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Serum Gamma-glutamyltransferase and Obesity: is there a Link?

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ABSTRACT

Background: Little data is available on gamma-glutamyltransferase (GGT) and body fat distribution in healthy individuals. We examined whether GGT within normal range is prospectively associated with total body fat (TF) and regional body fat distribution. **Methods:** We included 62 patients who were presented at Eureka Health and Research Foundation Clinic. GGT was measured by enzymatic photometry method. TF, android fat (AF), gynoid fat (GF) and android/gynoid ratio (A/G ratio) was assessed using Dual-energy X-ray absorptiometry. Regression coefficients and 95% Confidence Intervals were calculated using multivariate linear regression models adjusting for confounders. **Results:** Mean value of GGT of the study population was 21.64U/L (ranging from 6 to 48 U/L). There was no association between GGT and TF. Increased GGT was associated with higher AF (top tertile relative to the lowest: ß=0.35; 95% CI: 0.19, 0.52), lower GF(top tertile relative to the lowest: ß=-0.48; 95%CI: -0.69,.-0.27) and higher AF/GF ratio (top tertile relative to the lowest: ß=0.04; 95%CI: 0.03, 0.06). **Conclusions:** This study suggests that an increase in GGT concentrations is a sensitive and early biomarker of unfavorable body fat distribution.

Keywords: Serum Gamma-glutamyltransferase, obesity.

1. INTRODUCTION

Gamma-glutamyltransferase (GGT), a marker of alcohol consumption and liver disease, has been strongly associated with obesity related outcomes, including diabetes, hypertension, dyslipidemia, metabolic syndrome, cardiovascular diseases and cancer (1-6). Also, GGT levels correlate positively with markers of chronic inflammation, such as C-reactive protein (CRP) and fibrinogen (6, 7) which are associated with obesity and its phenotypes (8,9). Furthermore, an increase in serum GGT activity has been suggested to be used as a marker of increased oxidative stress in humans due to the pivotal role of GGT in oxidative stress (10, 11).

Recently, it has been reported a causal role of oxidative stress in the development of obesity (12) and a GGT-mediated oxidative stress is capable of inducing lipid oxidation (11). On the other hand, GGT plays a critical role in cysteine metabolism and is linked to insulin resistance as well, which have been shown to be obesogenic in both animals and human studies (13-15). Moreover, serum GGT levels seem closely related to liver fat and is included in the diagnostic criteria of fatty liver index (16). Despite this evidence, and the global epidemic of obesity, very little attention has been given to GGT and its role on obesity. Hence, we assessed whether GGT was associated with total body fat and body fat distribution.

2. PATIENTS AND METHODS

The present study used data from 62 patients who were presented in Eureka Health and Research Foundation Clinic. Fasting blood samples were collected by venipuncture, and immediately frozen (–20°C).

All liver biochemistry measurements were obtained in the laboratory Eureka Health and Research Foundation Clinic. Body composition was assessed by Dual-energy X-ray absorptiometry (DXA). Body weight (grams) was divided into bone mineral content, lean (non-fat) and fat mass.

Body fat distribution was determined by measuring fat mass at the total-body, and fat mass in android and gynoid regions. Body fat was assessed as percentage of body fat taking into consideration the weight of the individual and total fat as well (when using android and gynoid fat as outcomes). For every patient, we gathered information on age, current health status, smoking behavior, and socioeconomic status.

	(N=62)
Age	38 ± 5.88
Female % (n)	30 (48)
Smoking status n (%)	45 (14.1)
Education Level n (%)	
Low	20 (43.9)
Medium	25 (44.4)
High	9 (11.7)
Income n (%)	
Low	30 (49)
Medium	30 (49)
High	2 (2)
Prevalent cardio-metabolic disease n (%)	2 (2%)
GGT	21.64 ± 20.0
Total fat mass (%)	33.60 ± 8.40
Abdominal fat mass (%)	25 ± 1.95
Gynoid fat mass (%)	20 ± 2.13
Andorid/Gynoid fat mass rato	0.64 ± 0.20

Table 1. Selected characteristics of study participants. GGT: gamma glutamyltransferase; Plus minus values are mean ± SD

Statistical analysis

All analyses were performed by IBM SPSS Statistics 21. Data are presented as the mean ± SD unless indicated otherwise. We investigated the association between serum GGT with body fat both as continuous (one-standard deviation increment in GGT) variable and by tertiles. Multivariate linear regression was used to examine whether GGT was associated with, total body fat android fat mass (%), gynoid fat mass (%) and android/gynoid fat mass ratio. We built adjusted models, with age, sex, education level (low, intermediate, high), income status (low, middle, high), smoking status (ever, never) and presence of cardio-metabolic diseases AP-value lower than 0.05 was considered as statistically significant.

