



Effect of elevated HbA1c on liver and its function in patients with Type II diabetes-mellitus

Efecto de la HbA1c elevada sobre el hígado y su función en pacientes con diabetes mellitus tipo II

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Abstract

Background: Type II diabetes mellitus (T2DM) is a huge public health problem. T2DM patients are more prone to hyperlipidemia, which make the patients at great chance of developing macrovascular and microvascular diseases. Glycated hemoglobin (HbA1c) level is a great indicator for glycemic control and to determining the possibility of diabetes complications and mortality.

Materials, methods and subjects: This cross sectional study was performed at Al-Wafaa diabetic center in Mosul city from December 2021 to February 2022. All patients were known to have T2DM. Body mass index (BMI) was calculated, and patients were divided to two groups, patients with non-alcoholic fatty liver disease (NAFLD) and patients without NAFLD depending on ultrasonography examination. The biochemical blood tests were done to determine HbA1c, lipid profile and liver transaminases levels (GOT and GPT).

Results: One hundred T2DM patients were registered for our study, and of those patients, 68 (68%) male and 32 (32%) female they were divided to two groups depending on ultrasound finding: Group I: thirty nine (39) patients with non fatty liver. Group II: this group includes 61 patients with NAFLD.

Diabetic patients with NAFLD had a mean BMI of 30.90 vs. 26.66 for non fatty liver patients. The mean value for HbA1c, total cholesterol(TC), low density lipoproteins(LDL), triglyceride(Tg), high density lipoproteins(HDL), GOT and GPT values for diabetic patients with non fatty liver compared to FL diabetic patients were 7.2% vs. 9.1 %, 200.1 mg/dl vs.235.24 mg/dl .110 mg/dl vs 160 mg/dl, 145.5mg/dl vs. 230.3mg/dl, 42.4mg/dl vs. 44.4 mg/dl, 19.3 IU/L vs. 22.3 IU/L and 19.8 IU/L vs. 25.2 IU/L respectively. There was a highly significant positive correlation(r) between plasma HbA1c with triglyceride (Tg) and GPT.

Conclusion: Our study has showed that elevated HbA1c and triglyceride in T2DM with high GOT and GPT is significantly accompanied with NAFLD. Early detection of non alcoholic fatty liver in T2DM is important to prevent progress of the disease and minimize morbidity and mortality. Modified lipid profile is one of major feature of diabetes mellitus..

Key words: type II diabetes, glycated hemoglobin, liver enzyme, GOT, GPT, lipid profile.

Resumen

Fondo: La diabetes mellitus tipo II (DM2) es un gran problema de salud pública. Los pacientes con DM2 son más propensos a la hiperlipidemia, lo que hace que los pacientes tengan grandes posibilidades de desarrollar enfermedades macrovasculares y microvasculares. El nivel de hemoglobina glicosilada (HbA1c) es un gran indicador para el control glucémico y para determinar la posibilidad de complicaciones y mortalidad por diabetes.

Materiales, métodos y sujetos: Este estudio transversal se realizó en el centro para diabéticos Al-Wafaa en la ciudad de Mosul desde diciembre de 2021 hasta febrero de 2022. Se sabía que todos los pacientes tenían DM2. Se calculó el índice de masa corporal (IMC) y los pacientes se dividieron en dos grupos, pacientes con hígado graso (FL) y pacientes sin LF según el examen de ultrasonografía. Se realizaron análisis bioquímicos de sangre para determinación de HbA1c, perfil lipídico y niveles de transaminasas hepáticas (GOT y GPT).

Resultados: Cien pacientes con DM2 fueron registrados para nuestro estudio, y de esos pacientes, 68 (68%) hombres y 32 (32%) mujeres fueron divididos en dos grupos dependiendo del hallazgo ecográfico: Grupo I: treinta y nueve (39) pacientes con hígado. Grupo II: este grupo incluye 61 pacientes con LF. Se detectó hígado graso en el 61% de los pacientes.

Los diabéticos con LF tenían un IMC medio de 30,90 frente a 26,66 de los pacientes con hígado no graso. El valor medio de HbA1c, colesterol total (CT), lipoproteínas de baja densidad (LDL), triglicéridos (Tg), lipoproteínas de alta densidad (HDL), GOT y GPT para los pacientes diabéticos con hígado no graso en comparación con los pacientes diabéticos FL fue del 7,2 %. vs 9,1 %, 200,1 mg/dl vs 235,24 mg/dl 0,110 mg/dl vs 160 mg/dl, 145,5 mg/dl vs 230,3 mg/dl, 42,4 mg/dl vs 44,4 mg/dl, 19,3 UI /L frente a 22,3 UI/L y 19,8 UI/L frente a 25,2 UI/L respectivamente. Hubo una correlación positiva altamente significativa (r) entre HbA1c plasmática con triglicéridos (Tg) y GPT.

