

Could Liver Functions Predict Type 2 Diabetes Mellitus in Young Obese Men in Najran, Saudi Arabia?

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Abstract: Obesity prevalence is increasing worldwide and is correlated with T2DM. Insulin resistance is a key risk factor for development of T2DM. Liver enzymes activities were linearly correlated with IR. The present work aimed to investigate the usefulness of measuring liver enzymes as a predictor for T2DM in overweight and obese individuals. Blood samples were collected from 220 overweight and obese Saudi men in Najran area. Of these, 30 healthy control individuals (GI), 106 prediabetic overweight and obese (GII) and 84 diabetic overweight and obese (GIII). For all individuals, fasting serum glucose and insulin levels were estimated and HOMA-IR index was estimated. In addition, liver functions and lipid profile were estimated. The Body mass index was found to be significantly correlated with the HOMA-IR index ($r=0.77$) and most serum liver enzymes levels especially GGT, ALT and AST ($r=0.74$, 0.56 and 0.34 , respectively). BMI modified liver function tests. Such modifications were obvious in serum GGT, ALT and AST levels. Serum GGT levels were (33.75 ± 19.39 U/L) in GII and (37.23 ± 22.51 U/L) in GIII and (20.26 ± 4.51 U/L) in GI. Serum GGT levels were found to be significantly correlated with the body weight ($r=0.67$), BMI ($r=0.74$), fasting serum insulin ($r=0.66$), HOMA-IR index ($r=0.71$), serum total cholesterol ($r=0.32$), HDL ($r=-0.39$) and TG ($r=0.54$). While, serum ALT levels were (36.18 ± 10.85 U/L) in GII, (41.89 ± 15.17 U/L) in GIII and (16.73 ± 8.15 U/L) in GI. Serum ALT levels were found to be significantly correlated with the body weight ($r=0.46$), BMI ($r=0.56$), fasting serum insulin ($r=0.39$) and HOMA-IR index ($r=0.48$). Serum AST levels were (26.74 ± 10.79 U/L) in GII, (32.29 ± 9.23 U/L) in GIII and (18.19 ± 8.25 U/L) in GI. Serum AST levels were found to be significantly correlated with the body weight ($r=0.38$), BMI ($r=0.34$) and HOMA-IR index ($r=0.33$). Serum ALP levels were (78.67 ± 19.85 U/L) in GII, (84.79 ± 20.77 U/L) in GIII and (41.34 ± 15.13 U/L) in GI table. While, in case of serum albumin, total protein and total bilirubin, there were non-significant differences among the tested groups.

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1. Introduction

Obesity and type 2 diabetes (T2DM) are globally increasing health problems for young people, with significant individual and public health ramifications with respect to associated morbidity and mortality rates, *Ebbeling et al., (2002)* and *Silink (2002)*. Serum activities of hepatic enzymes have been associated with obesity in adults (*Clark et al., 2003*) and adolescents (*Strauss et al., 2000*). *WHO, (2012)* reported that overweight and obesity are the fifth leading risk for global deaths. At least 2.8 million adults die each year as a result of being overweight or obese. In addition, 44% of the diabetes burden is attributable to overweight and obesity. *WHO, (2004)* reported that Diabetes mellitus (DM) is a very

common metabolic disease with expected worldwide burden of 300 million populations in the year 2020, (*WHO, 2004*). Several factors are implicated in the development of T2DM including obesity, family history, physical inactivity and inherited factors (*American Diabetes Association, 2008*). However, obesity is considered the most important risk factor for the disease, as obese individuals are seven times more likely to develop T2DM than are normal weight individuals (*Bloomgarden, 2000*). The increased prevalence of childhood obesity is a major reason for the increased rates of IR and T2DM in children (*Ortega et al., 2006*). Hepatic dysfunction resulting from the IR syndrome may contribute to the development of T2DM (*Marchesini et al., 2001*).

