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Predictors of Non-Alcoholic Hepatic Steatosis Among Type 2 Diabetes Patients

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Abstract

Background: Because the number of people with other components of the metabolic syndrome, such as type 2 diabetes mellitus (T2DM), obesity, hypertension, and dyslipidemia, is rising annually, it is important to address the hepatic component of the syndrome, hepatic steatosis, as part of the spectrum of non-alcoholic fatty liver disease (NAFLD). This study aims to determine the predictors of non-alcoholic hepatic steatosis (HS) among type 2 diabetes mellitus patients.

Materials and methods: This study, which involved 138 persons with type 2 diabetes mellitus (T2DM), employed a simple random sampling technique. Clinical indicators, including weight and height, were measured. The biochemical parameters measured were Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), lipid profile, and the AST/ALT ratio. The data were analysed using IBM's Statistical Package for the Social Sciences, version 25.

Results: In T2DM patients with hepatic steatosis, a statistically significant increase was observed in total cholesterol (TC), low-density lipoprotein (LDL), triglycerides (TG), as well as ALT, and AST compared to T2DM subjects without evidence of Hepatic Steatosis (p=<0.001, <0.001, <0.001, <0.001 and 0.04, respectively). Predictors of Hepatic Steatosis among T2DM were Waist circumference (WC), TG, and LDL, with odds ratios of 14.28 (95% CI: 1.59-127.75), 5.46 (95% CI: 1.39-21.45), and 35.24 (95% CI: 1.82-681.43), respectively.

Conclusion: This study revealed that WC, TG, and LDL independently predict hepatic steatosis in individuals with T2DM.

Keywords: Type 2 diabetes mellitus, Non-alcoholic fatty liver, Predictors

Introduction

Over the past three decades, the number of persons with diabetes has increased. In every eleven adult individuals in the world, one person is affected with Type 2 diabetes (T2DM) (1).

Insulin resistance, relative insulin insufficiency, and hyperglycemia are the hallmarks of type 2 diabetes (2).

Diabetes mellitus is defined as either a two-hour plasma glucose value of 11.1 mmol/L (200 mg/dL) following an oral glucose tolerance test or higher, or a fasting blood glucose of 7 mmol/L or greater on two occasions, or a casual plasma glucose level >11.1 mmol/L (200 mg/dL) in a person with diabetes symptoms. These diagnostic criteria were developed by the World Health Organisation (WHO) and the

American Diabetes Association (ADA) in 1999. Fasting Plasma Glucose (FPG) <6.1 mmol/L was considered normal fasting glucose, while FPG ranging from 6.1 mmol/L to 6.9 mmol/L was considered impaired fasting glucose (3).

Non-alcoholic fatty liver disease (NAFLD) encompasses a variety of liver disorders, such as cirrhosis, non-alcoholic hepatic steatosis (HS), and non-alcoholic steatohepatitis (NASH). When hepatocyte lipid accumulation exceeds 5% of the total liver weight without significant alcohol consumption, NAFLD is the result (4). Worldwide, NAFLD prevalence ranges between 20% and 30% (5). The pathogenesis of non-alcoholic fatty liver disease (NAFLD) is complex. However, it was proposed that insulin resistance causes accumulation of fat in the liver, which may then cause apoptosis, ballooning of the liver cells, Mallory's hyaline deposition, hepatocyte necrosis, inflammation of the lobules, then obliteration of the small hepatic vein, fibrosis, and possibly even cirrhosis or hepatocellular carcinoma (HCC) (6). It was proposed that NAFLD was linked to the elements of the metabolic syndrome and is now referred to as the hepatic component of the syndrome. Obesity, diabetes, and elevated triglyceride levels are the most frequent causes of hepatic steatosis. Other causes include toxins, steroids, cytotoxic drugs, glucocorticoids, synthetic estrogen, amiodarone, tamoxifen, antiretroviral drugs, mushrooms, and methotrexate (7).

If left untreated, NAFLD can develop into primary liver cell cancer, liver fibrosis, and NASH. This is especially true when dealing with type 2 diabetes mellitus (8).

Non-alcoholic steatohepatitis is characterised by hepatocyte damage and inflammation, which is a progression of steatosis. Roughly about 25% of NAFLD patients go on to develop NASH. Of individuals who get NASH, 25% go on to get cirrhosis, and 1%–2% of them get HCC annually. The primary factor associated with all liver-related morbidity and death is the extent of liver fibrosis. Non-alcoholic fatty liver disease, however, does not always follow the disease's spectrum. Patients with non-alcoholic hepatic steatosis (HS) may progress to fibrosis without undergoing the NASH stage, or they may develop de novo HCC in the absence of cirrhosis or NASH histological characteristics. This can occur in about 10-70% of NAFLD-related HCCs (9).

