NON-ALCOHOLIC FATTY LIVER DISEASE AND RELATIONSHIP WITH ADIPOSITY IN NIGERIAN PATIENTS WITH TYPE 2 DIABETES MELLITUS: THE IBADAN EXPERIENCE

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ABSTRACT

Background: **Non-Alcoholic Fatty Liver Disease (NAFLD) is the commonest cause of chronic liver disease and is frequently found in patients with Type 2 diabetes (T2D). NAFLD is associated with excess adiposity and prevalence could vary by BMI sub-groups. There remain conflicting reports about the prevalence of NAFLD in T2D in Africa, particularly Nigeria. We studied the prevalence of NAFLD and its relationship to adiposity in a cohort of persons living with T2D.**

Methodology: **A cross-sectional study of 147 consecutive T2D patients, attending the Diabetes Clinic, at the University College Hospital, Ibadan, was conducted over a period of two months. Clinical history and anthropometric indices were obtained; in addition, blood samples were taken and analyzed for FBS, HbA1c, Fasting Lipids Profile, HBsAg, Anti HCV, ALT, AST, ALP, GGT and albumin. Hepatic ultrasound was conducted by an experienced sonologist. Data were collected with the aid of a pre-tested semi-quantitative questionnaire and were analysed using the SPSS software 15.0 version.**

Results: **Prevalence of NAFLD in persons living with T2D in 139 participants with complete data was 46% with a mean (SD) BMI of 27.4 (5.6). The participants with NAFLD had significantly excess adiposity, particularly the obese subgroup compared to those without [32 (50.0%) and 5 (6.7%), p = 0.001], respectively. Factors associated with NAFLD include female sex, older age, increased BMI, increased waist circumference, raised serum triglycerides, higher HbA1c levels, and raised alkaline phosphate levels. Sex, BMI, waist circumference and serum ALP were independently associated with NAFLD. Of notable interest is the raised serum ALP levels in subjects with NAFLD compared to those without NAFLD: mean (SD) = 30.6 (16.5) and 23.7 (15.3), respectively (p = 0.020).**

Conclusion: **NAFLD is relatively common in patients living with type 2 diabetes and is associated with excess adiposity and increased alkaline phosphatase. Dietary and lifestyle changes can play a pivotal role in reducing prevalence of these diseases. Further, ALP could be a useful marker to assess the progression of NAFLD.**

INTRODUCTION

The world is witnessing increasing burden of Non-Alcoholic Liver Disease (NAFLD) just as diabetes mellitus. The global prevalence of NAFLD or MAFLD (Metabolic-Associated Fatty Liver Disease) as described by some is 32.4%[1], while that of diabetes is 10.5%.[2] Notably, both conditions are associated, and the linkage is bidirectional.[3] The progression of NAFLD through NASH (Non-Alcoholic Steatohepatitis) and liver cirrhosis eventually results in hepatocellular cancer, the second commonest cause of short lifespan in cancer patients.[4] Similarly, diabetes is a leading cause of cardiovascular death, end-stage kidney failure, blindness and non-traumatic amputation.[5] The co-existence of both conditions expectedly leads to increased mortality.[6] A common risk factor for both NAFLD and type 2 diabetes (T2D) is obesity and its associated insulin resistance. However, NAFLD is sometimes found in lean individuals.[7]

Globally, the burden of NAFLD in diabetic patients varies between 30-80%, depending on factors including means of diagnosis of NAFLD, age, gender, BMI and diabetes duration.[8] Similarly, in sub-Saharan Africa, the prevalence rates of NAFLD in diabetic patients range widely between 50.3-73.0%.

