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Study Early Detection of Serum Transthyretin in Nonalcoholic Fatty Liver Disease and Its Complex Relation with Type 2 Diabetes Mellitus by Sonographic Features

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0Abstract

Background: Study role important in understand and treat the pathology of obesity and NAFLD to prevent metabolic syndrome. Treatments for obesity and NAFLD commonly include lifestyle management through weight loss, dietary restriction, exercise, etc. Objective: This study was aim to investigate the role of TTR, in the non-alcoholic fatty liver disease and nonalcoholic fatty liver disease (NAFLD) among the patients with type 2 diabetes mellitus (T2DM). The study will be, done at the National Diabetes Center of Mustansiriyah University. One hundred thirty-five subjects with age ranged from (35-65) years were in the serum TTR; concentrations were measured by radioimmunoassay in 150 patients. Diabetic patients were chosen from almost diagnosed patients on follow up visits to the center. The NAFLD diabetic patients were chosen according to clinical features of liver diseases had liver ultrasonic appearance and abnormal liver function tests. Patients were distributed; three study groups as following: Group one: 50 patients, T2DM with NAFLD Group two: 50 patients, T2DM without NAFLD; Group three 50 healthy controls. Results: There was a significant increase it was discovered that there is a positive relationship between transthyretin and that this relationship is statistically significant FSG HbA1c, LDL VLDL, were found to be positively correlated with. Transthyretin were found to be positively correlated at a moderate effect size and echogenicity.it is decrease HDL level found negative correlated with HDL. Conclusions: This study found that diabetic patients with NAFLD had a significant increase in serum levels of TG, LDL, and VLDL as compared to T2D, and lower levels of HDL. Treatment options for NAFLD patients include lifestyle intervention and weight loss and anti-diabetic drugs that target IR or bring benefits of weight loss have yielded positive results. More clinical data is needed to make a firm recommendation about the optimal treatment.

Keywords

Transthyretin (TTR), Nonalcoholic Fatty Liver Disease (NAFLD); Type 2 Diabetes Mellitus (T2DM); Metaboliciated Fatty Liver Disease (MAFLD); sonographer features.

Diabetes mellitus (DM) affects more than 463 million people globally, and this number is supposed to increase to 700 mil- lion by 2045 (1).]. Diabetes is one of the worst chronic diseases that is caused either by the lack of producing enough insulin inthe pancreas or by the lack of insulin in the cells. Someone is diagnosed to have diabetes when the level of plasma glucose density is more than 6.1 mmol/L(2). Non-alcoholic fatty liver disease (NAFLD)is one of chronic liver and defines by fat accumulation ≥ 5% in liver which can progresses to non-alcoholic steatohepatitis (NASH). NAFLD related to obesity as well as non-obese individuals (3). Transthyretin

(TTR), also known as prealbumin, is a protein primarily produced by the liver and serves as a carrier for thyroid hormones (T3 and T4) and retinol (vitamin A). It is involved in the transport of these molecules throughout the body and plays a role in maintaining their homeostasis (4).TTR is mainly synthesized in the liver, but it is also produced in other tissues such as the choroid plexus in the brain and the retinal pigment epithelium in the eye (5). It is a protein primarily synthesized by the liver and is involved in the transport of thyroid hormones and retinol (vitamin A) (6). In addition to its role in hormone and vitamin transport, TTR has been implicated in various other biological functions. It is believed to have antioxidant properties and may protect against oxidative stress. TTR also interacts with proteins involved in cellular signaling pathways, neuroprotection, and tissue repair (7).Target to mediate significant immune cells infiltration and inflammation contributing to systemic inflammation and IR in obese humans Therefore, it is important to understand and treat the pathology of obesity and NAFLD to prevent metabolic syndrome. Globosity commonly includes lifestyle management through weight loss, dietary restriction, exercise, etc. (8). Patients with NAFLD and T2DM develop a specific, atherogenic lipid profile defined by low levels of HDL-cholesterol as well as elevated concentrations of very low-density lipoproteins, triglyceride, and Apo lipoprotein B100 (apoB100) (9) A compensatory mechanism for reducing liver fat content is represented by the overproduction of VLDL particles which serve as transporters of TG to the peripheral tissues (10). This process stimulates the activity of cholesterol ester transfer protein (CETP). The main role of this enzyme is to exchange the TG/cholesterol esters between VLDL, HDL and LDL-cholesterol. Finally, this mechanism results in abnormal HDL-cholesterol metabolism, causing low HDL levels as well as alterations in lipoprotein profile, with an excess of small and dense LDL-cholesterol particles (11). Due to the effect of IR on hepatic and adipose tissue, pharmacological therapies that improve IS are an option for patients who associate NAFLD and T2DM. In addition, weight loss induced by some diabetes drugs is expected to induce improvements of NAFLD in T2DM (12).Generally, the first pharmacological line therapy for patients with T2DM is represented by metformin (13).