Non-alcoholic fatty liver disease raises the risk of cardiovascular morbidity, including peripheral artery disease and coronary artery disease, in patients with hepatic steatosis and type 2 diabetes.

It was suggested that NAFLD represents a hepatic component of the metabolic syndrome (10). Liver biopsy is the gold standard for diagnosing NAFLD. However, it is too expensive and intrusive to be used widely in large patient populations.

The only treatment that can halt the progression of hepatic steatosis is lifestyle modification. Therefore, in order to improve the therapeutic options for NAFLD, a better understanding of the factors that predict hepatic steatosis and encourage the progression from simple steatosis to NASH, fibrosis, and liver cancer is desperately needed (9).

Some studies conducted in Southern Nigeria have revealed varying prevalences of NAFLD in T2DM, ranging from 9.5% to 68.8% (11-13). However, no such studies are available from Northern Nigeria, which is the site of the index study. Likewise, these studies focused mainly on the prevalence of NAFLD, not emphasising factors that predict NAFLD, which is the aim of the study.

Materials and Methods

Study Setting and Population

The study was conducted at Aminu Kano Teaching Hospital (AKTH), located in Kano State, Nigeria's North-Western region. The institution serves as a referral centre for patients in Kano state and neighbouring states. According to the 2006 national census figures, Kano has an estimated population of 9.4 million.

The study used patients with T2DM attending the endocrinology and general outpatient clinics of AKTH as the sampling frame.

Sampling Size and Sampling Procedure

The minimum sample size for this study to allow for a meaningful statistically significant analysis of results was obtained using Fisher's formula: n = Z2pq/d2 (14), where n = sample size, Z= Standard deviation at 95% confidence interval=1.96, p = Prevalence of NAFLD in T2DM 9.5% according to Onyekwere et al (13), q = 1-p and the absolute precision "d" is set at 5%. Therefore, the calculated sample size was 132; by adding non-respondents, the minimum sample size used in the study was 138 subjects.

A cross-sectional study was used to recruit 138 adult patients with type 2 diabetes (T2DM) attending endocrinology and general outpatient clinics between March 2021 and July 2021 by simple random sampling. During sampling, ballot papers were used to select subjects who were recruited for the study at each clinic.

Inclusion Criteria and Exclusion Criteria

Inclusion criteria include all adult subjects with T2DM who fulfilled ADA diagnostic criteria (3).

Patients excluded were men who consumed more than 30 grams of alcohol per day, or 20 grams of alcohol per day for women (15), subjects with a background history of liver disease such as hepatitis B and hepatitis C, pregnant women, patients on drugs that cause steatosis such as steroids, cytotoxic medications, synthetic estrogen, amiodarone, tamoxifen, antiretroviral agents, mushrooms, and patients with severe co-morbidities (such as cancer, chronic kidney disease, or congestive heart failure).

Study Tool

T2DM patients who fulfilled the study's inclusion requirements and visited the AKTH endocrinology and general outpatient clinics were enrolled. Socio-demographic data, including age, gender, and occupation, were collected using a structured proforma. To assess the imaging evidence of HS, a 3.5 MHz transducer liver ultrasonography scan was conducted for each patient (11). Clinical indices were assessed using an analogue clinical weighing scale and a stadiometer for height and weight. Body mass index (BMI) was computed using the following formula: BMI = weight (kg) / height (m2). The waist/hip ratio was computed using the following formula: waist circumference (cm) / hip circumference (cm). Systolic and diastolic blood pressure were obtained using a validated mercury sphygmomanometer (Accoson). An automated chemistry analyser was used to assay biochemical profiles, including liver function test parameters: total bilirubin (TB), albumin, globulin, aspartate aminotransferase (AST), AST-to-ALT ratio, alanine aminotransferase (ALT), and alkaline phosphatase (ALP). The fasting blood sugar and lipid profile parameters, such as TG, HDL cholesterol, and total cholesterol, were measured using an automated chemistry analyser. The fasting LDL-cholesterol was calculated as (Total cholesterol−HDL-cholesterol) −TG/5.

Ethical Consideration

Before beginning data collection, ethical approval was obtained from the research and ethics committee of the Aminu Kano Teaching Hospital in Kano, Nigeria (AKTH) (AKTH/MAC/SUB/12A/P-3/VI/2954). Also, every patient provided written informed consent before the data was collected. Participation was entirely voluntary throughout the study.

