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Risk factors for macro vascular disease in type 2 diabetes mellitus patients with non-alcoholic fatty liver disease

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Abstract: This study investigates the connection between abnormal liver enzymes and macro vascular disease in type 2 diabetes mellitus (T2DM) patients with non-alcoholic fatty liver disease (NAFLD). Clinical data from 276 T2DM patients with NAFLD were retrospectively examined and divided into two groups based on the presence or absence of macro vascular disease. Various biochemical markers were tested, including fasting C-peptide, total bilirubin (TBil), total protein (TP), albumin (Alb), C-reactive protein (CRP) and the insulin resistance index (HOMA-IR). The study found no significant differences in demographic variables between the two groups. However, patients with macro vascular disease had significantly higher levels of fasting C-peptide, CRP, HOMA-IR, TBil, TP, Alb and certain blood lipid markers. The study concludes that in T2DM patients with NAFLD, increased blood lipids, liver function and inflammatory factors are risk factors for macro vascular disease, suggesting the importance of clinical management to lower macro vascular disease prevalence.

Keywords: Type 2 diabetes, non-alcoholic fatty liver, abnormal liver enzymes, macro vascular disease.

INTRODUCTION

Non-Alcoholic Fatty Liver Disease (NAFLD) is a medical condition typified by the excessive hepatic lipid accumulation, not attributable to alcohol consumption or other explicit hepatotoxic factors. This condition manifests as steatosis in hepatocytes, underpinned by the interplay of insulin resistance and genetic predisposition within the individual's metabolic profile (Cheng *et al*., 2018; Golabi *et al*., 2018). With the rising of obesity and related metabolic syndrome, NAFLD has become the leading cause of chronic liver disease in developed regions and has thus arouse public concern (Powell *et al*., 2021). Type 2 diabetes mellitus (T2DM) is a prevalent endocrine condition caused by insulin resistance or inadequate insulin production (Nauck *et al*., 2021). In the paradigm of Traditional Chinese Medicine (TCM), diabetes mellitus aligns with the classification of "Xiaoke". Within this designation, diabetes mellitus manifests in four distinctive patterns, namely Qi and Yin deficiency, Yin deficiency leading to excessive internal heat, internal resistance coupled with blood stasis, and a co-deficiency of Yin and Yang. This taxonomical approach facilitates the understanding and treatment of diabetes mellitus within the holistic framework of TCM (Fu *et al*., 2021). In this context, the most prevalent manifestations align with Qi and Yin deficiency, as per traditional Chinese medicine principles. Predominant clinical presentations encompass spontaneous nocturnal perspiration, xerostomia and dyspnea. Therapeutic interventions are primarily predicated upon the concept of syndrome differentiation, underscoring the necessity of individualized treatment strategies.

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T2DM patients with NAFLD are vulnerable to liver cirrhosis and hepatitis and cardiovascular disease (Targher *et al*., 2021). There accordingly exists an urgency to early identify high-risk NAFLD patients among T2DM patients (Ferguson and Finck, 2021; Garg *et al*., 2020; Stefan and Cusi, 2022). NAFLD often shows few specific clinical symptoms, and elevated liver enzymes is a common biochemical abnormality in patients with NAFLD. Liver enzymes alanine transaminase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT)] are important markers responding to liver cell damage in patients. NAFLD disease is also a major cause of liver cell damage. Some scholars believe that T2DM complicated with NAFLD is associated with higher incidence of macro vascular disease, and inflammation (Caussy *et al*., 2021; Tilg *et al*., 2021). The macro vascular disease might damage the blood flow to the brain due to its sudden onset, rapid progression, and high fatality rate. As a result, dizziness, tinnitus, vision impairment, disorientation and even paralysis may occur. Peripheral vascular disease mainly manifests as limb swelling and intermittent claudication. Most patients can recover through drug therapy (Ahmad *et al*., 2022; Cole and Florez, 2020; Viigimaa *et al*., 2020). Liver and adipose tissue are the most important sites of insulin action. NAFLD leads to increased insulin resistance in liver and adipose tissue and abnormal metabolites cause damage to islet β-cell function. The fasting C-peptide, total bilirubin (TBil), total protein (TP), albumin (Alb), C-reactive protein (CRP) are commonly used index for examining diabetes and NAFLD, so these parameters are observed to detect the disease (Vural *et al*., 2021). This study elucidates the relationship between abnormal liver enzymes and macro vascular disease in patients with T2DM and NAFLD. With the global rise in T2DM and NAFLD,

understanding this relationship is imperative for improved disease management. The findings could enhance risk prediction, guide therapeutic interventions, and mitigate macrovascular complications. Ultimately, by identifying these risk factors, we could refine preventative strategies, minimize healthcare burden, and bolster patient outcomes. This research is a substantial contribution to the clinical handling of T2DM and NAFLD.