Relationships between hepatic enzymes activities and insulin resistance (IR) were recorded elsewhere. Liver enzymes concentrations were linearly correlated with HOMA-IR (*Fei et al., 2012*). *André et al., (2007)* reported that gamma-glutamyltransferase (GGT) is considered the main predictor for the development of T2DM. GGT enzyme is a cell-surface protein contributing to the extracellular catabolism of glutathione (GSH). The enzyme is produced in many tissues, but most GGT in serum is derived from the liver (*Emdin et al., 2005*). Serum levels of GGT are determined by several factors including body fat content, plasma lipid/lipoproteins and glucose levels, and various medications, (*Brenner et al., 1997*). Obesity also has major effects on serum GGT activities (*Wannamethee et al., 1995*). GGT is considered to be a sensitive indicator of liver damage but is not specific (Penn and Worthington, 1983). The role of GGT is maintaining adequate levels of intracellular glutathione and serum GGT has been proposed as a marker of oxidative stress, (*Lee et al., 2004*). Serum GGT may be strongly associated with obesity or fat accumulation of liver and contributing to the development of insulin resistance, (*Marchesini et al., 2001*). A large number of studies (*Lee et al., 2003 and Nakanishi et al., 2004*) have shown that raised GGT or ALT could be risk predictive factors for the development of T2DM independent of BMI, (*Nakanishi et al., 2004, Wannamethee et al., 2005 and Fraser et al., 2009*). Moreover GGT could be a marker of hepatic steatosis or visceral obesity (*André et al., 2006*). Insulin sensitivity and liver function are inversely related, (*Ortega et al., 2006*). Other studies suggest that a normal-functioning liver may contribute to whole body insulin sensitivity (*Michael et al., 2000*).

The present work aimed to investigate the relationship between elevated liver enzymes and insulin resistance in overweight and obese individuals in Najran, Saudi Arabia and to investigate the usefulness of measuring liver enzymes as a risky predictor for development of T2DM in overweight and obese individuals.

2. Subjects and Methods

The *WHO (2004)* regards a BMI greater than 25 kg/m² is considered overweight and above 30 kg/m² is considered obese. Two hundred and twenty overweight and obese Saudi men in Najran area (age 18-35 years), were included in this study. Of these, 30 healthy control individuals (GI), 106 prediabetic overweight and obese individuals (GII) and 84 diabetic overweight and obese individuals (GIII). Blood samples were collected in the morning, after an overnight fasting (12 hours). All individuals of groups (I) and (II) were apparently healthy; none was taking any medication or had any medical condition known to influence body

composition, insulin secretion or action. This study was approved by the Ethics of Saudi community. All individuals were informed about the aim of the study and invited to join the study.

2.1. BMI and IR Calculations

BMI was calculated by the body weight in kilograms divided by the square of the height in meters. Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) is an indirect marker of insulin resistance. HOMA-IR was calculated according to *Matthews et al., (1985)*, using the Formula: HOMA-IR = [Fasting insulin (μU/ml)-fasting glucose (mmol/L)]/22.5].

2.2. Biochemical measurements

Liver function tests including gamma-glutamyltransferase (GGT), alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), total bilirubin (TB), albumin (ALB), total protein (TP) were measured using COBAS INTEGRA automatic analyzers (Roche Diagnostics GmbH, USA). Insulin was estimated by Access 2 machine (BECKMAN COULTER, INC) by using direct chemiluminescent technology. Fasting serum glucose and lipid profile including total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) and triglycerides (TG) were measured using the same method.

2.3. Statistical analysis:

All statistical analyses were performed using GraphPad InStat 3 (GraphPad Software, Inc. 2236 Avenida de la Playa La Jolla, CA 92037 USA). We used a two-tailed test and Spearman Correlation Coefficients and a value of P<0.05 was considered to be statistically significant.

3. Results

The present study was carried out on 220 men including 30 normal healthy controls (GI), 106 prediabetic overweight and obese individuals (GII) and 84 diabetic overweight and obese individuals (GIII). The age of the included individuals in the present study ranged from 18—35 years. The mean age of the subjects included in the study was 28.47±5.84 years in GI, 29.67±5.19 years in GII and 31.54±6.81 years in GIII and the statistical difference in the age between groups were not significant.

3.0 The mean BMI among studied groups:

An extremely significant difference was observed in the mean Body mass index, between the tested groups (20.76±2.13 kg/m² in GI and 27.71±4.56 kg/m² in GII and 34.15±6.25 kg/m² in GIII), all the values were highly increased in GII and GIII compared with GI, as shown in Table (1). The Body mass index was found to be significantly correlated with the HOMA-IR index (r=0.77) and most serum liver enzymes levels especially GGT, ALT and AST

($r=0.74$, 0.56 and 0.34 , respectively), as shown in table (2).