3. RESULTS

Table 1 displays the selected characteristics of the study population. The mean age was 38 ± 5.88 and the mean GGT was 21.64 ± 20.0 U/L (Table 1).

We analyzed association between GGT, total body fat and regional body fat distribution. There was no association between GGT analyzed continuously or in tertiles and total body fat (Table 2). Higher GGT was associated with higher android fat mass (per SD increase in GGT: ß=0.17; 95%CI: 0.09, 0.24 and top tertile relative to the lowest: ß=0.35; 95%CI: 0.19, 0.52; P for F-test, 3 df: 0.7 10-05 (Table 3), lower gynoid fat mass (per SD increase in GGT: ß=-0.25; 95%CI: -0.35, -0.16 and top tertile relative to the lowest: ß=-0.48; 95%CI: -0.69,.-0.27; P for F-test, 3 df: 5.9 10-07 (Table 3) and higher android/gynoid fat mass ratio (per SD increase in GGT: ß=0.023; 95%CI: 0.015, 0.03 and top tertile relative to the lowest: ß=0.04; 95%CI: 0.03, 0.06; P for F-test, 3 df: 7.4 10-08 (Table 4).

	Total body fat mass (%) β (95% CI)			
GGT	MODEL 1[a]	MODEL 2	MODEL 3	MODEL 4
1st tertile	reference	reference	reference	reference
2nd tertile	0.03 (-0.46, 0.53)	-0.03 (-0.53, 0.47)	-0.10 (-0.59, 0.40)	-0.03 (-0.52, 0.47)
3rd tertile	0.50 (-0.06, 1.06)	0.37 (-0.19, 0.94)	0.19 (-0.38, 0.76)	0.51 (-0.07, 1.09)
Continuous (per SD increase)	0.16 (-0.07, 0.39)	0.12 (-0.14, 0.38)	0.003 (-0.26, 0.27)	0.20 (-0.07, 0.47)

Table 2. Gamma-glutamyltransferase (GGT)and total body fat mass. Adjusted by age, gender and body mass index, smoking status, education level, income level, cardio-metabolic diseases

	Android/Gynoid fat mass ratio β (95% CI)			
GGT	MODEL 1[a]	MODEL 2	MODEL 3	MODEL 4
1st tertile	reference	reference	reference	reference
2nd tertile	0.02 (0.001, 0.03)	0.01 (-0.001, 0.03)	0.009 (-0.006, 0.02)	0.014 (-0.001, 0.029)
3rd tertile	0.05 (0.03, 0.06)	0.04 (0.03, 0.06)	0.03 (0.01, 0.05)	0.04 (0.02, 0.06)
Continuous (per SD increase)	0.024 (0.02, 0.028)	0.023 (0.015, 0.03)	0.016 (0.01, 0.024)	0.019 (0.01, 0.027)

Table 4. Gamma-glutamyltransferase (GGT) and android/gynoid fat mass ratio. Adjusted by age, gender and body mass index, smoking status, education level, income level, cardio-metabolic diseases

	Android fat mass (%) β (95% CI)				Gynoid fat mass (%) β (95% CI)			
GGT	MODEL 1	MODEL 2	MODEL 3	MODEL 4	Model 1	MODEL 2	MODEL 3	MODEL 4
1st tertile	reference	reference	reference	reference	reference	reference	reference	reference
2nd tertile	0.22 (0.07, 0.36)	0.20 (0.06, 0.35)	0.15 (0.003, 0.29)	0.20 (0.05, 0.34)	-0.09 (-0.27, -0.10)	-0.07 (-0.26, 0.11)	-0.01 (-0.20, 0.17)	-0.08 (-0.26, 0.11)
3rd tertile	0.39 (0.23, 0.54)	0.35 (0.19, 0.52)	0.23 (0.06, 0.40)	0.29 (0.12, 0.46)	-0.51 (-0.71, -0.30)	-0.48 (-0.69, -0.27)	-0.34 (-0.55, -0.13)	-0.50 (-0.71, -0.28)
Continuous(per SD increase)	0.18 (0.14, 0.22)	0.17 (0.09, 0.24)	0.10 (0.02, 0.18)	0.13 (0.05, 0.21)	-0.26 (-0.31, -0.21)	-0.25 (-0.35, -0.16)	-0.18 (-0.28, -0.08)	-0.27 (-0.37, -0.17)