Although there are fewer studies in Nigerian T2D, the available studies from the South-western region showed similar wide variation. However, interestingly, out of the three prevalence rates from the same region in Nigeria, two support very low rates - 8.7% and 16.7%,[9,10] while the remaining one reported a high prevalence rate of 68.8%.[11] Nevertheless, questions have been raised whether the low prevalence rates are true reflection of NAFLD burden in African diabetic patients.[12] Therefore, the true prevalence of NAFLD in Nigerian T2D patients, particularly from the South-western region remain unresolved. It is important to know the true burden of NAFLD in diabetic patients, so healthcare practitioners could appreciate the enormity and the requisite approach to care and interventions could be instituted.

In this work, we aimed to determine the prevalence of NAFLD and its relationship with excess adiposity among T2D patients attending the Nigerian premiere teaching hospital, the University College Hospital, Ibadan.

MATERIALS AND METHODS

Study Design and Subjects Recruitment

A cross-sectional study was carried out in the Diabetes Clinic of Medical Outpatient Clinic of the University College Hospital, Ibadan, Nigeria between September and October 2012. Ethical approval was obtained from the Joint University of Ibadan and University College Hospital Ethical committee.

We recruited 147 consecutive patients with type 2 diabetes attending the clinic and who gave written consent to participate in the study. Subjects must have been diagnosed based on the WHO 1999 Diagnostic Criteria were included in the study. The following subjects were excluded: those who ingested more than 40 g or 20g of alcohol per day for males and females respectively, patients who had known causes of chronic liver disease (e.g., alcohol or drug-induced liver disease, autoimmune or viral hepatitis), those with other co-morbid conditions such as congestive cardiac failure, chronic renal failure, chronic obstructive pulmonary disease, psychiatric illness, malignancies, those with past history of intestinal by-pass surgery and pregnant women. Also excluded were subjects on any of the following drugs: thiazolidinediones, glucocorticoids, tamoxifen, methotrexate, amiodarone, antiretrovirals, eostrogen and oral contraceptives.

Clinical Assessment

Socio-demographic information, history of alcohol ingestion, cigarette smoking, diabetes history, complications and treatment, hypertension and other comorbidities were obtained with the aid of a pre-tested semi-quantitative questionnaire.

We measured anthropometric indices including weight, height, waist and hip circumference. The waist and hip circumferences (WC and HC respectively) were measured with a flexible inelastic tape measure with graduation at 0.1cm intervals. Subjects were asked to remove belts and heavy outer clothing and measurement were made directly over the skin. The WC was taken midway between the inferior margin of the last rib and the crest of iliac bone in the mid-axillary plane and the circumference measured in a horizontal plane at the end of normal expiration and the hip circumference was taken with the arms relaxed at the sides and each subject stood with the feet together and measuring tape was placed around the maximum circumference of the buttocks. The waist to hip ratio (WHR) was calculated and recorded for all participants. The weight was measured in kilograms using a normal bathroom scale without subjects wearing heavy clothes or shoes. Height was measured with a stadiometer without the subject wearing shoes, caps or headgear and each subject stood with the straightened back to the measuring rod and looked straight ahead. Body mass index (BMI) was then calculated as: weight divided by square of height (kg/m2).

Laboratory Assays and Hepatic Ultrasonography

Ten (10 mls) of venous blood samples were collected for fasting blood glucose (FBG), glycosylated haemoglobin A1c (HbA1c), hepatitis B surface antigen (HBsAg), antibodies to hepatitis C virus (antiHCV), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), ã-glutamyltransferase (GGT), serum albumin and fasting lipid profile. HBsAg and antiHCV screening were done to exclude chronic liver disease caused by hepatitis B and C viruses.

AST, ALT and albumin were determined using the Randox kit and colourimetric assay. GGT was determined using the MaxDiscovery™ GGT enzymatic assay kith which is a plate-based colourimetric enzymatic assay, and ALP was assayed using the Alkaline Phosphatase kith manufactured by Quimica Clinica Aplicada (QCA) Spain. HbA1c was measured using iron exchange chromatography. Fasting lipid profile and FBG were determined using the Polymer Technology Systems (PTS) lipid and glucose test strips with aid of a CardioChek machine.