3.1. The relationship between BMI and HOMA-IR index:

We found that, there were highly increases in the fasting serum glucose level in the tested groups (6.23 ± 2.11 mmol/L in GII and 9.17 ± 4.83 mmol/L in GIII) compared with GI (4.91 ± 1.91 mmol/L) and the differences were extremely significant in GIII compared with that of GI and GII. Such findings were accompanied with high increases in the fasting serum insulin levels of the tested groups (19.77 ± 10.51 μ U/ml in GII and 32.35 ± 8.67 μ U/ml in GIII), while it was 13.57 ± 5.21 μ U/ml in GI. Such results were reflected on the ratio of the insulin resistance, where HOMA-IR index showed extremely significant increases between the tested groups (6.42 ± 1.32 in GII and 20.78 ± 8.14 in GIII) compared with GI (3.84 ± 1.59). The HOMA-IR index was found to be significantly correlated with the age ($r=0.38$), body weight ($r=0.64$), BMI ($r=0.77$), fasting serum glucose ($r=0.48$), fasting serum insulin ($r=0.78$), serum total cholesterol ($r=0.47$) and serum HDL ($r=-0.31$). At the same time, HOMA-IR index was found to be significantly correlated with most serum liver enzymes levels especially GGT, ALT and AST ($r=0.71$, 0.48 and 0.33 , respectively), as shown in table (2).

3.2. The relationship between BMI and liver function tests:

We found that increased BMI modified liver function tests. Such modifications were obvious in serum GGT, ALT and AST levels. The present study demonstrated that there were highly increases in the serum GGT levels in GII (33.75 ± 19.39 U/L) and (37.23 ± 22.51 U/L) in GIII compared with GI (20.26 ± 4.51 U/L). Serum GGT levels were found to be significantly correlated with the body weight ($r=0.67$), BMI ($r=0.74$), fasting serum insulin ($r=0.66$), HOMA-IR index ($r=0.71$), serum total cholesterol ($r=0.32$), HDL ($r=-0.39$) and TG ($r=0.54$),

table (2). Such significant differences were also noticed for the serum ALT levels which were (36.18 ± 10.85 U/L) in GII and (41.89 ± 15.17 U/L) in GIII compared with GI (16.73 ± 8.15 U/L). Serum ALT levels were found to be significantly correlated with the body weight ($r=0.46$), BMI ($r=0.56$), fasting serum insulin ($r=0.39$) and HOMA-IR index ($r=0.48$), table (2). In case of AST, we found high increases in the serum enzyme levels in GII (26.74 ± 10.79 U/L) and (32.29 ± 9.23 U/L) in GIII compared with GI (18.19 ± 8.25 U/L). Serum AST levels were found to be significantly correlated with the body weight ($r=0.38$), BMI ($r=0.34$) and HOMA-IR index ($r=0.33$), table (2). Regarding to the serum ALP level, the present study demonstrated that there were significant increases in the serum ALP levels among the tested groups (78.67 ± 19.85 U/L) in GII and (84.79 ± 20.77 U/L) in GIII compared with GI (41.34 ± 15.13 U/L), table (1). While, in case of serum albumin, total protein and total bilirubin, there were non-significant differences among the tested groups.

3.3. The relationship between BMI and lipid profile:

We found significant increased serum total cholesterol levels among the tested groups (253.61 ± 48.54 mg/dl) in GII and (301.25 ± 35.69 mg/dl) in GIII compared with GI (178.56 ± 18.14 mg/dl). At the same time, there were significant increases in the serum TG levels among the tested groups (205.34 ± 23.67 mg/dl) in GII, (215.14 ± 35.64 mg/dl) in GIII compared with GI (149.69 ± 25.26 mg/dl). Also, there were significant increases in the serum LDL levels among the tested groups (184.38 ± 38.68 mg/dl) in GII, (209.35 ± 40.28 mg/dl) in GIII compared with GI (115.28 ± 12.65 mg/dl). Regarding to the serum HDL level, the present study demonstrated that there were significant decreases in the serum HDL level in GII (31.17 ± 8.24 mg/dl) and GIII (27.65 ± 12.74 mg/dl) compared with GI (35.26 ± 6.27 mg/dl), table (1).