Table 3. Gamma-glutamyltransferase (GGT)android fat mass. Adjusted by age, gender and body mass index, smoking status, education level, income level, cardio-metabolic diseases

4. DISCUSSION

In this study, we found that GGT levels within normal range are associated with unfavorable body fat distribution. Previous studies reporting on obesity and GGT have mostly tested the hypothesis that obesity, and in particular central obesity may predict levels of GGT (17-21) and not vice versa. Furthermore, all these studies have been on cross-sectional design and therefore causality could not be addressed. Nevertheless, most of them have reported a strong positive correlation between GGT and abdominal obesity. For example, in a study of 2704 women and men, 35-80 years of age, a positive correlation was observed between GGT, waist circumference and waist to hip ratio (22). Similar correlations were reported also by Mager and colleagues in a study of 44 children (23). In addition, Iwasaki et al in a cross-sectional study of 257 Japanese patients, by using more accurate measures of body composition such as by dual-energy X-ray absorptiometry, showed that higher levels of GGT were significantly associated with higher visceral fat whereas no association was observed with subcutaneous fat, proposing that the serum GGT may be useful as a convenient indicator of visceral adiposity (24). However, in contrast to our study, Iwasaki and his colleagues did not examine the association of GGT with gynoid fat or android/gynoid fat ratio. Although the current study suggests that GGT may be used as a marker for abdominal fat, we did not measure visceral or subcutaneous fat separately and therefore we were not able to distinguish these fat compartments. It has been shown that visceral adipose tissue is associated with more adverse cardiometabolic risk factor profiles than abdominal subcutaneous adipose tissue (25). Measurement of serum GGT is reliable, easy and inexpensive and therefore, if serum GGT is a marker of unfavorable body fat distribution, it might have important implications both clinically and epidemiologically. Future research is thus needed to validate our findings and to assess if GGT within normal range can be a specific marker to visceral fat.

It is at present unclear the mechanism underlying the association between GGT and body fat. An increase in concentrations of GGT is conventionally interpreted as a marker of alcohol abuse, insulin resistance and/or liver damage (26). However, neither of these interpretations explains the observed association in the current study of GGT within what is considered its physiological normal range with body fat distribution. Nor chronic inflammation, as measured by CRP, could explain the association. GGT and body fat distribution has been shown to positively correlate with markers of chronic inflammation, such as CRP and fibrinogen (6) which on the other hand, closely correlate with obesity (8, 9). However, other mechanisms may explain the association of GGT with body fat distribution. Although GGT has been regarded as marker of liver diseases, GGT is widely distributed in the human body (27). There is evidence that cellular GGT plays a pivotal role in antioxidant defense system (11).

As a primary function, ectoenzyme GGT maintains intracellular concentrations of glutathione, the most important non-protein antioxidant of the cell (11). Increased GGT activity can be a response to oxidative stress, facilitating increased transport of glutathione precursors into cell (11). Also, ectoplasmatic GGT may be involved in the generation of reactive oxygen species (ROS), particularly in the presence of Fe3+ and CU2+25. Recently, oxidative stress was shown to induce obesity (28) and a GGT-mediated oxidative stress was reported to be capable of inducing oxidation of lipids (11). GGT plays an important role in homeostasis of plasma cysteine as well (13) which similar to GGT induces oxidative stress mainly in the presence of cooper ions (29). Cysteine has been related with body fat in both men and women, independent of GGT (13). Furthermore, GGT levels have been reported to correlate with adipokines such as adiponectin (30) which play an important role in obesity by different pathways i.e. increased energy expenditure, insulin sensitivity or fatty acid oxidation (28).