Results

The socio-demographic details of the research participants are shown in Table I. The female-to-male ratio among the research participants was 1.6:1, with an average age of 52.01±10.5 years. Of the total participants, 84.8% had completed formal schooling.

Table I: Socio-demographic Characteristics of the Study Population

Variables	**Study group (n=138) n (%)**
Age(years)	
20-30	1 (0.7)
31-40	22 (15.9)
41-50	41 (29.7)
51-60	47 (34.1)
61-70	22 (15.9)
>70	5 (3.6)
Gender	
Female	85 (61.6)
Male	53 (38.4)
Educational level	
Primary	8 (5.8)
Secondary	52 (37.7)
Tertiary	57 (41.3)
None	21 (15.2)
Occupation	
Civil servant	40 (29.0)
Self-employed	54 (39.1)
Unemployed	44 (31.9)
Mean age	
Mean ± SD	52.01 ± 10.45 years

Table II shows that participants with HS had significantly higher mean systolic blood pressure, diastolic blood pressure, BMI, and WC, in both male and female categories. Waist-Hip ratio (WHR) was also significantly higher in patients with HS, but only in males, not in females.

TABLE II: Clinical Profile of Hepatic Steatosis Subjects among T2DM

Variables	Hepatic Steatosis **positive n=29 (%)**	Hepatic Steatosis **negative n=109(%)**	**p-value** **Test-statistic**
Duration of DM (yrs)			
<5	10(34.5)	22(20.2)	p=0.348
5-9	6(20.7)	37(33.9)	x^2=3.457
10-15	11(37.9)	40(36.7)	
15-25	2(6.9)	10(9.2)	p=0.004*
Systolic BP Mean± SD	137.93±20.77	126.4±18.03	t= -2.957
			p<0.001*
Diastolic BP Mean± SD	87.24±11.31	79.54±9.27	t= -3.779
BMI≥30	21(72.4)	33 (30.3)	p<0.001*
			x^2=17.076
male	5 (17.4)	4 (3.7)	p<0.001*
female	16(55.2)	29(26.6)	Fisher exact
			p=0.046*
			x^2=4.664
W/H ratio	24(82.8)	61(56.0)	p=0.010*
			x^2=6.952
Male≥0.90	6 (20.7)	15(13.8)	p = 0.012*
Female≥0.85	18 (62.0)	46 (73.0)	Fisher exact
			p=0.568
			x^2=0.679
WC (cm)	25(86.2)	41(42.2)	p<0.001*
			x^2=21.675
Male>102	5(17.4)	3(2.8)	p<0.001*
Female>88	20(69.0)	38(34.9)	Fisher exact
			p=0.015*
			x^2=7.040

SD= Standard Deviation BP= Blood Pressure, BMI= Body mass index, WHR= Waist-Hip ratio, WC= Waist circumference

Table III shows that, compared to participants without HS, those with steatosis had a significantly higher percentage of elevated TC (≥ 5.1 mmol/L or 200 mg/dL) and TG (≥ 1.7 mmol/L or 150 mg/dL) (p-value < 0.001 for both observations). Similarly, individuals with positive liver steatosis showed a significantly increased mean TC and TG (p<0.001). No statistically significant difference was found in the mean HDL levels of males and females between persons with HS and those without HS (p = 0.32, p = 0.22, and p = 0.32). A significantly higher percentage of individuals with HS had increased LDL levels than those without the condition (p

< 0.001). Subjects with HS reported statistically elevated mean levels of very-low-density lipoprotein (VLDL). There was no significant difference (p = 0.49) in the mean fasting blood sugar (FBS) levels between participants with and without HS. ALT and AST levels were considerably higher in participants with HS than in non-steatosis subjects (p<0.001; p=0.04).