In light of this, we retrospectively analyzed 276 T2DM patients with NAFLD admitted to the Department of Endocrinology, Cangzhou Central Hospital, from August 2010 to August 2020 to further investigate the relationship between abnormal liver enzymes and macrovascular disease in T2DM patients with NAFLD.

METHODS AND MATERIALS

Study design and participants

A retrospective analysis was conducted on the clinical data of 276 T2DM patients with NAFLD who were admitted to the Endocrinology Department in Cangzhou Central Hospital from August 2010 to August 2020. The patients were divided into group A (hepatic enzyme abnormalities complicated with macro vascular disease, n=154) and group B (abnormal liver enzymes complicated with peripheral vascular disease, n=122) based on the presence of macro vascular disease. The baseline data including gender, medical history and demographic characteristics were collected, and their blood pressure was measured after resting for 15 minutes.

Prior to enrollment, the informed consent of the patients was obtained, and this study protocol was reviewed and granted by the hospital ethics committee (CCU9293). All procedures were conducted in line with the Declaration of Helsinki.

Inclusion criteria

(1) Patients aged 40 to 75 years old. (2) Patients who met the diagnostic criteria for type 2 diabetes mellitus (T2DM). (3) Patients who met the diagnostic criteria for NAFLD, i.e, no history of drinking or alcohol consumption in male <140 g/week, female <70 g/week; no exogenous viral hepatitis, viral liver disease, total parenteral nutrition, hepatolenticular degeneration, autoimmune liver disease or other specific diseases that may cause fatty liver; liver ultrasound showed the diffuse fatty liver; the near-field echo of the liver was more diffuse and stronger than that of the kidney; the structure of the intrahepatic duct was unclear; the far-field echo of the liver gradually weakened. (4) Patients who met the criteria of diabetic macro vascular disease. Macro vascular refers to the large blood vessels in the body. Macro vascular disease involves conditions that affect these large vessels, often leading to cardiovascular diseases. The primary types of macro vascular disease are coronary artery disease (affecting the heart), cerebro vascular disease (affecting the brain), and peripheral artery disease (affecting the limbs). Coronary heart disease: with a history of angina or myocardial infarction; electrocardiogram showed ischemic changes, infarct changes or myocardial enzymology changes; coronary angiography showed that at least one of the left main artery, left anterior descending artery, right circumflex artery, and right coronary artery had a ≥50% vascular inner diameter stenosis; vasculopathy: explicit clinical history of cerebral infarction or cerebral hemorrhage and other cerebrovascular diseases, combined with head TCD, CT, MRI and other examinations; neck lower extremity vascular disease: formation or occlusion of atherosclerotic plaque confirmed by color Doppler ultrasound. (5) Abnormal liver enzymes: ALT>40 U/L, and (or) AST>40 U/L, and (or) GGT>50 U/L.

Exclusion criteria

(1) History of acute injury, anemia, infection, surgery, mental illness, malignant tumor; (2) History of heavy drinking (>280 g/week for men, >140 g/week for women); (3) Abnormal hematopoietic function; (4) Pregnant women or lactating women; (5) Received clinical treatment within the past 1 month. (6) Patients with type 1 and other special types of diabetes; those with acute complications of diabetes; those with other endocrine or autoimmune diseases; thyroid gland dysfunction; severe liver and kidney insufficiency; mental and nervous system diseases, etc.

Testing indicators

3ml fasting venous blood was collected from the two groups of patients. After centrifugation (Thermo Scientific Medifuge, Thermo Fisher Scientific, Waltham, USA), the upper serum was obtained to detect the levels of TBil (BC5180, Solarbio, Beijing, China), TP (T1949, Sigma Aldrich, St. Louis, Missouri, USA), and Alb (MAK125, Sigma Aldrich, St. Louis, Missouri, USA), and the fasting C-peptide (20-1014-10, JINDE Biotech, Guangzhou, China) was determined by radioimmunoassay. Triglycerides (TG), high density lipoprotein cholesterol (HDL-C) and low density cholesterol (LDL-c) were tested with lipid analyzer (manufacturer: Shanghai Hanfei Medical Devices Co., Ltd.); levels of CRP were measured in a central laboratory by using a CRP Elisa kit (PC190, Beyotime, Jiangsu, China); The fasting blood glucose (FPG) (20-1011-10, JINDE Biotech, Guangzhou, China) and fasting insulin (FINS) (20-1015, JINDE Biotech, Guangzhou, China) levels of the two groups of patients were tested and calculated using a formula that HOMA-IR =FPG×FINS/22.5.

