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Assessment of the Relationship of Hepatic Enzymes with Obesity and Insulin Resistance in Adults in Saudi Arabia

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تقييم العلاقة بين الأنزيمات الكبدية والسمنة ومقاومة الأنسولين عند الأفراد البالغين في المملكة العربية السعودية

علي السلطان

الملخص: الهدف: أجريت الدراسة لتقييم علاقة الإنزيمات الكبدية والمستوى المصلي للألبومين بالسمنة ومقاومة الأنسولين عند الأفراد البالغين في المملكة العربية السعودية. **الطريقة:** هذه دراسة مقارنة ل 136 سعودي بالغ . مكونه من 68 بدينا و 68 غير بدين . تم أخذ المقاسات الأنثروبومترية . ومستوى الأنزيمات الكبدية والألبومين . وجلوكوز الدم . والأنسولين ومستوى الدهون وتحديد مقاومة الأنسولين بنموذج تقييم الاستتباب. **النتائج:** أظهرت الدراسة أن مستويات ناقلات ببيتايد غاما غلوتميل و إنزيم الفوسفاتيز القلوية والجلوكوز (بعد الصيام – بدون إفطار) والأنسولين وتحديد مقاومة الأنسولين بنموذج تقييم الاستتباب عالية عند البدينين ($p<0.0001$, $p<0.001$, $p<0.004$, $p<0.005$, و $p<0.0001$) . ارتبطت الأنزيمات الكبدية بالمقاسات الانثروبومترية (مؤشر كتلة الجسم ونسبة محيط الخصر إلى الورك) مع وصمات مقاومة الأنسولين (تحديد مقاومة الأنسولين بنموذج تقييم الاستتباب والأنسولين و جلوكوز ما بعد الصيام) . ومع ذلك فالدراسة بينت أن ارتباط ناقلات ببيتايد غاما غلوتميل هو الأقوى. أظهرت الدراسة ارتباطا عكسيا معتدا من الناحية الإحصائية بين مستوى الألبومين ومؤشر كتلة الجسم وتحديد مقاومة الأنسولين بنموذج تقييم الاستتباب والأنسولين ($p<0.05$, $p<0.01$, و$p<0.01$) على التوالي. **الخلاصة:** إن وظائف الكبد المعتلة وخصوصا مستوى ناقلات ببيتايد غاما غلوتميل هو الأقوى في ارتباطه بالسمنة ومقاومة الأنسولين بنموذج تقييم الاستتباب والأنسولين. إن مستوى ناقلات ببيتايد غاما غلوتميل قد يكون أكثر دلالة على التغيرات المرضية الكبدية المصاحبة للسمنة ومقاومة الأنسولين عند البالغين السعوديين حيث استهلاك الكحول مقيد. هذه النتائج تظهر احتمال تغير أيض الألبومين في السمنة .

مفتاح الكلمات: السمنة . مقاومة الأنسولين . أنزيمات ناقلات الأمين . ألبومين المصل . المملكة العربية السعودية.

ABSTRACT ***Objectives:*** This study was conducted to assess the relationship of hepatic enzymes and serum albumin to obesity and insulin resistance in adults in Saudi Arabia. ***Methods:*** A comparative study of 136 Saudi adults, comprising of 68 obese and 68 non-obese was conducted. Anthropometric measurements, hepatic enzymes, serum albumin, blood glucose, serum insulin, lipid profile, and homeostasis model assessment of insulin resistance (HOMA IR) were measured. ***Results:*** The study showed significantly higher levels of gamma glutamyl transpeptidase (GGT), alkaline phosphatase, fasting glucose, serum insulin, and HOMA IR $p < 0.001$, $<0.004 < 0.005$, <0.0001, <0.0001, among obese subjects. Hepatic enzymes correlated with both anthropometric measures (body mass index (BMI), and waist to hip ratio) and markers of insulin resistance (HOMA IR, insulin, and fasting glucose). However, the study found that GGT had the strongest associations. Significant inverse correlation was found between serum albumin and BMI, HOMA IR, and serum insulin, $p< 0.01$, <0.05, <0.01, respectively. ***Conclusion:*** Deranged liver functions, especially GGT, had the strongest correlations with obesity and HOMA IR. GGT might be a better marker of hepatic pathology associated with obesity and insulin resistance in Saudi adults with restricted alcohol intake. The results also propose that albumin metabolism might be altered in obesity.

