, 18]. In recent studies, anthropometric indices of obesity have been evaluated as predictors of metabolic syndrome risk factors. Waist to height ratio (WHtR) might be an optimal anthropometric predictor of metabolic syndrome risk factors [18, 19]. In our study group, and in obese women, only GGTP activity, but not uric acid, was associated with WC, WHR and especially with WHtR.

Gamma-glutamyltranspeptidase is often increased in obese subjects. An increase in the activity of liver

enzymes has been associated with hepatic steatosis, which could be due to the increased effect of insulin in the liver. A fatty liver appears to be a cause of hepatic insulin resistance. In consequence, this leads to the development of systemic insulin resistance and hyperinsulinaemia in obesity. Some data indicates that hyperuricaemia is indeed an inherent component of metabolic syndrome and could also be used as a simple marker of insulin resistance [16, 20, 21]. Although in our study no significant correlations between UA and indicators of insulin resistance were observed, in obese or overweight women significant associations between GGTP activity and these indicators were found. In line with the findings of others [22], our data demonstrated that increased GGTP values in women with excessive body mass were positively associated with elevations of HOMA-IR and fasting insulin. These findings suggest the possibility that increased liver enzymes, especially GGTP, might reflect metabolic alterations and could serve as a clinical indicator for insulin resistance syndrome.

Our results agree with other reports relating hyperinsulinaemia to raised GGTP activity. Similar observations have been described in nondiabetic patients with no history of liver disease, where Wallace et al. investigated the relationship of liver enzymes to insulin sensitivity and intra-abdominal fat. These subjects were divided into lean insulin-sensitive (LIS), lean insulin-resistant (LIR), and obese insulin-resistant (OIR) groups. In women, GGTP levels were also significantly higher in the OIR group than in the LIS group, and tended to be higher in the LIR than in the LIS group ($p = 0.09$) [23]. These findings raise the possibility that increasing GGTP levels (even within the normal range, as in our study) in the context of insulin resistance may be an indication for lifestyle changes with the aim of weight loss or treatment with peroxisome proliferators-activated receptor-gamma agonists [23].

Previous reports in obese children have shown UA levels to correlate positively with insulin and HOMA-IR after adjusting for age, gender and pubertal stage [10]. These findings suggest that in children, as in adults [24], hyperuricaemia may be a marker for insulin resistance, an underlying condition of metabolic syndrome [10]. We were not able to confirm these results, perhaps because our study was too small, which is a limitation of this study.

On the other hand, in the Framingham Heart Study, Lee et al. examined the relation of GGTP to cardiovascular disease (CVD) risk factors, and prospectively determined the risk of new-onset metabolic syndrome, incident CVD and death. They indicated that participants with GGTP in higher quartiles had higher concentrations of TC, LDL-C and TG ($p < 0.001$ for quartile trend). There was no significant association for HDL-C [12]. Similarly in our study, TC, LDL-C and TC/HDL-C ratio showed significantly higher mean values with increasing GGTP quartiles. We observed also trends to increasing concentrations of TG and value of TG/HDL ratio in relation to the activity of GGTP. Several studies have raised the possibility that the newly addressed lipid measures might be superior to the traditional ones for cardiovascular risk prediction [25]. It is well-known that small, dense low-density lipoproteins-cholesterol (sdLDL-C) susceptible to posttranslational oxidation and glycation are atherogenic. The TG:HDL-C ratio has been shown to be useful in assessing the presence of small LDL particles in non-diabetic subjects without prominent hyperlipidaemia [26]. We observed a trend to a higher TG/HDL-C ratio with increasing GGTP activity, which could indicate that serum GGTP may be associated with an elevated risk of new-onset components of metabolic syndrome and cardiovascular diseases risk factors.

Conclusions

We are aware of the limitations of this study, including a relatively small group of subjects with overweight and obesity; however, we believe that our data could have several important clinical implications. Our findings demonstrate that both GGTP activity and uric acid concentrations are higher in overweight and obese women, although only GGTP seems to be related to anthropometric parameters, insulin resistance and atherogenic indices, essential components of metabolic syndrome in young women. GGTP activity may be a surrogate marker of insulin resistance and metabolic syndrome.

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