Macrovascular disease in type 2 diabetes refers to complications that affect the large blood vessels in the body due to high blood glucose levels and other associated metabolic changes, including coronary artery disease, cerebrovascular disease and peripheral arterial disease.

STATISTICAL ANALYSIS

All data analysis were performed by SPSS 21.0 software, and GraphPad Prism 6 (GraphPad Software, San Diego, USA) was used for the image rendering of the data. The count data was examined by X^2 and represented by [n (%)]. The measurement data was examined by t and represented by (x ± s) that was performed firstly by F test for homogeneity of variance, independent samples *t* test for homogeneity of variance, and independent samples t' test for heterogeneity of variance. All tests were 2-sided, with a significance level of $P<0.05$.

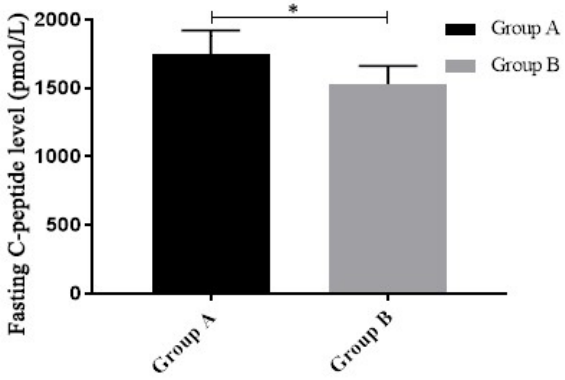
RESULTS

Comparison of clinical data between the two groups

The baseline data such as gender ratio, age, BMI, smoking history, drinking history, marital status, education level, systolic blood pressure and diastolic blood pressure between the two groups of patients were well-balanced ($P>0.05$) (table 1).

Comparison of fasting C-peptide levels between the two groups

Patients in group A had considerably higher fasting C-peptide levels than their counterparts in group B ($P<0.05$) (fig. 1).



Note: The horizontal axis represents group A and group B respectively and the vertical axis represents fasting C peptide level value, pmol/L; The fasting C-peptide level of patients in group A was (1623.36±246.55) pmol/L; the fasting C-peptide level of patients in group B was (1437.62±184.23) pmol/L;
*Indicates that there is a significant difference in the fasting C-peptide levels between the two groups of patients (t=6.928, P≤0.001).

Fig. 1: Comparison of fasting C-peptide levels between the two groups of patients (x ± s)

Comparison of CRP levels between the two groups of patients

Patients in group A had considerably higher CRP levels than those in group B ($P<0.05$) (fig. 2).

Comparison of TBil, TP and Alb levels between the two groups

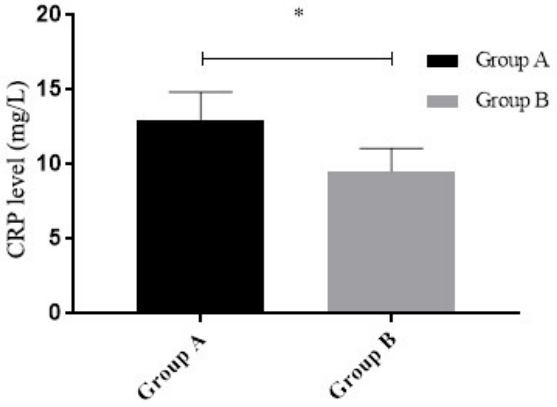
Group A had considerably greater amounts of TBil, TP and Alb than group B ($P<0.05$) (table 2).

Comparison of HOMA-IR levels between the two groups of patients

Patients in group A had significantly higher HOMA-IR levels than those in group B ($P<0.05$) (fig. 3).

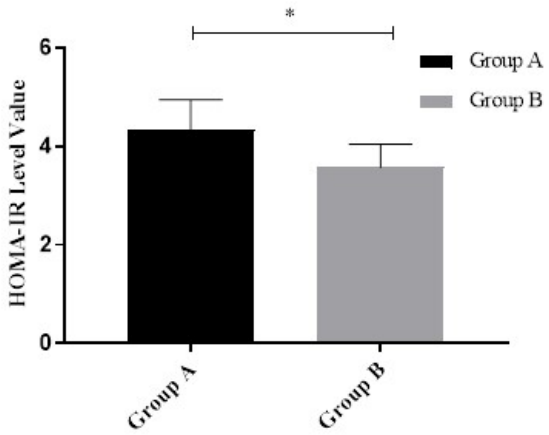
Comparison of TG, HDL-C and LDL-c levels in the two groups of patients

Significantly higher TG, HDL-C and LDL-C were observed in group A than group B ($P<0.05$) (table 3).