Keywords: Obesity; Insulin resistance; Transaminases; Serum albumin; Saudi Arabia.

Advances in Knowledge

- *Gamma glutamyl transpeptidase might be a better marker of hepatic pathology associated with obesity and insulin resistance in Saudi adults with restricted alcohol intake.*

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Application to Patient Care

- *In patients with non-alcoholic fatty liver disease, gamma glutamyl transpeptidase has a stronger positive correlation to obesity than other hepatic enzymes in Saudi adults.*

Obesity is a major health problem. Non-alcoholic fatty liver disease is a hepatic dysfunction frequently associated with obesity,[1, 2] and the fatty liver changes correlate with the severity of obesity.[3, 4] The literature is well documented for the association of the levels of hepatic enzymes and obesity,[5-11] and for measured percentage body fat.[12-14] This association with obesity had been shown for non-alcoholic fatty liver disease either diagnosed by ultrasound or liver biopsy.[1, 4, 15, 16] The relationship of hepatic enzymes as markers of non-alcoholic fatty liver disease and insulin resistance was appreciated by the prediction of metabolic syndrome and Type 2 diabetes mellitus. Alanine aminotransferase (ALT) predicts metabolic syndrome or correlates with its components,[8, 17, 18] as well gamma glutamyl transpeptidase (GGT),[6] or both.[2] ALT predicts diabetes mellitus,[8, 9] and similar observations are attributed to GGT,[19-23] or both.[10] ALT and GGT correlates with surrogates of insulin resistance,[2, 7, 10, 16, 24] and with directly measured insulin resistance.[9, 12] GGT is a sensitive marker for liver damage, but less specific than other hepatic enzymes. Alcohol intake is prohibited by religion and enforced by law in Saudi Arabia. The pattern of these enzymes in relation to obesity and insulin resistance is not well documented in such an environment. Glycated albumin is associated negatively with obesity in non-diabetic children.[25] It has been reported that serum albumin is low in obese individuals even with normal liver histology.[3]

The aim of the study was to assess the relationship of hepatic enzymes and serum albumin to obesity and insulin resistance in adult Saudi individuals.

METHODS

The study was conducted over a one year period (2004 - 2005) at the Departments of Internal Medicine in the Colleges of Medicine in Al-Ahsa and Dammam, at King Faisal University, Kingdom of Saudi Arabia. A total of 136 volunteer subjects were included. They were non-diabetic with normal blood urea nitrogen and serum creatinine, and had no microalbuminuria (urine albumin to creatinine ratio less than 0.03 mg/mg in overnight early morning sample). They were stratified into obese and non-obese groups according to international criteria. Serum liver chemistry, fasting glucose, insulin and lipid profile were measured. The scores for homeostasis model assessment of insulin resistance (HOMA IR) were calculated with the formula: fasting serum insulin (μU/ml) X fasting serum glucose (mmol/l) / 22.5 as described by Matthews and his colleagues.[26]

There were 68 (34 males and 34 females) non-obese subjects with normal body mass index (BMI) less than 25, and 68 (34 males and 34 females) obese subjects with BMI equal or more than 30. Non-obese subjects had normal blood pressure <18.66/11.99 KPa (<140 / 90 mmHg), normal oral glucose tolerance and within normal liver function tests. Obese subjects had normal liver chemistry except 8 subjects (11.7%) with only alanine aminotransferase (ALT) increased, which was less than 2 times the normal upper limit. There were nine subjects (13.2%) with blood pressure > 18.66/11.99 KPa (> 140 / 90 mmHg), eight subjects (11.7%) with impaired fasting glucose, two subjects (2.9%) with impaired glucose tolerance, and the rest had normal oral glucose tolerance.