Table III: Biochemical Profile of Hepatic Steatosis Among T2DM Subjects

Variables	Hepatic Steatosis positive n=29 (%)	Hepatic Steatosis negative n=109(%)	p-value
TC≥5.1mmol/L	22(75.9)	53(27.5)	p<0.001* x^2=22.793
TC Mean± SD	6.00±1.16	4.40±1.13	p<0.001* t= 6.728
TG≥1.7mmol/L	19(65.5)	31 (28.4)	p<0.001* x^2=13.629
TG Mean± SD	2.05±0.86	1.52±0.71	p<0.001* t= 3.412
HDL(mmol/L) Male<1.04	6(20.7)	25(22.9)	p=0.22 Fisher exact
Female<1.3	17(58.6)	43(39.4)	p=0.32
HDL Mean± SD	0.97±0.46	1.06±0.45	x^2=0.639 p=0.32 t= 0.992
LDL≥2.6	28(96.6)	61(56.0)	p<0.001* x^2=16.479
LDL Mean± SD	3.87±1.20	2.57±1.12	p<0.001* t= 5.492
VLDL Mean± SD	0.42±0.18	0.31±0.19	p<0.001* t= 2.695
TG/HDL Mean± SD	2.96±3.44	2.58±4.80	p=0.69 t=0.588
FBS Mean± SD	9.03±3.37	9.52±3.37	p=0.49 t= -0.695
ALT>ULN	3(10.3)	0 (0)	p<0.001* x^2=11.526
ALT Mean± SD	19.79±18.86	19.39±6.30	p=0.85 t= -0.186
AST>ULN	2(6.9)	0 (0)	p=0.04* x^2=7.62
AST Mean± SD	24.90±17.50	23.39±7.70	p=0.49 t=0.689
AST/ALT Mean± SD	1.15±0.33	1.16±0.38	p=0.91 t= 0.113
ALP Mean± SD	55.93±21.79	60.72±20.21	p=0.27 t= -1.115
TB Mean± SD	11.66±5.47	10.65±3.10	p=0.20 t= 1.168
Albumin Mean± SD	43.52±3.43	41.97±6.02	p=0.19 t= 1.324
Globulin Mean± SD	27.17±5.09	27.64±3.93	p=0.59 t= 0.536

TC=Total cholesterol, TG=triglyceride, HDL=High density lipoprotein, LDL=Low density lipoprotein, VLDL= Very low-density lipoprotein, FBS= Fasting blood sugar, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, ALP= Alkaline phosphatase, TB=Total bilirubin.

As shown in Table IV, a binary logistic regression was conducted on significant variables for Hepatic Steatosis identified (Clinical and Biochemical) on multivariate analysis. The Independent variables identified as having statistical significance were waist circumference (WC), LDL, and TG levels. Binary logistic regression analysis revealed that WC>upper limit of normal (88cm for females or 102cm for males) had a positive prediction for HS, with odds of 14 times in predicting HS compared to subjects with WC below that level, with p-value = 0.017. Likewise, TG ≥ 1.7 mmol/L (150mg/dL) had positive prediction odds of 5.46 for Hepatic Steatosis among T2DM subjects (p = 0.015), and LDL-c ≥ 2.6 mmol/L (100mg/dL) had odds 35.24 times more likely to predict the presence of hepatic steatosis. Other parameters were not significant.

Table IV: Predictors of Hepatic Steatosis Among T2DM Subjects

Variables	Coef(B)	Odds Ratio Exp(B)	95%CI lower upper	p-value
WC(cm) >ULNvs<ULN*	2.659	14.28	1.59 127.75	**0.017***
TG (mmol/l) ≥1.7vs<1.7*	1.698	5.46	1.39 21.45	**0.015***
LDL (mmol/l) ≥2.6vs<2.6*	3.562	35.24	1.82 681.43	**0.018***
BMI (kg/m^2) ≥30 vs< 30*	0.671	1.955	0.35 10.82	0.442
WHR >ULN vs<ULN*	0.576	1.779	0.43 7.37	0.426
TC (mmol/l) ≥5.1 vs<5.1*	1.165	3.205	0.76 13.55	0.113
HDL (mmol/l) >ULN vs<ULN*	-0.512	0.599	0.16 2.20	0.441
ALT >ULN vs<ULN*	1.399	4.052	0.72 22.80	0.112
AST >ULN vs<ULN*	1.458	4.291	0.80 23.07	0.090

* = Reference category, ULN = Upper limit of normal. ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, BMI= Body mass index, WHR= Waist-Hip ratio, WC= Waist circumference, =Total cholesterol, TG=triglyceride, LDL=Low density lipoprotein.

Discussion

This study ascertains the factors associated with Type 2 diabetes mellitus that predict HS.

In these results, participants of both genders with HS had significantly higher mean systolic blood pressure, diastolic blood pressure, BMI, WC, and WHR compared HS negative cohorts. William et al. observed similar results in a study on the prevalence of NAFD and NASH. They recruited around 2,000 participants aged between 18 and 70 and discovered a significant (p<0.05) relationship between HS and high blood pressure, T2DM, and BMI. However, unlike the current study's findings, the authors found no difference in WHR and WC between HS-positive and HS-negative cohorts. This discrepancy could be attributed to the

wide ethnic heterogeneity (represented by Hispanics, African Americans, and Caucasians) of the study participants (16). Our findings expand upon the existing literature, which reports that NAFLD is associated with obesity, hypertension, and other components of the metabolic syndrome (10, 17, 18).