One-step cassette style HBsAg RapidCard™ was used to test for HBsAg and one step HCV RapidCard™ InstaTest cassette style for anti-HCV.

Hepatic ultrasonography was performed using a 3.5-MHZ linear probe on a LOGIQ P5 ultrasound machine (General Electric) in 139 subjects by a single experienced sonologist. The degree of steatosis was assessed by the fall in echo amplitude with depth (rate of posterior beam attenuation), increasing discrepancy of echo amplitude between liver and kidney, and loss of echoes from the walls of the portal veins. A liver displaying increased but homogenous dot reflection, blurred but still discernible vascular profiles and weak portal vein echogenicity was defined as early-stage (mild steatosis). A medium-stage (moderate) fatty liver disease was characterized by the disappearance of the portal vascular wall and slightly increased liver volume.[18] Subjects with nebulous optical appearance in the liver, little portal vein echogenicity in more than 1/3-1/2 of the liver area and increased liver volume were considered to be in advanced stage (severe steatosis).[18]

Statistical Analysis

Data analysis was carried out using the statistical package for social sciences (SPSS Inc., Chicago, IL) software, windows 15.0 version. Categorical variables was summarized as percentage and presented using frequency tables. Continuous variables were expressed as means ± standard deviation. T2D subjects with NAFLD were compared with those without NAFLD, and those with normal and high BMI. Association between categorical variables was assessed using the chi square test while means were compared using the independent students t test. Independent factors associated with NAFLD were determined using logistic regression. Statistical significance cutoff was set at less than 5%.

RESULTS

Out of a total of 139 participants with complete data included in the analysis, the mean age was 60.7 (9.4) years and 85 (63.9%) were females (table 1). A total of 64 (46.0%) type 2 DM patients had NAFLD. The median (range) diabetes duration was 8.0 years (0.5-35.0 years), with a mean (SD) HbA1c of 7.4 (2.0) and BMI of 27.4 (5.6) kg/m2.

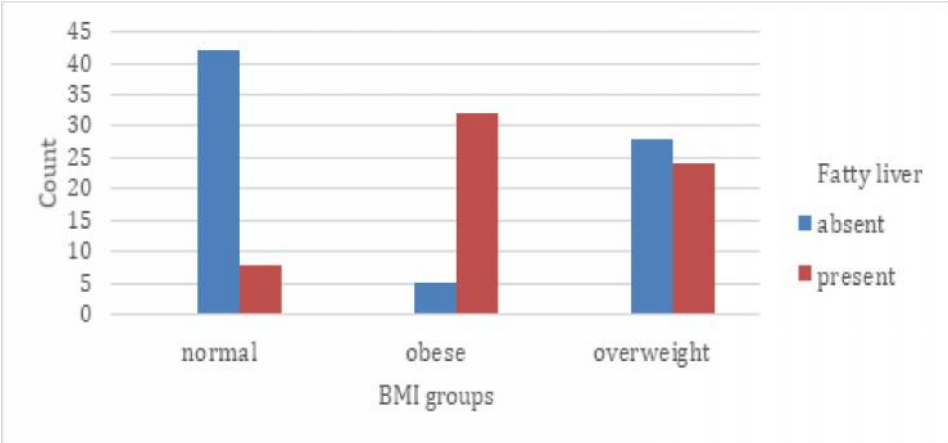
Table 2 shows the differences between type 2 DM patients with and without NAFLD. Of the 64 patients with NAFLD, 51 or 79.7% were females, significantly higher than male patients. The NAFLD positive patients were significantly older: Also, the NAFLD positive

