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A Study of liver enzymes in Type 2 Diabetes Mellitus

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Abstract— Type 2 Diabetes Mellitus (T2DM) is a common disease that describe within metabolic complication. In Iraq, the prevalence of T2DM about 1.4 million**.** In T2DM, the insulin resistance in liver cause decrease glycogen synthesis leading to fail glucose production. This defect perform enhances lipogenesis and proteins synthesis leading to free fatty acid accumulation on liver. This defect effected on liver function and leading to liver damage.Seventy two patients were participated (28 males and 44 females). Their ages ranged between 45-60 years old and the mean of BMI to patients 23.55±4.56kg/m^2. The means of random blood glucose (RBG) and HbA1c 288.42±68.63 mg/dl, 9.08±1.9% respectively. Thirty apparently healthy persons (12 males and 18 females) were selected as a control group. Their age ranges were comparable to that of patients and the mean of BMI equal 22.94±3.15kg/m^2. The means of RBG and HbA1c 101.9±11.18 mg/dl, 5.03±0.63% respectively. There was no significant differences in ALT, AST and ALP in the diabetes group compared to the healthy group (*P*-value > 0.05) and there was no significant changes between males and female patients in ALT, AST and ALP furthermore random blood glucose and HbA1c.It was noted that RBG and HbA1c were significantly positively correlated with level of ALT AST and ALP (P≤0.001). conclusion: there was no significant difference between liver enzymes and T2DM. Through these results, there is no relationship between diabetes mellitus and elevated liver enzymes.

Keywords: T2DM, Liver damage, AST, ALT and HbA1c.

1-Introduction

Type 2 Diabetes Mellitus (T2DM) is a common disease that describe within metabolic complication. There are two factors that leading to T2DM the first result from low insulin secretion and the second where tissues resistance to insulin (Roden, et al 2019). Continuously increased blood glucose leading to damage to many organs such as kidney, heart, eyes, nerves system, liver and many tissues (Defronzo, et al 2009).In 2019, the prevalence of T2DM reported to be approximately 9.3% (463 million) and caused 4.2 million deaths and may increase to 10.9% (700 million) by 2045 (Saeedi, et al. 2019). In Iraq, the prevalence of T2DM about 1.4 million which nearly 8.5% *(*WHO 2019). Almost T2DM patients areobese or over weight leading increase body fat percentage, that concentrated in the abdominal region. For these reasons, adipose tissue stimulatesinsulin resistance through many mechanisms, perform to release high amount of free fatty acid and adipokineirregular (Chatterjee et al, 2017). Liver is important organs that regulated many biomolecules levels such as lipids and carbohydrate by some hormones such as insulin and glucagon. (Titchenell,et al 2017). In the liver, glucose produce by effective of insulin in different ways either direct and indirect mechanisms, each mechanisms are unclear(Edgerton, et al 2006). In T2DM, the insulin resistance in liver cause decrease glycogen synthesis leading to fail glucose production. This defect perform enhances lipogenesis and proteins synthesis(Leclercq, et al 2007). Increase free fatty acid synthesis causes it high level in plasma and leading to accumulate in many tissues such as liver or muscle. The accumulation of free fatty acids in the liver result from reduced insulin that stimulates hepatic gluconeogenesis with increase the resistance therefore T2DM development (Unaiet al. 2020). Increase fatty acid in liver promote of chronic liver disease in T2DM patients, which is described by excess accumulation of fat in the liver and associated withinsulin resistance in the liver and T2DM risk (Ballestri, et al . 2016).The effects of hyperglycemia on liver functions is very likely where enhanced oxidative stress,

chronic inflammation and liver injury (Dahman, et al. 2021) Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) are enzymes found in the liver that consider as a biomarker for hepatic injury (Music et al. 2015). Changes in the levels of these enzymes are present in diabetic patients(Sheng et al 2018.).The incidence of T2DM and liver enzymes have been studied extensively in Europe (Sattar et al. 2004, Goesslinget al. 2008, Monamiet al. 2008 and Fraser A, et al. 2009,) and Asia (Tohidiet al, 2008,Schulze et al. 2009,Wang et al 2016). A Studies have linked elevated ALT and AST levels with insulin resistance, type 2 diabetes, and metabolic syndrome (Idriset al, 2011 And Sheng et al 2018). Increased liver enzyme levels are associated with cardiovascular risks in both diabetics (Targher et al. 2005) and non-diabetics (Schindhelmet al. 2005 and Schindhelm et al. 20), where they may be a precursor to T2DM (Vozarova et al. 2005)The mechanism behind the association between liver enzymes and metabolic syndrome is that liver enzymes effect many processes in the humanbody, such as obesity, liver fat levels, and glucose levels. A variation of these factors causes metabolic syndrome (Nikniazet al 2018).