Subjects were included with following criteria: age between 18 - 65 years, Saudi nationals, normal blood urea nitrogen and serum creatinine, normal total bilirubin and no microalbuminuria (urine albumin to creatinine ratio less than 0.03 mg/mg in overnight early morning sample). Subjects were excluded if they were diabetic, had abnormal hepatitis B or C serology, known liver disease, alcohol intake, medications, and current acute or chronic illness. The study was approved by the Research and Ethical Committee of King Faisal University and consent was taken from study subjects.

Height and weight was measured using Detecto scale to the nearest 0.5 cm and 0.1 kg respectively. Body mass index (BMI) was defined as the weight in kilograms divided by the square of the height in meters. Waist circumference was measured at the highest point of the iliac crest and hip circumference measured at the maximum circumference of the buttocks. Normal waist to hip ratio was < 0.9 for men and < 0.85 for women. A mean of two measurements of blood

Table 1: ***Clinical and biochemical characteristics of all 136 study subjects.***

Variable	Non-Obese	Obese	P value
Number of subjects	**68**	**68**	
Males (%)	**34 (50%)**	**34 (50%)**	
Age (years)	**24.6 + 3.7**	**28.8 + 6.9**	**<0.0001**
Body mass index	**22.7 + 2.2**	**36.5 + 7.3**	**<0.0001**
Waist to hip ratio	**0.796 + 0.094**	**0.885 + 0.083**	**<0.0001**
Systolic BP (KPa)	**15.13 + 1.73 (113.5 +13.0 mmHg)**	**16.17 + 1.97 (121.3 + 14.8 mmHg)**	**<0.007**
Diastolic BP (KPa)	**9.53 + 1.12 (71.5 + 8.4 mmHg)**	**10.29 + 1.28 (77.2 + 9.6 mmHg)**	**<0.002**
Albumin (g/L)	**42.9 + 2.6**	**40.0 + 3.0**	**NS**
ALT (U/l)	**38.6 + 11.8**	**44.9 + 19.5**	**NS**
AST (U/l)	**17.8 + 5.5**	**20.0 + 8.6**	**NS**
GGT (U/l)	**24.3 + 8.9**	**33.6 + 16.4**	**<0.001**
ALP (U/l)	**73.96 + 20.83**	**85.79 + 18.84**	**<0.004**
HOMA-IR	**2.09 + 1.4**	**3.86 + 1.9**	**<0.0001**
Insulin (pmol/L)	**56 + 35 (9.35 + 5.85 µU/ml)**	**98 + 44 (16.36 + 7.32 µU/ml)**	**<0.0001**
Fasting glucose (mmol/L)	**4.9 + 0.3 (89.3 + 6.3 mg/dl)**	**5.2 + 0.6 (94.5 + 10.6 mg/dl)**	**<0.005**
Total cholesterol (mmol/L)	**4.40 + 0.73 (170.0 + 28.2 mg/dl)**	**4.76 + 0.84 (184.2 + 32.5 mg/dl)**	**<0.023**
Triglyceride (mmol/L)	**0.82 + 0.41 (72.9 + 36.2 mg/dl)**	**1.15 + 0.59 (101.6 + 52.6 mg/dl)**	**<0.002**
HDL-Cholesterol (mmol/L)	**1.47 + 0.40 (56.9 + 15.6 mg/dl)**	**1.29 + 0.33 (50.0 + 12.8 mg/dl)**	**<0.02**

Values are means $\pm$ SD; NS = not significant.

Legend: BP s= Blood pressure; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; GGT = Gamma glutamyl transpeptidase; ALP = alkaline phosphatase; HOMA IR = homeostasis model assessment of insulin resistance; HDL = High Density Lipoprotein

pressure at lying and sitting positions was calculated.

Serum glucose, total cholesterol, triglycerides, high-density lipoprotein (HDL)-cholesterol, blood urea nitrogen (BUN), creatinine, serum albumin, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferas (AST), gamma glutamyl transpeptidase (GGT), and alkaline phosphatase (ALP) were measured by the Dimension RXL analyzer (Dade Behring). Serum insulin was measured by a microenzyme immunoassay using IMX analyzer (Abbott Diagnostics). Urine for micro-albumin was measured by a particle-enhanced turbidimetric inhibition immunoassay using the ACA Star analyzer by Dade Behring.