Patients And Methods

The study will be done at the National Diabetes Center of Mustansiriyah University and Al-Yarmook Teaching Hospital during the period from January 2022 until the end of May 2022. One hundred fifty five subjects with age ranged from (35-65) years were in the serum RBP4, TTR, and Clustrin concentrations were measured by radioimmunoassay in 150 patients. Diabetic patients were chosen from almost diagnosed patients on follow up visits to the center. The NAFLD diabetic patients were chosen according to clinical features of liver diseases that had liver ultrasonic appearance and abnormal liver function tests. Patients were distributed; three study groups as following: Group one; 50 patients, T2DM with NAFLD Group two; 50 patients, T2DM without NAFLD; Group three 50; healthy controls.

Biochemical Assessment

Blood samples were collected after 12 hours of fast. Fasting blood glucose (FBG), glycated hemoglobin (HbA1C), Echogenicity Liver surface Feature by liver imaging device, and lipid profile including total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C) were estimated by enzymatic colorimetric methods using auto-analyzer (Spectrophotometer, Kenza 240 TX France).

Statistical Analysis

Statistical analysis of data were done using SPSS , USA. Statistical tests used ANOVA to analysis of variance. Data were expressed as means (±SD); statistical significance was approved at $P < 0.05$. Transthyretin, and all the other variables in the study were subjected to a Pearson correlation analysis. Coefficients between.10 and.29 were considered to indicate a weak relationship, coefficients between.30 and.49 were considered to indicate a moderate effect size, and coefficients above.50 were considered to indicate a strong effect size using Cohen's standard.

Results

All of the groups had an equal number of male and female members (n = 25, or 50%) χ^2 0.00, P = 0.001. Echogenicity and liver of size Table 1. In this study showed Echogenicity was seen in equal numbers (n = 50, 100% in each normal and T2D groups). While the (DM+NAFLD) group showed the highest prevalence of mild Echogenicity. Liver surface feature Clinical and anthropometric data for T2DM and control group demonstrates in table1.In this study have shown that patients with type 2 diabetes are more likely to have increased liver echogenicity compared to those without diabetes. This increased echogenicity is often due to the accumulation of fat in the liver, which is a hallmark

feature of NAFLD (14). In this study have showed the relationship between liver surface features and NAFLD severity ,The researchers used ultrasound imaging to assess liver surface smoothness and found that patients with more severe NAFLD had more irregular liver surfaces compared to those with less severe NAFLD, A may be not specific studies on liver surface features in patients with both NAFLD and type 2 DM, ultrasound imaging can be used to assess the liver surface in these patient provide useful information on disease severity and progression.(15). Fasting serum glocose (FSG) According to another study found that FSG was significantly higher in patients with both type 2 diabetes and NAFLD compared to those with type 2 diabetes alone. The study also found that FSG was positively associated with the presence and severity of NAFLD (16). Study reported HbA1c that the use medication that helps improve insulin sensitivity, also was significantly higher in patients T2D associated with significant reductions in HbA1c levels in patients with NAFLD and T2D compar to control. (17).Study showed both groups patients show a significant increase ($p<0.001$) compared to control group, Also In the current study, high levels of HbA1c are due to poor glycemic control in type 2 diabetic group, Also in patient groups themselves there is significant decrease ($p<0.001$) in HbA1c level in diabetics on metformin immunotherapy compared to only DM (without therapy) (18).According study explain drug is ezetimibe, which is a medication that helps reduce cholesterol absorption in the intestine, evaluated the effect that ezetimibe on liver fat content and cholesterol levels in patients with NAFLD and T2D, reported study that ezetimibe treatment for 24 weeks resulted in significant reductions in liver fat content and cholesterol levels(19). Patients with NAFLD and T2D are often found to have elevated triglyceride (TG) levels. Elevated TG levels can contribute to the development and progression of NAFLD. Lifestyle changes such as diet and exercise can help reduce TG levels in these patients, According to study published that patients with NAFLD and type 2 diabetes had significantly higher TG levels compared to patients with type 2 diabetes alone(20). LDL cholesterol is often referred to as "bad" cholesterol because it can contribute to the buildup of plaque in the arteries, which increases the risk of heart disease. In patients with NAFLD and T2DM, LDL cholesterol levels can be affected by several factors. According study reported that elevated LDL cholesterol levels were significantly associated with the severity of NAFLD in patients with T2DM (21). The results of the ANOVA were significant, $p < .001$, indicating there were significant differences in VLDL among the studied groups, in VLDL. Multiple pairwise comparison revealed that the mean of VLDL for Control was significantly smaller than for (DM+NAFLD) $p < .001$, and that the mean of VLDL for DM ($M = 18.38 \pm 7.87$) was significantly smaller than for (DM+NAFLD) $< .001$.as showed in figure(3),VLDL is a type of lipoprotein that carries triglycerides in the blood. In patients with NAFLD and type 2 diabetes, VLDL cholesterol levels can be affected by several factors, Agreement to study published in 2014 reported that elevated VLDL cholesterol levels were significantly associated with NAFLD patients with T2DM. (22). HDL cholesterol is known as the good" cholesterol because it helps remove other forms of cholesterol from the bloodstream and transport it back to the liver for processing and elimination. In patients with NAFLD and T2D, HDL levels can be affected by several factors, A ccording to study published in 2018 reported that lower HDL cholesterol levels were significantly associated with the severity of NAFLD in patients with T2D. (23). showed in study 2021 demonstrated a highly significant increase in the means of HDL in control group compared to diabetic group. (24). In this study, there was an elevation in FSG, HbA1c, and in diabetic patients as compared to the controls. This study exposed a significant elevation in FBG and HbA1c in diabetic patients comparing with control group. These results are probable due to the fact that the main distinguishing feature of DM is hyperglycemia (25).Globally, NAFLD affects almost a quarter of the population, though its prevalence may vary with the used diagnostic tool. Despite its high prevalence, frequent association with T2DM, and high mortality rates (mostly due to CV causes), NAFLD remains underdiagnosed and under evaluated, mainly due to the lack of specific public health strategies (26). The prevalence of NAFLD in T2DM individuals is higher than in the general population NAFLD doubles the risk of incident T2DM, varying with the fat and fibrosis liver scores, and accelerates the development of CVD. On the other hand, the presence of T2DM increases the risk of fatty liver progression to NASH, cirrhosis, or hepatocellular carcinoma (27). In this study, lipids appeared among diabetic patients with NAFLD whom show a significant increase in serum levels of LDL, and VLDL as compare to T2D, lower level of HDL in diabetes with NAFLD as compared to diabetic patients which is similar to previous studies (28). The cholesterol noticed in diabetic patients group increase in diabetes type 2 as compare to T2D with NAFLD groups.(23). The results in this study showed that role that transthyretin levels were lower in patients with T2D and NAFLD compared to those with T2D alone, suggesting that transthyretin may be a potential biomarker specific for NAFLD in T2D patients, may be serve as a potential biomarker specific for NAFLD in T2D patients (29). Also, TTR in agreement with other studies which found that TTR levels showed higher significant values in diabetic group as compared to control groups (30).

