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Comparative analysis of indices of the metabolic syndrome in patients with and without non-alcoholic fatty liver disease at a teaching hospital in Nnewi, South-East, Nigeria

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ABSTRACT

Background: Non-Alcoholic fatty liver disease (NAFLD) has become a worldwide health concern with increase in the global incidence of obesity and it is now considered the hepatic component of the metabolic syndrome. **Aims and Objective:** The study's aim was to compare the indices of the metabolic syndrome in compensated chronic liver disease patients with and without NAFLD at NAUTH, Nnewi. **Materials and Methods:** A total of 136 consecutive patients with compensated chronic liver disease were recruited into the study. A structured questionnaire was administered to obtain relevant socio-demographic data. NAFLD was diagnosed based on clinical, biochemical, ultrasonographic and in a few histological features. The Adult Treatment Panel III criteria were used to identify patients with the metabolic syndrome. **Results:** Of the 136 participants recruited into the study, 52 (38.2%) fulfilled 2 or more diagnostic criteria for NAFLD with a male: female ratio of 1:1.36. The mean (SD) age of persons with NAFLD was 45.12 (±8.07) years compared to 47.49(±11.79) years for persons without NAFLD. The difference was not statistically significant (p=0.2). Body mass index (BMI), central obesity (waist circumference), fasting blood sugar, blood pressure, total cholesterol and triglycerides were significantly higher in the NAFLD group (p= <0.05) respectively. **Conclusion:** Indices of the metabolic syndrome were more prevalent in persons with NAFLD. It is recommended that patients with NAFLD be screened for metabolic syndrome and appropriate therapy instituted to decrease the risk of both hepatic and cardiovascular complications.

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INTRODUCTION

Non Alcoholic fatty liver disease (NAFLD) is a chronic liver disease which refers to the presence of hepatic steatosis without significant intake of alcohol.[1] A significant alcohol intake is considered as ingestion of >20g/day or >140g/week of alcohol for males and >10g/day or >70g/week of alcohol for females.[2]

NAFLD is an asymptomatic disease that can progress to non alcoholic steatohepatitis (NASH), fibrosis, cirrhosis and hepatocellular carcinoma.[1] Most patients with this condition are asymptomatic and few present with vague right upper abdominal pain, malaise and fatigue. Others present with abnormal liver function tests or incidental finding of fatty liver on abdominal ultrasound scan for other reasons.[3-5] At present, the global prevalence of

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NAFLD is estimated at about 9% in developing countries and 30% in developed countries.[6]

NAFLD has become a worldwide health concern. It is frequently associated with obesity, type 2 diabetes mellitus and hyperlipidemia and has been described as the hepatic component of the metabolic syndrome.[7] The reported prevalence of obesity in several series of patients with NAFLD varied between 30 and 100 percent, the prevalence of type 2 diabetes mellitus varied between 10 and 75 percent, and the prevalence of hyperlipidemia varied between 20 and 92 percent.[7,8] About 80% of NAFLD patients have associated features of metabolic syndrome.[6] Metabolic syndrome is an important risk factor for cardiovascular disease incidence and mortality.[9]

A descriptive study of the clinical characteristics of NAFLD in South Africa showed that NAFLD affects all spheres of the society especially the poorest and least educated with more than one third presenting with steatohepatitis, while 17% had advanced liver fibrosis.[10] In a study carried out in South west Nigeria among persons with diabetes, the prevalence of NAFLD was 9.5% compared to 4.5% in persons without diabetes.[11] it has been postulated that NAFLD is closely associated with the other indices of the metabolic syndrome[12] but few researchers have explored this association in Eastern Nigeria.

The purpose of this study was to compare the indices of the metabolic syndrome in patients with and without NAFLD attending the medical out-patient clinic and medical wards of Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi in South-east Nigeria.