A 75 g oral glucose tolerance test and early morning urine sample for microalbuminuria were carried out for all subjects. Venous blood samples were obtained in the morning after 12 hours overnight fast. Serum specimens were stored at - 70c until analysis. Normal ranges for liver chemistries in our hospital were total bilirubin 1.7 – 17.1 µmol/l, total protein 60 - 80 g/l, albumin 35 - 48 g/l, ALT 20 - 65 U/l, AST 7 - 41 U/l, GGT 5 - 85 U/l, and ALP 50 -140 U/l.

A quality control program was carried out regularly in our laboratories including system check, quality controls, and calibrations/verifications according to system manufacturers' instructions and recommendations.

The sample size is based on assuming the worse acceptable probability of the adverse outcome: 'elevated hepatic transaminases' to be 20% in obese and 2% in non-obese adult individuals with a type II error of 20% to achieve statistical significance at a confidence level of 95% and power of 80%. The least total number of obese and non-obese subjects would be 56 each.

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) statistical software version 12.0. Student t - test, and Mann-Whitney test were carried out according to the results of Levene's test of homogeneity for equal variances as appropriate. Pearson correlation coefficients were

Table 2: ***Correlations of hepatic enzymes and serum albumin with the clinical and biochemical parameters of all 136 study subjects.***

	Serum Albumin (g/dl)	ALT (U/l)	AST (U/l)	GGT (U/l)	ALP (U/l)
Body mass index	- 0.426 **	0.263 **	0.320 **	0.339 **	0.290**
Waist to hip ratio	- 0.041	0.302 **	0.313 **	0.509 **	0.145
Systolic blood pressure	0.117	0.263 **	0.313 **	0.369 **	0.273**
Diastolic blood pressure	- 0.055	0.085	0.000	0.189	0.257*
HOMA-IR	- 0.251 *	0.462 **	0.354 **	0.481 **	0.143
Insulin	- 0.279 **	0.414 **	0.318 **	0.476 **	0.146
Fasting glucose	- 0.053	0.280 **	0.278 **	0.230 *	0.132
Total Cholesterol	- 0.039	0.204 *	0.150	0.295 **	0.228*
Triglyceride	- 0.144	0.314 **	0.206 *	0.493 **	0.189
HDL-Cholesterol	0.047	- 0.311 **	- 0.285 **	- 0.365 **	- 0.118

* $p < 0.05$ and ** p value < 0.01

Legend: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; GGT = Gamma glutamyl transpeptidase; ALP = alkaline phosphatase; HOMA IR = homeostasis model assessment of insulin resistance; HDL = High Density Lipoprotein

measured. Results are presented as mean $\pm$ standard deviation.

RESULTS

The clinical and biochemical characteristics of study subjects are shown in Table 1. The obese subjects were significantly older than non-obese (p<0.0001). Obese individuals had a mean age 28.8 $\pm$ 6.9 years with a median 27.00 and a minimum and maximum age of 19 and 47 respectively. Non-obese individuals had a mean age 24.6 $\pm$ 3.7 years with a median 24.00 and a minimum and maximum age of 20 and 41 respectively. Obese subjects had higher BMI, waist-to-hip ratio (WHR), systolic and diastolic blood pressure (p< 0.0001, <0.0001, < 0.007 and <0.002 respectively).

The means of serum albumin levels were lower, and ALT and AST levels were higher in obese individuals, but there was no significant statistical difference. The obese subjects had significantly higher GGT, and ALP levels (p < 0.001 and 0.004 respectively). Obese individuals had significantly higher fasting blood glucose, (p < 0.005). HOMA IR scores, and insulin were significantly higher in obese subjects (p <0.0001). Total cholesterol, triglycerides, and HDL- cholesterol were significantly higher in obese individuals (p <0.023, <0.002, and <0.02 respectively).