Table 1: Clinical and metabolic characteristics of all participants

Characteristic	Mean (SD)	Frequency (%)
Age (years)	60.7 (9.4)	
Sex		
Male		48 (36.1)
Female		85 (63.9)
Diabetes duration (years)	8.0 (0.5-35.0) *	
Hypertensive n (%)		100 (70.1)
BMI (kg/m^2)	27.4 (5.6)	
Waist circumference (cm)		
Males	92.3 (10.0)	
Females	94.3 (11.3)	
ALP (U/L)	26.5 (16.1)	
AST	11 (3.5)	
ALT	8.1 (3.8)	
GGT	27.8 (12.9)	
Albumin	4.9 (4.7)	
HbA1c	7.4 (2.0)	
Total cholesterol (mg/dL)	151.3 (32.4)	
Triglyceride (mg/dL)	82.9 (25.6)	
LDL cholesterol (mg/dL)	83.7 (26.8)	
HDL cholesterol (mg/dL)	50.2 (20.8)	

*BMI: Body Mass Index AST: Aspartate Transaminase ALP: Alkaline Phosphatase ALT: Alanine Aminotransferase HbA1c: Glycated haemoglobin LDL: Low-Density Lipoprotein HDL: High-Density Lipoprotein *Median (range)*

Figure 1: Distribution of BMI categories between type 2 diabetic patients with and without NAFLD



BMI: Body Mass Index; NAFLD: Non-Alcoholic Fatty Liver Disease

Table 2: Clinical and laboratory characteristics of type 2 diabetic patients with NAFLD and those without NAFLD

Characteristic	NAFLD Absent Mean (SD) or Median (Range)	NAFLD Present Mean (SD) or Median (Range)	P
Age (years)	62.1 (9.4)	58.6 (9.1)	**0.034**
Sex: Males	37 (74.0)	13 (26.0)	**0.001**
Females	38 (42.7)	51 (20.3)	
Diabetes duration (yrs.)*	8.0 (0.5-30.0)	6.5 (0.5-35)	0.317
Family history of DM	33 (53.2)	29 (46.8)	0.877
Hypertensive	49 (50.0)	49 (50.0)	0.148
BMI	24.7 (3.0)	30.6 (6.3)	**0.001**
Waist circumference (cm	88.3 (8.4)	99.8 (10.2)	**0.001**
ALP (U/L)	23.7 (15.3)	30.6 (16.5)	**0.020**
AST (U/L)	10.9 (3.6)	11.0 (3.2)	0.822
ALT (U/L)	8.6 (4.5)	7.5 (2.9)	0.130
GGT (U/L)	26.7 (11.7)	29.4 (14.4)	0.280
Albumin (g/dL)	4.5 (3.0-6.0)	4.2 (3.7-4.4)	0.271
Creatinine (mg/dL)	1.3 (0.4)	1.2 (0.4)	0.253
FPG	106.5 (48.9)	111.0 (45.7)	0.561
HbA1c	7.0 (1.9)	7.7 (1.9)	**0.034**
Total cholesterol	151.2 (32.1)	156.3 (34.0)	0.369
Triglycerides	78.5 (23.6)	89.0 (27.7)	**0.018**
LDL cholesterol	84.2 (25.4)	87.0 (29.4)	0.575
HDL cholesterol	49.0 (22.3)	51.0 (19.3)	0.682

BMI: Body Mass Index *AST: Aspartate Transaminase*
ALP: Alkaline Phosphatase *ALT: Alanine Aminotransferase*
HbA1c: Glycated haemoglobin *LDL: Low-Density Lipoprotein*
HDL: High-Density Lipoprotein *GGT: Gamma-glutamyl transferase*
FPG: Fasting Plasma Glucose *DM: Diabetes Mellitus*
NAFLD: Non-Alcoholic Fatty Liver Disease **Median (range)*

participants had significantly higher BMI and waist circumference than the non-NAFLD patients: 30.6 (6.3) versus 24.7 (3.0), p = 0.001 for BMI and 99.8 (10.2) versus 88.3 (8.4), p = 0.001 respectively. Compared to the NAFLD negative patients, the NAFLD positive had relatively poorer glycaemic control as reflected by HbA1c: 7.0 (1.9) and 7.7 (1.9), p = 0.034, respectively. Among the lipid parameters,