MATERIALS AND METHODS

This was a cross-sectional descriptive study. A total of 136 patients with suspected chronic liver disease were recruited into the study. A detailed history was taken from the participants with emphasis on the alcohol intake, history of risk factors of CLD, patient's medications, symptoms suggestive of cardiac, respiratory and renal co-morbidities. A thorough clinical examination was performed looking for stigmata of chronic liver disease. Blood pressure was measured in a sitting position after a minimum of 15 minutes of acclimatization and before blood sampling using a mercury sphygmomanometer (Accoson-England). Weight (kg) and height (centimeters) was measured with patient on light clothes and shoes/hat/cap off using the RGZ-12O health scale stadiometer. Body mass index was calculated using the formula: Weight (kg)/Height^2 (m^2). Waist and hip circumference (centimeters) was taken at the midpoint between the lower margin of the last palpable rib and the superior border of the iliac crest and at the widest portion of the buttocks respectively with a measuring tape. Waist–hip ratio was calculated thus: Waist (cm)/Hip (cm).

Ten ml of fasting venous blood sample was taken from all participants to assess the fasting lipid profile, fasting blood sugar (those with impaired fasting glucose values had repeat blood sugar done 2 hours after food), liver function tests, serum proteins, full blood count, Prothrombin time, HBsAg, anti-HCV were estimated in respective laboratories by designated senior laboratory scientists. All biochemical assays were run on an automated system (spectrophotometer Apoel PD-303) except HBSAg and anti-HCV which were assessed by the ELISA method using test strips (one step hepatitis B surface antigen test strip and one step hepatitis C virus test strip respectively) manufactured by Zhejiang aittone biological pharmaceutical co., Ltd, China. Total cholesterol (TC) was assayed using Lieberman Burchard reaction,[13] while high-density lipoprotein (HDL) cholesterol was assayed by precipitation method,[14] triglcerides(TG) was estimated using a serum triglyceride determination kit, catalog number TR0100 employing enzymatic analysis of triglycerides with lipases[15] and low-density lipoprotein (LDL) cholesterol was calculated using the Friedwald formula[16] [LDL = (TCHOL - HDL-C)-TG/5]. Fasting blood sugar was done using the glucose oxidase method described by Middleton and Griffiths[17]

Abdominal ultrasound was performed on all study participants using a 3.5MHz probe of the Aloka prosound SSD-3500SX scanning machine. Diagnosis of fatty liver was established according to Gomercic and colleagues[5] as the presence of Hepatic steatosis identified as the characteristic appearance of diffuse increase in parenchymal echo brightness on ultrasound associated with blurring of the vascular wall, hepatorenal contrast and attenuation of the diaphragm. NAFLD was diagnosed in those study participants who satisfied the following-

- Imaging finding of fatty liver by abdominal ultrasound and/or
- Histology confirmation of NAFLD of one or more of the following- steatosis, mixed inflammatory cell infiltration, hepatocyte ballooning and necrosis, glycogen nuclei, mallory's hyaline and fibrosis.

The Adult Treatment Panel III criteria[18] were used to identify patients with the metabolic syndrome.

Inclusion criteria

1. Adult patients (18 years and above) who gave written informed consent.
2. History of vague right sided abdominal pain.
3. Clinical finding of hepatomegaly.
4. Finding of fatty liver on abdominal ultrasound

Exclusion criteria

1. History of significant alcohol history defined as >20g/day or >140g/week for males and >10g/day or >70g/week for females.
2. Patients with liver disease due to other causes such as HBV, HCV, HIV.
3. Jaundiced patients and patients with clinically shrunken liver.
4. Age <18 years.
5. Pregnancy.
6. Patients with any form of malignancy
7. Patients on medications that predispose to NAFLD or alter the lipid profile eg amiodarone, corticosteroids, anti-lipaemic agents.

Ethical approval

This was obtained from the Nnamdi Azikiwe University Teaching Hospital Ethical committee (NAUTHEC). Informed written consent was obtained from all study participants.

Data analysis

Data analysis was done using the Statistical package for Social Sciences, version 20 software (SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation and compared using Student t-test. Categorical variables were compared using chi-square (X^2) analysis. Comparisons between variables were done using one way analysis of variance (ANOVA). A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 136 study subjects with features of liver disease were recruited into the study. There were 54 (39.7%) males and 82 (60.3%) females giving a male to female ratio of 1:1.5. Their ages ranged from 24 to 74years with a mean (SD) of 46.58 (±10.56) years. Only 52(38.2%) fulfilled 2 or more diagnostic criteria for NAFLD. They were 22 (42.31%) males and 30(57.69%) females giving a male to female ratio of 1:1.36.The mean (SD) age of the NAFLD cases was 45.12(±8.07) with a range of 36 to 74years. This is shown in Table 1.