Table 1: BMI, Glucose, Insulin Resistance and Lipid profile in healthy control (GI), Prediabetic overweight and obese individuals (GII) and Diabetic overweight and obese individuals (GIII)

Mean \pm S.D.	GI (n=30)	GII (n=106)	P1	GIII (n=84)	P1	P2	
BMI (kg/m ²)	20.76 \pm 2.13	27.71 \pm 4.56	<0.0001***	34.15 \pm 6.25	<0.0001***	<0.0001***	
Fasting glucose mmol/L	4.91 \pm 1.91	6.23 \pm 2.11	0.002**	9.17 \pm 4.83	<0.0001***	<0.0001***	
Insulin μ U/ml	13.57 \pm 5.21	19.77 \pm 10.51	0.002**	32.35 \pm 8.67	<0.0001***	<0.0001***	
Insulin Resistance (HOMA-IR)	3.84 \pm 1.59	6.42 \pm 1.32	<0.0001***	20.78 \pm 8.14	<0.0001***	<0.0001***	
Liver function tests	GGT U/L	20.26 \pm 4.51	33.75 \pm 19.39	<0.0001***	37.23 \pm 22.51	<0.0001***	<0.0001***
	ALT U/L	16.73 \pm 8.15	36.18 \pm 10.85	<0.0001***	41.89 \pm 15.17	<0.0001***	0.02*
	AST U/L	18.19 \pm 8.25	26.74 \pm 10.79	<0.0001***	32.29 \pm 9.23	<0.0001***	0.0002***
	ALP U/L	41.34 \pm 15.13	78.67 \pm 19.85	<0.0001***	84.79 \pm 20.77	<0.0001***	0.04*
	Alb g/L	49.78 \pm 5.34	47.83 \pm 5.67	0.09	48.14 \pm 8.45	0.32	0.85
	TP g/L	68.52 \pm 6.54	67.24 \pm 8.25	0.44	65.82 \pm 9.13	0.14	0.26
Lipid profile	T.Bilmmol/L	5.45 \pm 2.71	5.97 \pm 4.83	0.57	6.32 \pm 5.74	0.43	0.65
	Chol mg/dl	178.56 \pm 18.14	253.61 \pm 48.54	<0.0001***	301.25 \pm 35.69	<0.0001***	<0.0001***
	TG mg/dl	149.69 \pm 25.26	205.34 \pm 23.67	<0.0001***	215.14 \pm 35.64	<0.0001***	0.02*

	LDL mg/dl	115.28 ± 12.65	184.38 ± 38.68	<0.0001***	209.35 ± 40.28	<0.0001***	<0.0001***
	HDL mg/dl	35.26 ± 6.27	31.17 ± 8.24	0.013*	27.65 ± 12.74	0.002**	0.022*

P1: Compared to healthy control (GI) P2: Compared to Prediabetic overweight and obese individuals (GII)
P<0.05: Significant P<0.01: Very Significant P<0.001: Extremely Significant

Table 2: Correlations between serum hepatic enzyme activities and anthropometric and metabolic characteristics of all overweight and obese individuals

Parameters	GGT	ALT	AST	ALP	HOMA-IR
Age	0.14	0.10	0.09	0.12	0.38 ^a
Body weight	0.67 ^c	0.46 ^c	0.38 ^b	0.08	0.64 ^c
Height	0.16	0.19	0.14	0.11	0.21
BMI	0.74 ^c	0.56 ^c	0.34 ^a	0.19	0.77 ^c
Fasting Glucose	0.25	0.20	0.13	0.21	0.48 ^c
Fasting Insulin	0.66 ^c	0.39 ^b	0.29	0.16	0.78 ^c
HOMA-IR	0.71 ^c	0.48 ^c	0.33 ^a	0.22	
Total Cholesterol	0.32 ^a	0.06	0.04	0.26	0.47 ^c
HDL	-0.39 ^b	-0.21	-0.17	-0.16	-0.31 ^a
LDL	0.09	0.11	0.14	0.10	0.21
TG	0.54 ^c	0.08	0.10	0.09	0.16

Variables without superscripts were not significantly related.

(^aP<0.05 ^bP<0.01 ^cP<0.001)

4. Discussion

Our study demonstrated that, serum liver enzymes (ALT, AST, and GGT) activities in overweight and obese individuals were significantly correlated with HOMA-IR index and could be used as a good predictor for T2DM in overweight and obese individuals. The present study was carried out on 220 men including 30 normal healthy controls (GI), 106 prediabetic overweight and obese individuals (GII) and 84 diabetic overweight and obese individuals (GIII). The aim of this study was to evaluate the association of serum liver enzymes levels with hepatic IR in overweight and obese individuals with and without impaired serum glucose levels.