Table 4: Logistic regression analysis of NAFLD on variables

Variable	Odds ratio	95% CI OR	P value
Sex			
Male	0.22	0.06 – 0.80	0.022
Female(ref)	1		
Hypertensive			
Yes	3.70	0.58 - 16.67	0.080
No (ref)	1		
Waist circumference (cm)	1.14	1.03 – 1.25	0.008
Hip circumference (cm)	0.93	0.87 – 1.00	0.057
BMI	1.32	1.04 – 1.69	0.025
ALP (mEq/L)	1.05	1.01 – 1.09	0.017
Albumin	2.75	0.90 – 8.34	0.075
Creatinine	0.21	0.04 – 1.05	0.058
HbA1C (%)	1.30	0.94 – 1.81	0.111
Triglyceride (mg/dL)	1.00	0.98 – 1.03	0.870

NAFLD: Non-Alcoholic Fatty Liver Disease
BMI: Body Mass Index
ALP: Alkaline Phosphatase
HbA1c: Glycated haemoglobin
95% CI OR: 95% Confidence Interval Odd Ratio

only triglyceride is significantly different (p = 0.018), higher in patients with NAFLD than those without: 89.0 (27.7) and 78.5 (23.6).

Figure 1 shows a more detailed distribution of excess adiposity, comparing type 2 DM patients with and without NAFLD. Overall, the participants with NAFLD had significantly excess adiposity compared to those without (p = 0.001). Looking more closely, there was equal percentage of NAFLD and non-NAFLD with overweight. However, 50% of NAFLD patients compared with 6.7% of non-NAFLD participants had obesity.

Table 4 shows the results of comparison of clinical and biochemical characteristics of type 2 diabetes participants with NAFLD, according to whether they had normal or high BMI (overweight and obese). The weight circumferences were significantly higher in both males and females with high BMI: 92.7 (5.5) versus 105.3 (8.6), p = 0.037 for males versus 87.4 (4.9) and 101.2 (10.0) for females, p = 0.004, respectively. Additionally, alkaline phosphatase was significantly lower in those with excess weight: 28.3 (16.4) versus 41.8 (10.8), p = 0.029, respectively. Also, only triglyceride among the lipid profile was different, significantly higher in type 2 DM NAFLD with excess weight, 90.7 (28.9) than type 2 DM NAFLD with normal weight, 76.7 (11.5), p = 0.021.

Performance of logistic regression showed that sex, BMI, waist circumference and alkaline phosphatase were independently associated with NAFLD (table 5).

DISCUSSION

The burden of NAFLD in type 2 DM, which is on a disturbing rise globally, remains unresolved in Nigeria. Our study, consistent with most findings in the world including Africa (13) showed a large prevalence of 46%. Excess adiposity, particularly the obese sub-group and triglyceride were significantly associated with NAFLD. Finally, alkaline phosphatase (apart from sex and anthropometry) was independently associated with NAFLD in type 2 diabetes patients.

The prevalence of NAFLD of 46.0% from this present study at Ibadan, South-West Nigeria, is much higher than the prevalence of 2 of the 3 previously reported studies (8.7% and 16.9%) in Nigeria, both in Lagos.[9,10] However, our finding is less than 68.8% reported by Afolabi and colleagues in Ile-Ife.[11] Interestingly, all these Nigerian studies including the present one were carried out in the same region of the country, populated predominantly by Yoruba speaking tribe and NAFLD diagnosis was based mainly on ultrasound. Also, they were all cross-sectional studies. The reason for the conflicting prevalence of NAFLD in the studies could be related to the level or proportion of overweight/obesity in the participants. In both studies from Lagos, less than half of their sampled population had excess adiposity. However, well over 50% of the participants in our study and the one in Ile-Ife had overweight/obesity. Similarly, the prevalence of obesity among the cohorts in other African studies with reported huge burden of NAFLD range between 33.3 – 92.9%.[14-16] A most recent study demonstrated a significantly much higher prevalence of NAFLD in obese compared with non-obese Nigerians.[17] Furthermore, in our study, the difference in excess weight between NAFLD and non-NAFLD patients was seen only in the obese sub-group. The same pattern is reported in the study by Almobarak et al in Sudan (16) and Wiafe and co-workers in Ghana.[14] However, unlike our finding, the study by Afolabi and colleagues in Ile-Ife[11] showed that both overweight and obese subgroups accounted for significant differences in excess weight between NAFLD and non-NAFLD subjects. NAFLD is reported to increase by three-fold in those with overweight and obesity.[18,19]