In spite of the fact that the prevalence of diabetes in expanding around the world and its predominance is higher creating nation , no thinks about were explained the relationship between raised liver proteins and T2DM patients. Hence the display consider was centered on the liver as the crucial organ contributing to glucose homeostasis and affected on hyperglycemia.

2-Materials and Methods

2-1 Subjects

2-1-1-Patients: One hundred Arabic Iraqi patients with type two Diabetes mellitus participated in the present study. Only 72 patients were completed (28 males and 44 females) all biochemical analysis tests. Their ages ranged between 45-60 years old and the mean of BMI to patients 23.55±4.56kg/m^2. The means of random blood glucose and HbA1c 288.42±68.63 mg/dl, 9.08±1.9% respectively. These patients were registered as diabetes mellitus patients in "Diabetes and endocrine Unit" at Al , Sadr General Hospital " in Najaf city-Iraq and "DiabetesUnit" at "Al , Hakim General Hospital" in Najaf city-Iraq within January to April 2021 period. The patients had Diabetes mellitus recorded in their files, and diagnosis was established by clinical symptoms and biochemical test.

- Exclusion Criteria: The present study excluded the patients with hypertension, those with endocrinitis infection and inflammation, heart diseases and also the patients from non-Arabic ethnic group.

2-1-2-Control group: Thirty apparently healthy persons (12 males and 18 females) were selected as a control group. Their age ranges were comparable to that of patients and the mean of BMI equal 22.94±3.15kg/m^2. The means of random blood glucose and HbA1c 101.9±11.18 mg/dl, 5.03±0.63% respectively. The people with anemic or has an obvious systemic diseases were excluded.

2-2-Collection Samples

Diabetes was diagnosed established on medical history, current medication intake, or American Diabetes Association (ADA) criteria(ADA 2016). The definition of T2DM was fasting blood glucose ≥126 mg/dl (≥7.1 mmol/L), random plasma glucose ≥200 mg/dl (≥11.1 mmol/L), or an HbA1c of 6.5(ADA 2016).

2.3. Anthropometric

Body Mass Index (BMI) was classified by the World Health OrganizationWeight and height were measured according to WHO guidelines(WHO1995) Using WHO guidelines, BMI was calculated as weight/height2 (Kg/m^2). Obese individuals were defined as having BMI more than 30 kg/m^2, whereas normal individuals had a BMI of 18-25 (WHO1995).According to the American College of Gastroenterology (ACG), a healthy ALT level ranges for men from 29 to 33 IU/l, and for women 19 to 25 IU/l, and levels above this need to be evaluated (Kwo, et al 2017).

2.4. Biochemical Investigations

2-4-1-Blood samples: Five milliliters of venous blood samples were drown using a disposable needle and plastic syringes from each patient and control subject. Blood divided into two tubes anticoagulant tubes and gel tubes. The blood in gel tube was left at room temperature for 15 minutes for clotting, centrifuged 3000 Xg for 5 minutes, and then serum was separated and transported into new disposable tubes

2-4-2- Experimental Apparatus: DRI-CHEM NX500V (Fuji film), AFIAS – 6, Centrifuge 800B China, water bath China,Adjustable Micropipettes China (25),(10-100), (100-1000) uL Dargon. Balance and tape measure.

Chemicals: B.Glucose, s.AST, s.ALT, S.ALP and HbA1c Kits

Biostatistical Analysis

The student T-test was employed to assess differences in scale variables between diagnostic categories and analysis of contingency tables (χ2-test) was used to check associations between nominal variables. Associations among variables were computed using Pearson's product-moment and Spearman's rank-order correlation coefficients. All tests were 2-tailed and a p-value of 0.05 was used for statistical significance. All statistical analyses were performed using IBM SPSS windows version 25, 2017.