Table 2 shows correlations of liver function tests with clinical and biochemical variables. All hepatic enzymes (ALT, AST, GGT, and ALP) were associated with measures of obesity including BMI, and WHR, but GGT had the strongest correlations with r 0.339, r 0.509 respectively, (p < 0.01). Figure 1 shows the line graph of the correlation of ALT, AST, and GGT with BMI. Serum albumin was inversely associated with BMI r - 0.426, (p < 0.01). Systolic blood pressure correlated significantly with ALT, AST, GGT, and ALP, (p <0.01, <0.01, <0.01, and <0.01 respectively). Diastolic blood pressure correlated significantly with ALP, (p <0.05).

ALT, AST, and GGT correlated with measures of insulin resistance including HOMA IR, insulin, and fasting glucose. GGT had the strongest correlations with HOMA IR, and insulin r 0.481, r 0.476, respectively (p < 0.01). Figure 2 shows the line graph of the

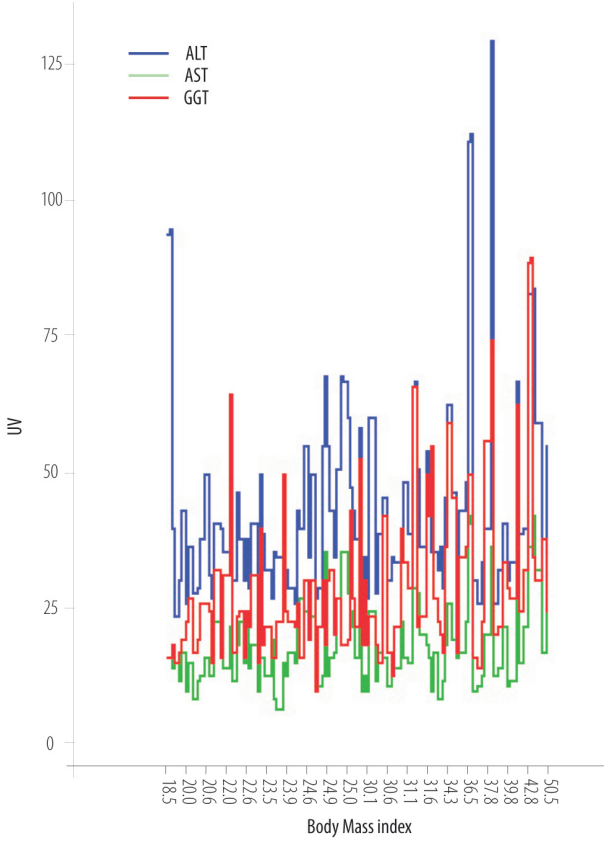

Figure 1: ***Correlation of alanine aminotransferase (ALT), aspartate aminotransferas (AST), and gamma glutamyl transpeptidase (GGT) with body mass index***

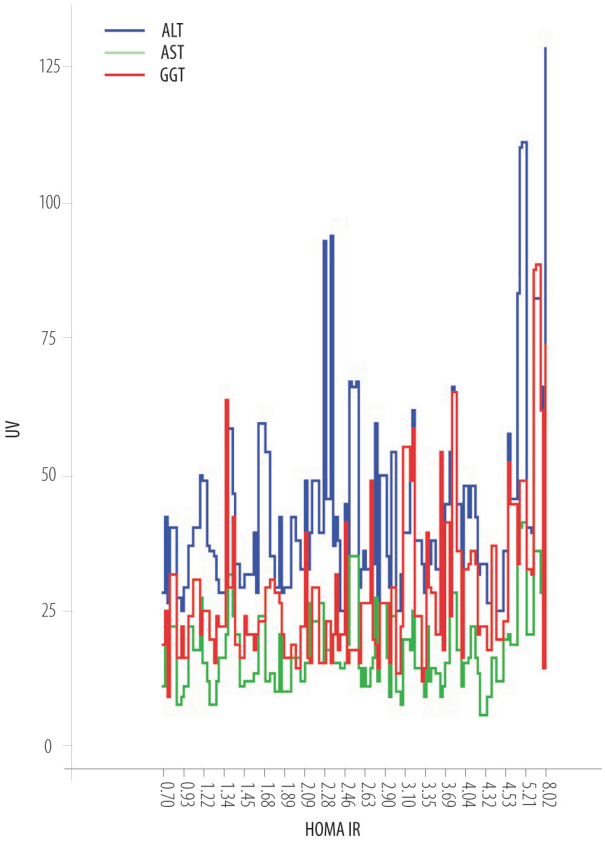

Figure 2: ***Correlation of alanine aminotransferase (ALT), Aspartate aminotransferase (AST), and gamma glutamyl transpeptidase (GGT) with homeostasis model assessment of insulin resistance (HOMA IR).***