We observed that the mean values of the weight, BMI, WC and HC were all significantly higher in the NAFLD group. P= 0.01, 0.002, <0.001and <0.001 respectively. There were significant differences in the systolic and diastolic blood pressures of those with NAFLD as against those without NAFLD. (P=0.01&<0.001 respectively). Details are shown in Table 2.

Table 1: Demographic characteristics of NAFLD versus Non-NAFLD subjects

Parameter	NAFLD (%) N=52	NON-NAFLD(%) N=84	P-Value
Age (years)			
21-30	-	5 (100)	0.2
31-40	25 (55.5)	20 (45.5)	
41-50	13 (36.1)	23 (63.8)	
51-60	12 (32.4)	25 (67.5)	
>60	2 (15.3)	11 (84.6)	
Gender			
Male	22 (40.7)	32 (59.2)	0.63
Female	30 (36.5)	52 (63.4)	
Education			
None	7 (25)	21 (75)	0.001
Primary	1 (5.5)	17 (94.4)	
Secondary	17 (56)	13 (44)	
Tertiary	27 (45)	33 (55)	
Marital status			
Single	2 (18.1)	9 (81.8)	0.28
Married	44 (39.6)	67 (60.3)	
Separated	5 (55.5)	4 (45.5)	
widowed	1 (20)	4 (80)	
Occupation			
Traders	28 (40.5)	41 (59.4)	0,22
Civil servants	17 (47.2)	19 (52.7)	
Others	7	24	

More NAFLD patients (78.8%) had metabolic syndrome compared to the non NAFLD patients (33.3%) and the difference was statistically significant. Of the 52 NAFLD patients, 98% had low HDL, 67.3% had hypertriglyceridemia, 71.2% had elevated blood pressure while 53.9% had abnormal fasting blood sugar values (Table 3).

DISCUSSION

NAFLD has become a worldwide health concern. It was previously thought to be uncommon and usually classified under the cryptogenic causes of chronic liver diseases. It is now recognized that NAFLD results in hepatic metabolic stress damage, and is closely related to insulin resistance (IR) and genetic susceptibility.[19,20] NAFLD cases among suspected liver disease patients appear to be uncommon in young adults in our environment but common in the fourth decade of life. This is supported by the study done in Calabar and Ilorin, Nigeria.[21,22] This probably reflects unhealthy lifestyle with subsequent risk of obesity in this era of technology and westernization of the African diet in young adults[23] It also supports the observation that obesity is not yet a problem of childhood/adolescent in this part of the world compared to western countries[24] Although there were more females than males in the study, more males tended to have NAFLD than females but the difference was not statistically significant. Some studies have suggested that the female hormone is protective against NAFLD.[6]

Table 2: Comparison of clinical/laboratory parameters between the NAFLD and non-NAFLD cases

Clinical Parameters	NAFLD N=52 Mean (SD)	NO NAFLD N=84 Mean (SD)	P value
Height of participants (m)	1.64 (±0.06)	1.65 (±0.08)	0.56
Weight of participants (kg)	94.55(±19.56)	84.60 (±13.86)	0.01
BMI (kg/m^2)	35.24(±8.21)	30.86 (±7.56)	0.002
WC (cm)	106.29(±9.91)	95.83(±14.22)	<0.001
HC (cm)	108.29(±9.62)	97.23(±11.33)	<0.001
Systolic BP (mmHg)	134.81(±20.44)	126.55(±17.66)	0.01
Diastolic BP (mmHg)	87.88(±13.77)	79.76(±11.08)	<0.001
TC (mmol/l)	5.73 (±0.86)	5.31 (±1.14)	< 0.001
HDL-C (mmol/l)	1.23(±0.33)	1.17(±0.25)	0.02
LDL-C (mmol/l)	3.18(±0.98)	2.95(±0.98)	0.18
TG (mmol/l)	1.90(±0.68)	1.56(±0.65)	<0.001
FBS (mmol/l)	5.57(±1.49)	5.42 (±1.66)	0.2

Keys: m=meter, cm=centimeter, kg=kilogram, BMI=body mass index, WC=waist circumference, HC=hip circumference, BP=blood pressure, mmHg=millimeters of mercury, NAFLD=non alcoholic fatty liver disease, TG=triglycerides, HDL=high density lipoprotein, LDL=low density lipoprotein, TC=total cholesterol