Note: The horizontal axis represents group A and group B, and the vertical axis represents CRP level, mg/L; The CRP level of patients in group A was (11.65±2.62) mg/L; the level of CRP in group B patients was (8.42±2.16) mg/L;
*Indicates that there is a significant difference in CRP levels between the two groups of patients (t=10.978, P≤0.001).

Fig. 2: Comparison of CRP levels between the two groups of patients (x ± s)



Note: The horizontal axis represents Group A and Group B and the vertical axis represents the HOMA-IR level; The HOMA-IR level of patients in group A was 3.92±0.85; the HOMA-IR level of patients in group B was 3.24±0.67;
*Indicates that there is a significant difference in HOMA-IR levels between the two groups (t=7.233, P≤0.001).

Fig. 3: Comparison of HOMA-IR levels between the two groups of patients (x ± s)

DISCUSSION

Recent years witness a rising trend and diabetes ranks third among chronic disease threatening people's life and health, second only to tumor and cardiovascular

disease (Tinajero and Malik, 2021; Yun and Ko, 2021). Diabetes constitutes a high morbidity and mortality rate, and is mainly manifested by elevated blood sugar. It would result in cardiovascular and cerebrovascular diseases, retinopathy, diabetic nephropathy and organ failure, compromising the patient's quality of life (Artasensi *et al*., 2020; Bellary *et al*., 2021).

Traditional Chinese medicine believes that exogenous toxins, improper diet, internal emotional injury are contributors the occurrence of diabetes (Liu *et al*., 2022). "A syndrome of xiaoke originates from the middle-jiao". From the point of view of the viscera, it is most closely related to the spleen and stomach of the middle-jiao. The spleen and stomach mediate the qi activities, transforming qi and blood (Liu *et al*., 2022). In terms of function, the pancreas of modern medicine belongs to the spleen and stomach of traditional Chinese medicine, which is not only involved in food digestion, but also in energy metabolism. Dysfunction of the spleen and stomach is the key to the pathogenesis of T2DM (Atkinson *et al*., 2020, Chan and Harper, 2006).

The pathogenesis of T2DM combined with NAFLD is complex, and inflammation and abnormal glucose and lipid metabolism centered on insulin resistance are involved. T2DM can exacerbate NAFLD by promoting the progression of hepatic steatosis or fibrosis, and NAFLD can lead to diabetes complications in T2DM patients. The role of adipokines in the pathogenesis of insulin resistance and metabolic syndrome is immensely prominent (Francisco *et al*., 2022). NAFLD is a chronic disease characterized by hepatic fat accumulation (not caused by excessive alcohol consumption or other factors), and is closely associated with T2DM [16-18]. Dai *et al*. (2017) conducted a meta-analysis of 24 clinical studies involving 35,599 patients with type 2 diabetes, of whom 20,264 were diagnosed with NAFLD, and found that the combined prevalence of type 2 diabetes with NAFLD was 59.67%. Subgroup analyses indicated that the prevalence of NAFLD in T2DM patients differed by gender, obesity, hypertension, dyslipidemia, coronary heart disease, and chronic kidney disease. It has been found through clinical studies that NAFLD may be related to cardiovascular disease (Chong *et al*., 2021; Javed *et al*., 2019, Peng *et al*., 2022; Targher *et al*., 2020). Ultrasound diagnosis showed that the incidence of atherosclerosis and carotid artery complications in both lower extremities in patients with T2DM and NAFLD was significantly higher than that in non-NAFLD patients. NAFLD leads to the occurrence and progression of macro vascular disease under the influence of risk factors such as lipid metabolism disorders, persistent hyperinsulinemia and inflammatory states (Bahreynian *et al*., 2018, Wu *et al*., 2018). NAFLD can cause an increase in ALT in T2DM patients' liver cells. ALT may be found in a variety of human body cells (mainly in liver cells). ALT is released in high quantities into the blood during the acute phase of different viral hepatitis and drug-toxic liver cell necrosis, and has thus become an important signal for the identification of viral hepatitis and toxic hepatitis (Liu *et al*., 2018). Wu *et al*. (2018) found in the study that disorder of glucose metabolism in patients with type 2 diabetes can increase liver enzyme levels and lipid deposition in hepatocytes, lipid deposition and cause hepatic gluconeogenesis, which further leads to hepatic insulin resistance and reduces insulin sensitivity. Excessive lipid deposition in hepatocytes manifests as NAFLD, which is closely related to the accumulation of visceral fat and obesity in patients and is an important cause of cardiovascular disease.