correlation of ALT, AST, and GGT with HOMA IR. ALT, GGT, and ALP correlated with total cholesterol. ALT, AST, and GGT correlated with triglycerides, and inversely with HDL-cholesterol. Serum albumin had significant negative correlation with HOMA IR, and insulin r - 0.251, r - 0.279 (p < 0.05 and <0.01 respectively).

DISCUSSION

GGT and ALP were significantly higher in obese than non-obese subjects, while ALT and AST did not show a significant difference. ALT, AST, and GGT correlated significantly with BMI. A similar significant correlation was found with WHR and systolic blood pressure. HOMA-IR and serum insulin correlated significantly with ALT, AST, and GGT. In various studies, aminotransferases, especially ALT, have been shown to correlate with obesity,[7-11, 27] and insulin resistance.[7, 9, 12, 16, 27, 28]

Among hepatic enzymes, ALT is the most specific indicator of hepatic pathology in non-alcoholic fatty liver disease. GGT is considered to be a sensitive marker of hepatic damage, but it is not specific especially in societies with abundance of alcohol intake. In this study, GGT had the strongest correlations for BMI r 0.339, WHR r 0.509, systolic blood pressure r 0.369, insulin levels r 0.476, and HOMA IR r 0.481, compared to other liver enzymes. In addition, GGT correlated significantly with fasting glucose, total cholesterol, triglycerides, and inversely with HDL-cholesterol, r 0.230, r 0.295, r 0.493, r 0.365 (p <0.05, <0.01, <0.01, and <0.01 respectively). Previous studies have shown positive correlation between GGT and measures of obesity and insulin resistance,[2, 5, 6, 10, 13, 24, 30] and to predict diabetes mellitus.[19-23] It is also reported to be increased in patients with ischaemic heart disease.[5] The findings of this study and the literature suggest a major role of GGT in the manifestation of liver pathology associated with obesity and insulin resistance.

In this study, ALP correlated significantly with BMI, systolic and diastolic blood pressure, and to-

tal cholesterol. It had been reported to be higher in obese than non-obese subjects as has been observed in this study,[3, 31, 32] without significant correlation with HOMA-IR.

Serum albumin showed significant inverse correlation with BMI, HOMA IR, and serum insulin. It has been reported that glycated albumin is associated negatively with obesity in non-diabetic children,[25] and more recently in non-diabetic adults.[33] Glycated albumin is lower in obese diabetics,[34] and correlates negatively with body mass index.[35] The etiology of this observation is not yet known. In this study, a negative association between serum albumin and obesity was found. Serum albumin level reflects the rate of synthesis, degradation, and volume of distribution. Increase vasopermeability is suggested by literature reports of increase in albumin extravasation in skeletal muscles in the obese Zucker rat model, [36] and as well by an increase in transcapillary escape rate of albumin in hypertensive patients with metabolic syndrome.[37] Endothelial dysfunction had been reported to be related to elevated ALT levels among patients with diabetes mellitus.[38] Although microalbuminuria was not present in the study subjects as per inclusion criteria, it is another potential explanation and mechanism for the observed relationship of albumin and obesity. Microalbuminuria is an established marker of cardiovascular disease and reflects vascular dysfunction as a manifestation of a proposed low grade inflammation associated with obesity and insulin resistance.[39] Obesity is an independent risk for microalbuminuria,[40, 41] with the risk being parallel to changes in weight.[42]

CONCLUSION

In conclusion, ALT, AST, and GGT correlated with measures of obesity, and HOMA-IR. GGT had the strongest correlations and might be a better marker of hepatic pathology associated with obesity, and insulin resistance in Saudi and other subjects with no alcohol intake. Serum albumin correlated inversely with BMI and HOMA-IR suggesting an altered metabolism or handling of albumin in obesity.

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