Conclusión:Nuestro estudio ha demostrado que la HbA1c y los triglicéridos elevados en la DM2 con GOT y GPT elevados se acompañan significativamente de enfermedad FL. La detección precoz del hígado graso no alcohólico en la DM2 es importante para prevenir el progreso de la enfermedad y minimizar la morbilidad y mortalidad.

El perfil lipídico modificado es una de las principales características de la diabetes mellitus.

Palabras clave: diabetes tipo II, hemoglobina glicosilada, enzima hepática, GOT, GPT.

Introduction

Diabetes mellitus (DM) is a global endemic metabolic disorder increasing in its prevalence in both developing and developed countries; it originates from disorders in insulin secretion or action those results in increment in blood glucose which is considered the main cause of complication of diabetes as organ failure¹.

T2DM affects most of the organs of the body, and the liver is not spared from it. Evidence has shown that patients with cirrhotic liver about 70% of them can be diagnosed with T2DM which may initiate and exacerbate chronic hepatic disease². The American Diabetes Association (ADA) has suggested that HbA1c as a good alternative for fasting blood glucose level for diagnosis of diabetes mellitus. HbA1c it's a great indicator test for chronic hyperglycemia and can correlates with the probability of having serious complications. High level of HbA1c has been considered as a risk factor for coronary heart disease (CHD) and cerebrovascular accident (CVA) in patients with diabetes³.

Testing of HbA1c reflect the cumulative glycemic history and gives idea about an mean blood glucose levels through out the last 2 - 3 months, which is the life span of the red blood cells (RBC)⁴. The HbA1c is highly suggested for diagnosing and follow up for diabetic patients, particularly for T2DM patients⁵.

One of the major risk factor for type II diabetes is obesity, with the change to the modern living style the percentage of obese people increased which leads to the increase in DM^(6,7).

NAFLD is a dominant cause for hepatic disease worldwide. It is mostly asymptomatic and progresses slowly^{8,9}. In fact, 25% of world wide population is recently start to complain of NAFLD, because of the world wide increase in obesity, and the main concern is the silent onset and bad prognosis in advanced stages of the disease¹⁰.

NAFLD is the most known cause of chronic hepatic disease specially in the developed countries. In patients with T2DM, NAFLD has more severe course and bad prognosis and can result in earlier onset of chronic hepatic disease. Although many noninvasive tests as ultrasonic examination can give an idea about the severity of the disease, but hepatic biopsy still the gold standard to diagnose NAFLD¹¹.

Common risk factors related with NAFLD are age, gender, ethnicity, T2DM and special characteristics of the metabolic syndrome, which include resistance to insulin, hypertriglyceridemia, central obesity, and low high-density lipoprotein cholesterol (HDL)^{12,13}.

The onset of NAFLD starts with resistance to insulin then followed by fat accumulation. This will lead to secondary categories including an inflammatory process, oxidative stress, altered hepatocyte apoptosis and genetic polymorphisms¹⁴.

Aim:

Our study was done to determine the prevalence of NAFLD and liver enzyme in T2DM patients by using liver sonography and determine its correlation with the body mass index (BMI), lipid profile, HbA1c and highlights the role of HbA1c in diagnosis and prognosis of diabetes patients.

Materials and methods

The present study is a cross sectional study was done at Al-Wafaa diabetic center in Mosul city from December 2021 to February 2022.

One hundred Patients with an confirmed diagnosis of T2DM for the last 5-9 years were selected according to the American Diabetes Association criteria 68 male with a mean of age \pm SD (48.78 \pm 16.22 years) and 32 female with a mean of age \pm SD (52.46 \pm 12.54 years).

An ultrasound examination of the liver was done for all the patients in our study and they were classified into two groups fatty and non-fatty liver.

Blood samples were collected from all diabetic patients, after fasting 12 to 14 hours and the plasma was used for measuring fasting plasma glucose (FPG) the glycated hemoglobin (HbA1c), using an automated glycohemoglobin analyzer (model: A1CEZ 2.0) total cholesterol(TC), high density lipoprotein(HDL), low density lipoproteins (LDL), triglyceride (Tg) using enzymatic colorimetric method and liver transaminases (serum glutamic oxaloacetic transaminase(GPT) and serum glutamic pyruvic transaminase(GOT) using optimized UV method.

Height and weight were measured and body mass index (BMI) were obtained by the equation = weight(Kg)/height (m²).

Patients with history of thyroid disorders, pregnant ladies, hepatitis, and those on lipid lowering treatment or on hepatotoxic medications were excluded from our study, also patients with type I DM and history of alcohol consumption were also excluded.