We found that, increased BMI in overweight and obese individuals significantly increased both fasting serum glucose and insulin levels of the tested groups (GII and GIII) compared with GI. Such results were reflected on the ratio of the insulin resistance, where HOMA-IR index showed extremely significant increases between the tested groups compared with GI.

Our results agree with that reported by many authors. Increased incidence of T2DM is mostly due to IR and is correlated with obesity, (*Ortega et al., 2006*). *Cummings and Schwartz, (2003)* reported that obesity is the most important factor for IR and the relationship is usually of combined polygenetic and environmental origin. *Bloomgarden, (2000)* reported that obese individuals are seven times more likely to develop T2DM than are normal weight individuals. The driving force in the development of IR was attributed to the visceral adipose tissue that resists the antilipolytic effect of insulin and consequently

releases excessive amounts of free fatty acids, (*Greenfield and Campbell, 2004*). In addition, adipokines (cytokines from adipose tissues) also contribute to IR, (*Greenfield and Campbell, 2004 and Grundy et al., 2004*). Moreover, *Mlinar et al., (2007)* supposed that excess of free fatty acids directly affect insulin signaling, diminish glucose uptake in muscle, drive exaggerated TG synthesis and induce gluconeogenesis in the liver. Conversely, weight reduction and physical activity improve insulin sensitivity, (*Grundy et al., 2004*).

In the present study, we found that increased BMI in the tested groups (GII and GIII) modified liver enzymes activities (GGT, ALT and AST). Such modifications were most obvious in serum GGT levels. BMI was found to be significantly correlated with most serum liver enzymes levels especially GGT, ALT and AST ($r=0.74$, 0.56 and 0.34 , respectively) and the HOMA-IR index ($r=0.77$). At the same time, increased serum GGT levels in overweight and obese individuals were found to be significantly correlated with the body weight ($r=0.67$), BMI ($r=0.74$), fasting serum insulin ($r=0.66$), HOMA-IR index ($r=0.71$), serum total cholesterol ($r=0.32$), serum HDL ($r=-0.39$) and serum TG ($r=0.54$). Such significant differences were less noticed for the serum ALT and AST levels in GII and GIII compared with GI. At the same time, serum ALT levels were found to be significantly correlated with the body weight ($r=0.46$), BMI ($r=0.56$), fasting serum insulin ($r=0.39$) and HOMA-IR index ($r=0.71$). Serum AST levels were found to be significantly correlated with the body weight ($r=0.38$) and HOMA-IR index ($r=0.33$).

Our results agree with that observed by many authors. *Rantala et al., (2000) and Vozarova et al., (2002)* reported that serum activities of hepatic enzymes have been strongly associated with obesity and correlated to IR and T2DM. *Michael et al., (2000)* stated that a normal-functioning liver may contribute to whole body insulin sensitivity. Changes in GGT levels were correlated with changes in markers of IR (fasting insulin, HOMA index), *Andre et al., (2005, 2006 and 2007)*. They added that, among hepatic markers, GGT is the main predictor for the development of T2DM. Furthermore, serum levels of GGT, *(Nannipieri et al., 2005 and Lee et al., 2004)*, ALT *(Vozarova et al., 2002, Hanley et al., 2004, Nannipieri et al., 2005)* and AST *(Hanley et al., 2004)* are independent predictors of T2DM. *Vozarova et al., (2002)* concluded that higher ALT is a risk factor for T2DM and indicates a potential role of increased hepatic gluconeogenesis and/or inflammation in the pathogenesis of T2DM. *Fei et al., (2012)* reported that, serum ALT and/or GGT concentrations were independently related to newly diagnosed T2DM. Moreover, GGT has been regarded as a clinical marker for free-radical formation and proinflammation, *Karp et al., (2001)*.

On the other hand, hepatic IR is a late phenomenon in the natural history of T2DM. Therefore, other pathophysiological mechanisms, in addition to liver damage, might explain the association between elevated hepatic enzyme activities and the development of T2DM, *Ortega et al., (2006)*.

5. Conclusion:

Serum liver enzymes ALT and GGT concentrations were found to be closely related to prediabetes and diabetes in overweight and obese individuals in Najran population and positively associated with insulin resistance. Periodical estimation of liver enzymes ALT and GGT activities will be helpful in the prediction of T2DM in risky individuals.

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