3-Results

In this study, the main results showed in Table 1. Out of 102 persons, 72 were T2DM (28 male and 44 female) and 30 were healthy participants (12male and 18 female). The age range for T2DM subjects was 45-60 years and 42-62 years for healthy subjects. The BMI in T2DM group had (23.55±4.56 kg/m^2) than the participants in the control group (22.94±3.15kg/m^2). Therewas no significant differences in ALT, AST and ALP in the diabetes group compared to the healthy group (*P*-value > 0.05).

Table 2 shown there was no significant changes between males and female patients in ALT, AST and ALP furthermore random blood glucose and HbA1c. The correlation coefficient was exposed in Table 3.

Table 1: Random blood Glucose, HbA1c, ALT, AST and ALP in patients with T2DM as compared with Healthy group.

Parameters	Patients Mean ± SDV	Controls Mean ± SDV	P- values
RBG mg/dl	288.42±68.633	101.97±11.18	<0.001
HbA1c %	9.08±1.9	5.027±0.63	<0.001
ALT IU/L	30.55 ±7.15	30.33±5.75	0.69
AST IU/L	32.12±8.4	30.03±7.26	0.27127
ALP IU/L	83.13±15.13	81.13±9.97	0.386

Table 2: *Random blood sugar, HbA1c, ALT, AST and ALP in males patients as compared and with females patients.*

Parameters	Male Patients Mean ± SDV	Female Patients Mean ± SDV	P- values
RBG mg/dl	293.46±64.63	285.13±71.67	0.613
HbA1c %	9.51±2.3	8.79±1.57	0.059
ALT IU/L	31.39 ±8.48	30.0 ±6.18	0.362
AST IU/L	31.79±9.87	32.3±7.29	0. 799
ALP IU/L	83.26±18.26	83.2±12.67	0.938

Table 3*: Correlation between RBG, HbA1c,ALT,AST and ALP.*

		RBG	HbA1c	ALT	ALP
ALT	Rho	0.02**	0.02**		
	P	<0.001	<0.001		
ALP	Rho	0.07**	-0.068**	-0.172**	
	P	<0.001	<0.001	<0.001	
AST	Rho	0.11**	0.25**	-0.0077	-0.179**
	P	<0.001	<0.001	0.18	<0.001

Pearson correlation coefficient with corresponding p-value ($p < 0.05$ is considered a significant). ** Correlation is significant at less than 0.01 level (2-tailed).

4-Discussion

Un controlled blood glucose and glycation is the most prevalenceproblem of T2DM that results from oxidative stress in tissues such as liver (Bigagliet al2019). This oxidative stress and cytokine creation in the liver cause alterations of liver enzymes due to the hepatocellular damage (Sunithaet al. 2015and Mathuret al 2016)therefore,hyperglycemia and uncontrolled blood glucose plays a main role liver dysfunction(Prabhudevaet al 2014). As a result of this condition, liver enzymes are abnormally introduced into the blood and become high (Shibabaw*et al.* 2019).In the present study, there was observed no significant difference between T2DM and healthy group for ALT shown in Table1. This study corresponding to Dahman et al studies where found there was no significant change between patients and controls groups for ALT in Yemeni Population (Dahman et al. 2021) also other research agreement this study was established no significant change between T2DM and healthy group for ALT (Elizabeth et al 2005andKim 2009). This result was consistent with those reported by Vozarova et al, Wannamethee et al and Jiamjarasrangsi(Vozarova et al. 2002, Wannamethee et al. 2005 ,Jiamjarasrangsi et al 2008 and. Kunutsoret al 2013) , who found no association of liver enzymes with diabetes patients as risk factor for diabetics.The reasons behind not changing the liver enzymes may be caused by diabetes medications, according to the results of the research Choi et al were found that ALT decreased in T2DM patients which consumed dapagliflozindruge (Choi et al 2018), or that diabetic patients take fat-reducing treatments and thus the accumulation of fat on the liver decreases, in addition to the fact that BMI is close to patients and control or the number on samples is few. In contrast, the Bangladesh study found increased liver enzymes ALT, AST and ALP than controls (Islam et al 2020) also other studies was established Serum ALT (71.65 ± 23.3) levels were elevated significantly among 36 (40%) of the T2DM participants (Ni et al 2012 and Music et al.. 2015). Moreover, Cho NH, et al. reported increase liver enzyme and correlation between ALT activity and increased fatty liver (Cho, et al. 2007).