The glycaemic control, as measured by glycated haemoglobin, was significantly poorer in our type 2 DM with NAFLD. This is a consistent finding across most studies in Nigeria and globally.[11,20] The observed finding of same proportion of hypertensive participants in those with and without NAFLD is interesting. This could just be a reflection of patients who happened to participate in the study. In any case, hypertension is a very common comorbidity in type 2 diabetes.[21,22] Also, all the lipid parameters were higher in our diabetic subjects with NAFLD compared to non-NAFLD participants. Dyslipidaemia is a frequent comorbidity in diabetic patients with NAFLD. A meta-analytic systematic review found a higher prevalence of 46.69% of dyslipidaemia in diabetic patients with NAFLD compared with 43.08% in those without (23). In this study, only triglyceride is significantly higher in diabetic patients with NAFLD. Similar works from Ethiopia and Sudan also reported significantly elevated triglyceride in NAFLD positive type 2 diabetes.[15,16] Interestingly, PNPLA3, the most frequently genetic variant associated with development of NAFLD is one of the key genes that regulate mobilisation of triglyceride from lipid droplets.[24]

The elevation of alkaline phosphatase in our diabetic patients with NAFLD in this study is a notable finding. There is very scanty report of this finding in other studies; the other liver enzymes, i.e., alanine aminotransferase, aspartate aminotransferase and gamma glutamyl-transferase are frequently reported.[25] The only Nigerian study[9] that included alkaline

phosphatase in their studies reported no significant difference between diabetic patients with NAFLD and those without. Alkaline phosphatase was not part of the reports of other studies in Nigeria and Africa known to the authors. Alkaline phosphatase, a phosphorylating enzyme is abundantly expressed in the liver and bones. Often, when elevated due to hepatic conditions, it is as a result of obstruction of hepatic duct or severe inflammatory process. Therefore, elevated alkaline phosphatase could be an indicator of severity of liver disease such as progression of NAFLD to steatosis (NASH), and even fibrosis and cirrhosis. Given this possibility, alkaline phosphatase could a useful marker to monitor progression of NAFLD in type 2 diabetes.

A key limitation of this study is the use of ultrasound to diagnose NAFLD. The gold standard is liver biopsy, and where there is reluctance due to the invasive nature of the procedure, other non-invasive tests such as use of FibroScan, FIB-4 score along with elastography can be used. However, liver ultrasound is well acceptable and sensitive because it is cheap (an important consideration in resource poor setting and large population studies) and widely available. Despite the important finding of this study, agreeing with one of the three already published studies that the prevalence of NAFLD in Nigerian patients with type 2 diabetes is very high, more studies, especially population-based, large and multi-sites are needed to fully resolve this issue. Although we excluded patients with several causes of liver disease, we could not completely rule out the possibility of bone disorders, drugs and intestinal diseases as the underlying or contributing factor to the observed increased alkaline phosphatase. Longitudinal studies will be needed to further elucidate the importance of this finding.

CONCLUSION

The prevalence of NAFLD in patients with type 2 diabetes in Ibadan, Nigeria is high, and associated with excess weight gain, hypertriglyceridaemia and increased alkaline phosphatase. This suggests a compelling indication to institute lifestyle measures such as dietary modification and exercise to reduce morbidity and mortality consequent on this co-existence. Also, periodic monitoring of patients with alkaline phosphatase, perhaps may help in early detection of progression of NAFLD.

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