Statistical analysis

The statistical analysis for the laboratory and clinical data were done using SPSS software (version 17) software. Data were expressed as mean \pm standard deviation (SD). Analysis of the data was done using student's t-test. Pearson correlations were calculated to measures the association for the variables. $P < 0.05$ was significant

The results of analyzing our data are presented in the following tables.

One hundred T2DM patients were included in our research and of those patients, 68 (68%) male and 32 (32%) female, they divided into two groups depending on the ultrasound finding:

Group(I): thirty nine (39) patients with non fatty liver. The mean \pm SD of their age was 46.78 ± 12.56 years. This group includes 22 males (56%) and 17 females (44%)

Group II: this group includes 61 patients with NAFLD. Their mean age \pm SD was 50.22 ± 10.45 years. This group includes 46 males (75%) and 15 females (25%). (Table 1)

Table (1): Characteristic of group (I) and (II).

Groups	Numbers	Age/years mean \pm SD	Male %	Female %
Non-fatty liver	39	46.78 ± 12.56	56	44
Fatty liver	61	50.22 ± 10.45	75	25

Body mass index was higher in group II with a mean (30.90 Kg/m^2) than group I with a mean (26.66 Kg/m^2) and it was statistically significant ($P < 0.001$).

Different biochemical parameters were measured for all subjects in both group (I) and group (II). The results showed a significant differences between the two groups in HbA1c, TC, Tg and GPT.

The mean of plasma HbA1c level was (7.2 %) in group (I), which was less than group II (9.1%), ($P < 0.001$). Also, a significant difference ($P < 0.001$) was found in total cholesterol, which was lower in group (I) with a mean (200.1 mg/dl) and for group II, it was (235.24 mg/dl).

Triglyceride in group (I) (a mean of 145.5mg/dl) differed significantly ($P < 0.001$) from group II, mean (230.3 mg/dl). It was higher in group (II). the two groups showed a significant difference in GPT with a mean of (19.8 IU/L, 25.2 IU/L) for group (I) and (II) respectively ($P < 0.001$).

Although LDL was higher in group (II) than group (I) but it was statistically not significant. Also, no significant difference was found in HDL and GOT. Table 2 clarifies these results.

Table (2): Comparison of the body mass index and biochemical parameters between the patients with nonfatty liver group(I) and NAFLD group(II).

Parameters	Group(I) Mean \pm SD	Group (II) Mean \pm SD	P - value
Age(years)	46.78 ± 12.56	50.22 ± 10.45	0.08
BMI (Kg/m ²)	26.66 ± 2.88	30.90 ± 3.90	$< 0.001^*$
HbA1c%	7.2 ± 0.4	9.1 ± 2.3	$< 0.001^*$
Total cholesterol(mg/dl)	200.1 ± 10.1	235.24 ± 41.1	$< 0.001^*$
LDL (mg/dl)	110.5 ± 25.3	160.9 ± 40.1	0.535
Tg (mg/dl)	145.5 ± 43.9	230.3 ± 63.3	$< 0.001^*$
HDL (mg/dl)	42.4 ± 6.4	44.4 ± 8.2	0.221
GOT (IU/L)	19.3 ± 5.1	22.3 ± 7.1	0.024
GPT (IU/L)	19.8 ± 3.8	25.2 ± 9.9	$< 0.001^*$

*significant according to unpaired t –test

Group (I) N=39, Group (II) N = 61

Table (3) shows the correlation between plasma HbA1c and other parameters. There was a significant positive correlation(r) between plasma HbA1c with Tg ($r = 0.164$, $P < 0.02$) and GPT($r = 0.160$, $P < 0.02$) .

No significant correlation(r) was observed between plasma HbA1c and the remaining categories.

Table (3): Correlation(r) between plasma HbA1c and other parameters

Parameters	r	P - value
Age(years)	-0.066	0.346
BMI(kg/m ²)	0.035	0.614
TC(mg/dl)	0.132	0.06
HDL(mg/dl)	-0.084	0.186
Tg(mg/dl)	0.164	0.02*
FPG(mmol/l)	0.092	0.191
GOT (IU/L)	0.025	0.512
GPT(IU/L)	0.160	0.02*

Comparison between male and female in T2DM. (table 4).

There were significant differences between males and females regarding BMI it was higher in female group($P < 0.002$)

The level of HbA1c TC, HDL for females were higher than male and they were statistically significant ($P < 0.009$, $P < 0.001$, $P < 0.003$ respectively).

Male group showed a higher Tg and GPT than female group and they were statically significant ($P < 0.001$).