Table (1) Frequency and percentage Sociodemographic and liver Sonographic features in the studied groups.

	Variable	Control	DM	(DM+NAFLD)	X^2	P
Echogenicity	Normal	50 (100.0%)	50 (100.0%)	--	150	< 0.001
	Mild	--	--	42 (84.0%)		
	Moderate	--	--	7 (14.0%)		
	Severe	--	--	1 (2.0%)		
	Total	50 (100.0%)	50 (100.0%)	50 (100.0%)		
Liver surface Feature	Smooth	50 (100.0%)	50 (100.0%)	42 (84.0%)	16.90	< 0.001
	Irregular			8 (16.0%)		
	Total	50 (100.0%)	50 (100.0%)	50 (100.0%)		

Table (2) Physiological and biochemical means comparison between the studied groups.

Variable	Groups	Mean ± SD	F-test	P value
FSG	Control	84.30± 5.06	128.732	< 0.001
	DM	223.90± 72.06		
	(DM+NAFLD)	245.24± 60.70		
Hb1Ac	Control	4.91± 0.59	467.092	< 0.001
	DM	9.15± 0.88		
	(DM+NAFLD)	9.64± 1.03		
TTR	Control	1.702 ± 0.277	634.725	< 0.001
	DM	2.750 ± 0.261		
	(DM+NAFLD)	3.821 ± 0.347		

Table (3) Characteristic and serum Transthiretin for the studied groups.

Cholesterol	Control	138.46± 16.02	49.658	< .001
	DM	195.10± 41.57		
	(DM+NAFLD)	183.00± 26.51		
TG	Control	84.19± 14.94	68.218	< .001
	DM	196.26± 65.40		
	(DM+NAFLD)	200.82± 71.39		
HDL	Control	47.80± 4.49	42.940	< .001
	DM	38.05± 6.67		
	(DM+NAFLD)	39.86± 5.42		
LDL	Control	83.42± 7.32	19.709	< .001
	DM	122.16± 40.94		
	(DM+NAFLD)	119.98± 43.31		
VLDL	Control	17.07± 4.19	78.521	< .001
	DM	18.38± 7.87		
	(DM+NAFLD)	38.36± 13.87		

Conclusions

In this study, there was an elevation in FSG, HbA1c, and in diabetic patients as compared to the controls.. These. Globally, NAFLD affects almost a quarter of the population, though its prevalence may vary with the used diagnostic tool. Despite its high prevalence, frequent association with T2DM, and high mortality rates (mostly due to CV causes), NAFLD remains underdiagnosed and under evaluated, mainly due to the lack of specific public health strategies. In this study, lipids appeared among diabetic patients with NAFLD whom show a significant increase in serum levels of TG, LDL, and VLDL as compare to T2D, lower level of HDL in diabetes with NAFLD as compared to diabetic patients which is similar to previous studies. The cholesterol noticed in diabetic patients group increase in diabetes type 2 as compare to T2D with NAFLD groups.Also, The results in this study showed that role that transthyretin levels were lower in patients with T2D and NAFLD compared to those with T2D alone, suggesting that transthyretin may be a potential biomarker specific for NAFLD in T2D patients TTR in agreement with other studies which found that TTR levels showed higher significant values in diabetic group as compared to control groups.

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