Table 3: Prevalence of components of metabolic syndrome among all participants

Metabolic syndrome parameters	NAFLD N=52(%)	No NA6FLD N=84(%)	P-value
FBS			
<5.6mmol/l	24 (46.15)	58 (69.1)	
≥5.6mmol/l*	28 (53.9)	26 (30.9)	0.002
Blood pressure			
Normal blood pressure	15 (28.8)	50 (59.5)	
Hypertension*	37 (71.2)	34 (40.5)	0.003
HDL levels			
Low HDL*	51 (98.1)	16 (19)	0.004
Normal HDL	1 (1.9)	68 (81)	
Triglyceride levels			
<1.69mmol/l	17 (32.7)	69 (82.1)	
≥1.69mmol/l*	35 (67.3)	15 (17.9)	0.01
Waist circumference (WC)			
Normal WC	3 (5.8)	41 (48.8)	
Elevated WC*	49 (94.2)	43 (51.2)	0.003
Metabolic syndrome			
Present	41 (78.8)	28 (33.3)	<0.001
Absent	11 (21.2)	56 (66.6)	

Keys: Hypertension (systolic ≥130mm/hg±diastolic ≥85mmhg, Low HDL (male ≤1.03mmol/l, female ≤1.29mmol/l, Elevated WC (males >102cm, females >88cm)

There was a significant relationship between NAFLD and BMI. The BMI also known as the Quetelet's index, a simple anthropometric measurement used to assess obesity, showed that subjects with NAFLD cases had higher BMI (35.24kg/m^2 vs 30.86kg/m^2) than subjects without NAFLD and this was statistically significant. This is similar to the work done by Almabarak et al.[5] in Sudan and Olusanya et al.[6] in Nigeria where they reported a direct relationship between BMI and NAFLD. Obesity is present in the majority of individuals with NAFLD as seen in the index study. Obesity is an independent risk factor for NAFLD and it is strongly associated with the progression of the disease.[26] The role of central adiposity seems crucial because visceral fat is an important source of triglycerides leading to steatosis.[27] This probably explains why central obesity as determined by waist circumference was also significantly associated with NAFLD.[26]

This study showed that the prevalence of impaired glucose tolerance and type 2 diabetic mellitus was significantly higher in participants with NAFLD when compared to non NAFLD patients. This concurs with finding in the literature.[7]NAFLD and T2DM frequently coexist as they share the pathogenic abnormalities of excess adiposity and insulin resistance.[20] Both type 2 DM and NAFLD are associated with adverse outcomes of the other; Type 2 DM is a risk factor for progressive liver disease and liver-related death in patients with NAFLD, whereas NAFLD may be a predictor of cardiovascular risk and mortality in individuals with T2DM.[9]

The characteristic findings in NAFLD include increased cholesterol (VLDL and LDL), increased triglyceride and low HDL.[28] This was essentially the same pattern seen in this study. HDL-C was lower in the NAFLD group and is similar to some other studies.[7,9] There are changes in HDL composition and metabolism in NAFLD essentially

via the reverse cholesterol transport of which the Apo A-1-predominant member of the HDL2 subfraction appears to be more active.[21,28] There was also increased triglyceride levels in the NAFLD group due to over production of VLDL particles during lipid metabolism associated with insulin resistance. In the blood, the TG content of VLDL is progressively reduced by the action of lipoprotein lipase eventually resulting in intermediate density lipoproteins and LDL with high cholesterol content.[20]

The prevalence of hypertension was significantly higher in NAFLD when compared to non NAFLD subjects and was similar to findings from other studies.[6,7].

Limitations of the study

Some causes of hepatic steatosis such as iron overload, Wilson's disease could not be ruled out because iron and caeruloplasmin levels were not assayed. However, these conditions are uncommon in our locality.

CONCLUSION

Indices of the metabolic syndrome were more prevalent in patients with NAFLD. It is recommended that patients with NAFLD be screened for metabolic syndrome and appropriate therapy instituted to decrease the risk of both hepatic and cardiovascular complications

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NSC- Concept and design of the study, statistically analyzed and interpreted data, manuscript preparation, reviewed the literature; **UCO-**critical revision and preparation of the manuscript; **AI-** Concept and design of the study and review of the study.

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