Table (4) Comparison of BMI and measured biochemical parameters between male and female in patients with T2DM.

parameter	Female group Mean \pm SD	Male group Mean \pm SD	P - value
Age(years)	48.78 \pm 16.22	52.46 \pm 12.54	<0.001*
BMI(kg/m ²)	29.88 \pm 5.22	28.68 \pm 6.42	<0.002*
HbA1c%	8.96 \pm 2.11	8.20 \pm 2.35	<0.009*
Total cholesterol (mg/dl)	240.50 \pm 31.85	220.55 \pm 41.8	<0.001*
HDL (mg/dl)	46.55 \pm 11.02	43.43 \pm 10.56	<0.003*
LDL (mg/dl)	158.46 \pm 42.31	140.82 \pm 41.40	<0.001*
Tg (mg/dl)	180.26 \pm 56.14	210.67 \pm 83.53	<0.001*
FPG (mmol/l)	7.55 \pm 2.12	8.83 \pm 2.87	0.07
GOT (IU/L)	19.3 \pm 5.1	20.4 \pm 9.0	0.08
GPT(IU/L)	19.3 \pm 3.8	23.6 \pm 11.4	<0.001*

*significant according to unpaired t –test

Male N=68, female N=32

nase is still not well known but accumulation of fat in the liver leading to NAFLD or the second possible hypothesis is the predisposition of the liver to the inflammation which change the hepatic function and trigger a change in hepatic biomarkers¹.

Because of the high relation of NAFLD with T2DM and obesity, the latest models can predict the enhancement of NAFLD and nonalcoholic steatohepatitis, causing a tremendous clinical and economic burden and poor patient outcomes¹⁰.

Dyslipidemia is known as a risk factor for NAFLD. In this study, patients with NAFLD group had an elevated total cholesterol, TG as compared to those with non-fatty liver group. Similar results indicated by the study of Mansour-Ghaneaie R et al., so it's essential to do ultrasound to patients when lipid profile changes are observed, to avoid future complication by early diagnosis²².

NAFLD is characterized by excess lipid buildup in the liver, TG is well known as the most important lipid that accumulates in the liver, recent researches has proven that free cholesterol, polyunsaturated fatty acid (PUFA), and phospholipid levels are modified in human NAFLD²³.

In our study, we evaluated the differences between male and female in HbA1c and lipid profile, female diabetics were found to have higher HbA1c, total cholesterol, HDL levels than male, also male group showed a higher Tg and GPT than female group.

These results are in consonance with a previous study found that females had higher total cholesterol and (HDL), lower (Tg) and a correspondingly lower [TC/HDL] ratio than males²⁴.

High (Tg) levels and low (HDL) in men are frequent lipid abnormalities in the clinical situation of primary and secondary preventions. Male and female differences in the lipid profile are obvious in patients presented with dyslipidemia and might be of likely importance for determination, prevention and therapy for atherosclerosis²⁴.

Elevated lipid profile levels were evident between female with diabetes while the prevalence of diabetes was found to be elevated in middle age. The percentage of diabetics with high levels of FPG, urea, creatinine, TC, TG and LDL after 10 years of therapy were lower if compared with the percentage after 6 years of therapy^{25,26}.

Discussion



Our study has been undertaken to show the effect of elevated HbA1c on liver dysfunctions in diabetics as elevated GOT and GPT in T2DM patients.

The finding in the present study of high level GOT and GPT in NAFLD with T2DM patients, this is in agreement with past published research also shows the correlation of hepatic transaminases with T2DM in Ethiopian patients and found significant correlation with elevated levels in T2DM patients¹⁵.

Elevated GOT, GPT values and NAFLD are significantly correlated with prediabetes and diabetes and are used to indicate the disturbance in glucose metabolism¹⁶.

The general prevalence of NAFLD among T2DM patients is highly significant. high GPT, triglyceride and HbA1c levels may be correlated with the beginning of NAFLD in diabetic patients¹¹.

It is well established that the incidence of elevated ALT, AST, and GOT levels amongst Mexican patients could be caused by metabolic diseases, such as obesity, diabetes mellitus and resistance to insulin^{17,18}. A higher prevalence of abnormal liver function test has been linked with patients with T2DM than patients without T2DM¹⁹.

The pathologic process of NAFLD extending from build-up of fat in the liver to inflammatory steatohepatitis, cirrhotic liver and fibrosis²⁰.

Elevated triglyceride (Tg) levels were also correlated with NAFLD in a study by Leite et al.²¹.

In our study BMI was higher in group(II) than group(I) diabetic patients, the explanation for that in DM, the exact pathogenesis to induce disturbance in hepatic transami-

The present study has revealed that elevated HbA1c and triglyceride in T2DM with high GOT and GPT is significantly associated with NAFLD disease. Early detection of NAFLD in T2DM is important to prevent progression of the disease and minimize morbidity and mortality. Altered lipid profile levels is a feature of diabetes mellitus.

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