5. CONCLUSION

Our findings suggest that serum levels of GGT within physiological normal range could be an early biomarker of unfavorable body fat distribution and that the well-known associations of obesity with cardiometabolic and other chronic disease may be modified by serum GGT.

- Conflict of interest: The authors declare no conflict of interest.

REFERENCES

1. Rantala AO, Lilja M, Kauma H, Savolainen MJ, Reunanen A, Kesaniemi YA. Gamma-glutamyl transpeptidase and the metabolic syndrome. J Intern Med. 2000; 248 :230-8. doi: 10.1046/j.1365-2796.2000.00723.x.
2. Lee DH, Ha MH, Kim JH, Christiani DC, Gross MD, Steffes M, et al. Gamma-glutamyltransferase and diabetes - a 4 year follow-up study. Diabetologia. 2003; 46: 359-64. doi: 10.1007/s00125-003-1036-5.
3. Lee DS, Evans JC, Robins SJ, Wilson PW, Albano I, Fox CS, et al. Gamma glutamyl transferase and metabolic syndrome, cardiovascular disease, and mortality risk - The Framingham Heart Study. Arterioscl Throm Vas. 2007; 27: 127-33. doi: 10.1161/01.Atv.0000251993.20372.40.
4. Kunutsor SK, Apekey TA, Khan H. Liver enzymes and risk of cardiovascular disease in the general population: A meta-analysis of prospective cohort studies. Atherosclerosis. 2014; 236: 7-17. doi: 10.1016/j.atherosclerosis.2014.06.006.
5. Kunutsor SK, Apekey TA, Van Hemelrijck M, Calori G, Perseghin G. Gamma glutamyltransferase, alanine aminotransferase and risk of cancer: Systematic review and meta-analysis. Int J Cancer. 2015; 136: 1162-70. doi: 10.1002/ijc.29084.
6. Lee DH, Jacobs DR, Gross M, Kiefe CI, Roseman J, Lewis CE, et al. gamma-glutamyltransferase is a predictor of incident diabetes and hypertension: The coronary artery risk development in young adults (CARDIA) study. Clin Chem. 2003; 49: 1358-66. doi: 10.1373/49.8.1358.
7. Yamada J, Tomiyama H, Yambe M, Koji Y, Motobe K, Shiina K, et al. Elevated serum levels of alanine aminotransferase and gamma glutamyltransferase are markers of inflammation and oxidative stress independent of the metabolic syndrome. Ath-