additional, Sudan research were studied conducted on Sudanese diabetes and apparently healthy control subjects. The result of this study showed that the mean values of ALT and AST were significantly higher in T2DM than the control group (Idris. 2011andSheng et al 2018). Although the mean values were within the normal value, 11 participants (22%)with T2DM had at least one or more abnormal ALT and AST, (Idris et al 2011and Atibaet al 2013) this study agreement Getnet research was showed there a significant raise in ALT, AST and ALP which conducted on 159 patients and 159 healthy . *(Getnetet al 2019*) . Others research illustrated the increases liver enzymes result from complication of T2DM. This could be related to an increase in the action of glycogen and insulin on liver cells. The increase of glycogenolysis and gluconeogenesis stay the main metabolic pathway (Balajiet al. 2013). As a result, increases in substrate delivery (e.g. alanine) and alanine to glucose conversion may be regulated as a compensatory mechanism for reduced hepatic insulin communication transduction, which lets the enzyme to leak out of hepatocytes, primarily due to fat accumulation and hepatic cell damage (Wang et al. 2016). An irregular accumulation of fats and their mobilization in hormone-sensitive tissues such as the liver and hepatocytes demonstratethatthe metabolicshiftby insulin resistance is identified earlier than the increase in blood sugar at the start. The excessive release of free fatty acids by insulin resistance induces fat mobilization and leads to hepatocellular toxicity (Sunithaet al 2015). Elevated transaminases are directly related to liver cell damage. Plasma membrane rupture at high concentrations of metabolites, loss of mitochondrial activity, and inactivation of regulatory metabolic enzymes lead to hepatocellular injury (Harris 2005).Chines study as established that ALT elevated in T2DM while there was no significant change in both AST and ALP in the same study (Wang et al. 2016), which was consistent with previous studies, Vozarovaet al 2002, Wannamethee, et al. 2005, Jiamjarasrangsi et al.2008 and. Kunutsoret al 2013). and this may be due to their lack of specificity for liver diseases.

The compassion between males and females illustrated in Table 2. There was no significant differences between males and females in both RBG, HbA1c, ALT AST and ALP. A study of male Korean workers found that AST was independently associatedwith diabetes (Ahn, et al . 2014), while in a study of male Japanese office workers AST was not associated with T2D risk (Nakanishi, et al 2004). Some studies also reported that ALT is a significant predictor of diabetes while AST is not (Vozarova, et al . 2002). These findings are in agreement with present research as AST does not show considerable relationship with the studied parameters. Besides, Clark et al. also suggested that mild or chronic elevations of these aminotransferases may be due to NAFLD (Clark, et al 2003.and Clark, 2003) .

In Table 3, It was noted that RBG and HbA1c were significantly positively correlated with level of ALT AST and ALP ($P \leq 0.001$) similarity with *Getnet et al (Getnetet al* 2019) and Islam et al (Islam, et al 2020) except HbA1c was significantly negatively correlated with ALP reverse result *Deepika et al.(Deepika et al. 2016)*. Also other study was found There was a positive correlation between FBS and HbA1c, and ALT and AST ($P=0.0001$). There was a negative correlation with ALP and HbA1c (Sangappaet al 2017). Sunita S et al (Sunithaet al 2015) and Deepika G et al (Deepikaet al 2016) in their study, showed that FBS and HbA1c correlated significantly with ALP; similar findings were observed by Bora K et al (Bora et al 2016). In contrast, other study did not show correlation between ALP and FBS or HbA1c. But ALT was significantly negatively correlated with AST and ALP ($P \leq 0.001$). AST was significantly negatively correlated with ALP($P \leq 0.001$).

5-Conclusion

The result of this study showed that there was no significant change of the liver enzymes (AL, AST and ALP) between T2DM Patients and healthy groups. Through these results, there is no relationship between diabetes mellitus and elevated liver enzymes. It may be diabetes medications, or that

diabetic patients take fat-reducing treatments and thus the accumulation of fat on the liver decreases, in addition to the fact that BMI is close to patients and control or the number on samples is few. RBG and HbA1c were significantly positively correlated with level of ALT AST and ALP

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