This study emphasises the link between dyslipidemia and hepatic steatosis with significant differences in LDL, TG and TC ($p<0.05$). In NAFLD patients, increased triglyceride synthesis overwhelms the liver's defences, resulting in ineffective fatty acid excretion (13).

This study highlights the correlation between Hepatic Steatosis and dyslipidemia. Increased triglyceride synthesis in individuals with NAFLD overburdens the liver's protective mechanisms, resulting in inefficient fatty acid excretion. A study conducted in Lagos, Nigeria, found lower HDL-c in men, suggesting possible demographic differences. However, no significant correlation was found between triglycerides, LDL-C, and NAFLD in patients with type 2 diabetes. Also, significant changes in ALT and AST was observed in the previous study (11). The resulting differences could probably be because of demographic characteristics of the study participants, where obese individuals who are likely to have dyslipidemia were higher in our study. The development of hepatic steatosis is linked to the production of reactive oxygen species (ROS), which can impair liver function, leading to inflammation and elevated liver enzyme levels (19).

Logistic regression analysis revealed that increased waist circumference was a predictor with odds above 14 (95% CI: 1.59-127.75). Elevated TG among T2DM also had a positive prediction with an odds ratio of 5.46 (95% CI; 1.39-21.45), while elevated LDL-c had a probability of predicting Hepatic Steatosis more than 35 times that of normal LDL-c among T2DM (95% CI; 1.82-681.43). The predictive properties of these parameters have also been reported in studies from different parts of the World (7, 20-22). A study in Iran on predictors of Hepatic Steatosis among T2DM reported the positive predictive properties of TG, WC, and BMI. The study further demonstrates that weight reduction improves the ultrasound features of NAFLD (7). Similarly, Williamson et al. (23) found that a shorter period of diabetic mellitus, a higher TG, and a BMI have a positive prediction. Silaghi et al. (24), in their study of Fatty liver index among T2DM, found LDL-c to have a favourable prediction of Hepatic Steatosis alongside ALT and gender. Other studies noted obesity, liver transaminases, TC, and HDL to be predictors of Hepatic Steatosis (20-22). One of the factors contributing to differences in the predictors across the various studies was the variables that were analysed, which significantly differ from one study to another. The findings of TG, LDL-c, and WC as predictors of Hepatic Steatosis were consistent with what was earlier documented that NAFLD is a components of metabolic syndrome (25, 26). The occurrence of dyslipidemia, hyperinsulinemia, and insulin resistance in subjects with hepatic steatosis is common, and these conditions can occur independently of obesity markers. The higher the WC, the faster visceral adipose tissue deposition, which could facilitate the development of insulin resistance and hepatic steatosis by producing free fatty acids and adipocytokines (24). It is crucial to stress that NAFLD encompasses a range of liver pathologies, including cirrhosis, steatohepatitis, and hepatic steatosis, and that there is no way to distinguish between these disorders using clinical or biochemical indicators (5).

The study findings are relevant to clinical practice and public health interventions. Clinicians should integrate liver assessment into routine care for individuals with T2DM, particularly those with central obesity and dyslipidemia. The study also emphasises the need for public health policies encouraging early screening of HS, lifestyle changes, and diabetes prevention programs.

The fact that malaria-induced hepatopathy can increase liver inflammation and worsen HS in diabetes patients, especially in malaria-endemic areas (27), underscores the need for comprehensive liver assessment and malaria screening in diabetes individuals with diabetes, especially when the liver markers are elevated.

The study was limited by the absence of a control group, which would have allowed for precise comparisons of some findings. Additionally, being a hospital and single-centre study, its generalizability may be restricted.

Future research may include multi-centre population-based studies, which would enhance generalisation in the general population. Prospective cohort studies may also explore the long-term outcomes of NAFLD in T2DM subjects.

Conclusion

Higher levels of TC, LDL-c, VLDL, triglycerides, and transaminases were associated with hepatic steatosis among patients with T2DM. Likewise, Waist circumference, triglycerides, and LDL-c were independent predictors of Hepatic Steatosis among the T2DM population. Thus, subjects with such elevated clinical parameters, especially T2DM patients, require early evaluation for Hepatic Steatosis to halt its progression to CLD.

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