erosclerosis. 2006; 189: 198-205. doi: S0021-9150(05)00787-2
8. Kahn SE, Zinman B, Haffner SM, O'Neill MC, Kravitz BG, Yu DH, et al. Obesity is a major determinant of the association of C-reactive protein levels and the metabolic syndrome in type 2 diabetes. Diabetes. 2006; 55: 2357-64. doi: 10.2337/Db06-0116.
9. Park JS, Cho MH, Nam JS, Ahn CW, Cha BS, Lee EJ, et al. Visceral adiposity and leptin are independently associated with C-reactive protein in Korean type 2 diabetic patients. Acta Diabetol. 2010; 47: 113-8. doi: 10.1007/s00592-009-0125-4.
10. Lim JS, Yang JH, Chun BY, Kam S, Jacobs DR, Lee DH. Is serum gamma-glutamyltransferase inversely associated with serum antioxidants as a marker of oxidative stress? Free Radical Bio Med. 2004; 37 :1018-23. doi: 10.1016/j.freeradbiomed.2004.06.032.
11. Lee DH, Blomhoff R, Jacobs DR. Is serum gamma glutamyltransferase a marker of oxidative stress? Free Radical Res. 2004; 38: 535-9. doi: 10.1080/10715760410001694026.
12. Youn J-Y, Siu KL, Lob H, Itani H, Harrison DG, Cai H. Role of Vascular Oxidative Stress in Obesity and Metabolic Syndrome. Diabetes. 2014; 63: 2344-55. doi: 10.2337/db13-0719.
13. Elshorbagy AK, Kozich V, Smith AD, Refsum H. Cysteine and obesity: consistency of the evidence across epidemiologic, animal and cellular studies. Curr Opin Clin Nutr. 2012; 15: 49-57. doi: 10.1097/Mco.0b013e32834d199f.
14. Bonnet F, Ducluzeau PH, Gastaldelli A, Laville M, Anderwald CH, Konrad T, et al. Liver Enzymes Are Associated With Hepatic Insulin Resistance, Insulin Secretion, and Glucagon Concentration in Healthy Men and Women. Diabetes. 2011; 60: 1660-7. doi: 10.2337/Db10-1806.
15. Elshorbagy AK, Valdivia-Garcia M, Refsum H, Butte N. The Association of Cysteine with Obesity, Inflammatory Cytokines and Insulin Resistance in Hispanic Children and Adolescents. Plos One. 2012; 7. doi: ARTN e44166DOI 10.1371/journal.pone.0044166.
16. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. Bmc Gastroenterol. 2006; 6:33. doi: Artn 33Doi 10.1186/1471-230x-6-33.
17. Robinson D, Whitehead TP. Effect of Body-Mass and Other Factors on Serum Liver-Enzyme Levels in Men Attending for Well Population Screening. Ann Clin Biochem. 1989; 26:393-400. doi: 10.1177/000456328902600503
18. Choi JW. Association between elevated serum hepatic enzyme activity and total body fat in obese humans. Ann Clin Lab Sci. 2003; 33: 257-64.
19. Lin J, Zhang SM, Cook NR, Lee IM, Buring JE. Dietary fat and fatty acids and risk of colorectal cancer in women. American Journal of Epidemiology. 2004; 160: 1011-22. doi: 10.1093/Aje/Kwh319.
20. Salvaggio A, Periti M, Miano L, Tavanelli M, Marzorati D. Body-Mass Index and Liver-Enzyme Activity in Serum. Clin Chem. 1991; 37(5): 720-3.
21. van Barneveld T, Seidell JC, Traag N, Hautvast JG. Fat distribution and gamma-glutamyl transferase in relation to serum lipids and blood pressure in 38-year old Dutch males. Eur J Clin Nutr. 1989; 43: 809-18.
22. Stranges S, Dorn JM, Muti P, Freudenheim JL, Farinaro E, Russell M, et al. Body fat distribution, relative weight, and liver enzyme levels: a population-based study. Hepatology. 2004; 39: 754-63. doi: 10.1002/hep.20149.
23. Mager DR, Yap J, Rodriguez-Dimitrescu C, Mazurak V, Ball G, Gilmour S. Anthropometric measures of visceral and subcutaneous fat are important in the determination of metabolic dysregulation in boys and girls at risk for nonalcoholic fatty liver disease. Nutr Clin Pract. 2013; 28: 101-11. doi: 0884533612454884.
24. Iwasaki T, Yoneda M, Kawasaki S, Fujita K, Nakajima A, Terauchi Y. Hepatic fat content-independent association of the serum level of gamma-glutamyltransferase with visceral adiposity, but not subcutaneous adiposity. Diabetes Res Clin Pract. 2008; 79: e13-4. doi: S0168-8227(07)00325-7
25. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation. 2007; 116: 39-48. doi: CIRCULATIONAHA.106.675355.
26. Teschke R, Brand A, Strohmeyer G. Induction of Hepatic Microsomal Gamma-Glutamyltransferase Activity Following Chronic Alcohol Consumption. Biochem Bioph Res Co. 1977; 75: 718-24. doi: 10.1016/0006-291x(77)91531-5.
27. Hanigan MH, Frierson HF. Immunohistochemical detection of gamma-glutamyl transpeptidase in normal human tissue. J Histochem Cytochem. 1996; 44: 1101-8.
28. Fernandez-Sanchez A, Madrigal-Santillan E, Bautista M, Esquivel-Soto J, Morales-Gonzalez A, Esquivel-Chirino C, et al. Inflammation, Oxidative Stress, and Obesity. Int J Mol Sci. 2011; 12: 3117-32. doi: 10.3390/Ijms12053117.
29. Muniz P, Saez P, Iradi A, Vina J, Oliva MR, Saez GT. Differences between cysteine and homocysteine in the induction of deoxyribose degradation and DNA damage. Free Radic Biol Med. 2001; 30: 354-62. doi: S0891-5849(00)00480-9.
30. Kaser S, Moschen A, Cayon A, Kaser A, Crespo J, Pons-Romero F, et al. Adiponectin and its receptors in non-alcoholic steatohepatitis. Gut. 2005; 54: 117-21. doi:10.1136/gut.2003.037010.