C-peptide is a secreted product of insulin β-cells. If it is not degraded by the kidney, it will be inactivated, so it has guiding significance for the diagnosis of diabetes and the identification of hypoglycemia. Studies have found that C-peptide is an instructive risk factor for lower extremity vascular lesions in diabetic patients, and there is C-peptide deposition in carotid artery lesions in T2DM patients (Guo *et al*., 2018). This study confirmed that the fasting C-peptide level of group A patients was significantly higher than that of group B. C-peptide is thought to be involved in the progression of vascular disease in T2DM patients with NAFLD (Wang *et al*., 2020). C-peptide has been linked to the promotion of inflammation, the proliferation and migration of smooth and endothelial cells, and the onset of macrovascular disease in diabetes patients. Furthermore, a rise in CRP levels in T2DM patients with NAFLD is a significant serum marker of macro vascular disease (Aryan *et al*., 2018).

CRP is a common human serum protein that rises dramatically when the body is sick or tissue is injured. In this study, the CRP level of patients in group A was substantially greater than that of patients in group B, which is attributable to abnormal glucose metabolism in T2DM patients with NAFLD. Lipoprotein can lead to the accumulation of CRP and other inflammatory cells in blood vessels, causing the occurrence and progression of macro vascular diseases. In addition, this may also be because the combination of NAFLD will enhance the body's insulin resistance, and lead to lipid metabolism disorders, subclinical inflammatory state, excess reactive oxygen species, abnormal fibrinolysis, hypoadiponectinemia and elevated CRP, etc, leading to the occurrence and progression of atherosclerosis in the body, and ultimately the occurrence of macrovascular disease. Cao *et al.* (2018) had a similar conclusion that "the CRP level of diabetes patients with macro vascular disease is (11.59±2.35) mg/L, which is significantly higher than that of diabetes patients with peripheral vascular disease (8.38±2.21) mg/L", indicating that CRP can reflect the vascular disease of diabetic patients and provide basis for clinical treatment.

CONCLUSION

In summary, higher blood lipids, liver function and inflammatory cell levels in T2DM patients with NAFLD are risk factors for macro vascular disease.

Table 1: Comparison of clinical data between the two groups

Category	Group A (*N*=154)	Group B (*N*=122)	X^2/t	*P*
Gender			0	0.996
Male	82 (53.25%)	65 (53.28%)		
Female	72 (46.75%)	57 (46.72%)		
Mean age (years)	51.24±6.72	51.28±6.75	0.049	0.961
BMI (kg/m^2)	21.58±1.32	21.55±1.36	0.185	0.853
Smoking history			2.040	0.153
No	119 (77.27%)	85 (69.67%)		
Yes	35 (22.73%)	37 (30.33%)		
Drinking history			0.900	0.343
No	108 (70.13%)	79 (64.75%)		
Yes	46 (29.87%)	43 (35.25%)		
Marital status			0.024	0.877
Unmarried	18 (11.69%)	15 (12.30%)		
Married	136 (88.31%)	107 (87.70%)		
Educational level			0.764	0.382
High school and below	97 (62.99%)	83 (68.03%)		
Above high school	57 (37.01%)	39 (31.97%)		
Systolic pressure (mmHg)	136.77±4.31	136.73±4.35	0.076	0.939
Diastolic pressure (mmHg)	85.37±5.21	85.34±5.23	0.047	0.962

Table 2: Comparison of TBil, TP and Alb levels between the two groups of patients (x ± s)

Groups	N	TBil (μmol/L)	TP (g/L)	Alb (g/L)
Group A	154	4.39±1.65	66.93±5.63	40.88±3.23
Group B	122	3.65±1.56	64.31±5.42	38.29±3.17
t		3.790	3.903	6.670
P		≤0.001	≤0.001	≤0.001

Table 3: Comparison of TG, HDL-C and LDL-C levels in the two groups of patients (x ± s, mmol/L)

Groups	*N*	TG	HDL-C	LDL-C
Group A	154	3.79±0.53	1.72±0.22	3.83±1.21
Group B	122	2.44±0.52	1.52±0.24	2.84±0.24
t		21.191	7.204	8.896
P		≤0.001	≤0.001	≤0.001

Accordingly, symptomatic therapy for T2DM patients with NAFLD is imperative in order to manage blood lipids, decrease inflammation, and enhance clinical effectiveness.

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