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Original Article

Insulin resistance and plasma glucose tolerance abnormalities in Nigerians with chronic liver disease

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ABSTRACT

Aims: Glucose tolerance abnormalities are frequently observed in patients with chronic liver disease (CLD). Insulin resistance (IR) has been suggested to be a major factor responsible for these abnormalities in CLD. However studies relating IR with severity of CLD are scarce in Nigeria. This study assessed insulin resistance and glucose tolerance abnormalities in CLD and their relationship with the severity of CLD in a tertiary hospital in South-West, Nigeria.

Methods: This cross sectional study involved 100 subjects with CLD. Ethical clearance was obtained and informed consent was granted by participants. Participants were interviewed using a structured proforma; physical examination and relevant investigations were performed. Insulin resistance was measured using the homeostasis model assessment (HOMA-IR) Data was analysed using Statistical Package for Social Sciences version 20.0 and p value of <0.05 was considered significant.

Results: Mean age of the study participants was 51.9 ± 11.9 years, and mean duration of CLD was 15.9 ± 5.8 months. Glucose tolerance abnormalities were present in 66 subjects (66%) and increased from 16.1% in Child Pugh's class A to 90.0% in class C.

HOMA-IR positively correlated with age, body mass index, serum blood glucose, duration and severity of CLD. Increasing age, presence of hepatocellular carcinoma, Child Pugh's class B and class C were associated with glucose tolerance abnormalities.

Conclusion: Glucose tolerance abnormalities and insulin resistance were highly prevalent among chronic liver disease subjects studied and seemed to parallel the severity of CLD, determined by the Child Pugh's score.

1. Introduction

Glucose tolerance abnormalities (GTA) refer to a continuum of impaired fasting glucose, impaired glucose tolerance and type 2 diabetes mellitus, and they have evolved to become a global health problem especially in developing countries like Nigeria where westernisation, urbanisation and sedentary life are vital contributors [1]. The pathogenesis and manifestations of these metabolic abnormalities are evident in most tissues and organs of the body. The liver plays an important role in carbohydrate metabolism and in the balance of blood glucose levels through glycogenolysis and gluconeogenesis, and this metabolic homeostasis may be impaired in chronic liver disease (CLD) due to disorders such as insulin resistance, glucose intolerance and diabetes [2,3].

Chronic liver disease is a disease of the liver resulting from an inflammatory, infiltrative, immunologic, circulatory or metabolic injury to the liver, a process which has been on-going for a period of time, usually about 6 months or longer without complete resolution [4]. Chronic liver disease, like glucose tolerance abnormalities is a major global health problem with high morbidity and mortality, and may present as inflammation (chronic hepatitis), liver cirrhosis(LC) and hepatocellular carcinoma(HCC) [4]. In Nigeria, the

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burden of CLD is particularly enormous because of the high prevalence of chronic hepatitis B virus (HBV) infection, with prevalence of current HBV infection ranging from 7.3% to 24% in Nigeria and past infection rate of 70% [5,6].

Association of diabetes mellitus (DM) and CLD was first described by Bohan [7], and later referred to as *hepatogenous diabetes* by Megyesi et al. [8]. Glucose tolerance abnormalities are known to aggravate CLD by accelerating liver fibrosis and inflammation giving rise to more severe liver failure and HCC, and DM may potentiate the incidence of bacterial infections and other complications in cirrhotic patients and this can lead to increased mortality [9,10]. Glucose metabolism impairment in CLD patients, both in the fasting state and in response to oral glucose or meals, has since then been widely documented in various studies [11–13]. The pathogenesis of glucose tolerance abnormalities in CLD is complex and remains precisely unknown. Insulin resistance in peripheral tissues (adipose and muscular tissue) is suggested to play a central role in the disturbance of glucose metabolism [14,15]. Glucose intolerance and insulin resistance may be found from the early stages of CLD, but diabetes manifests clinically as the liver function deteriorates, and thus may be considered as an indicator of advanced liver disease [16–18]. The determinants and possible role of insulin resistance in relation to GTA in CLD has not been investigated in this environment.

This study was conducted among subjects with CLD to study the magnitude of glucose tolerance abnormalities in them, and to establish the relationship between β-cell function (using HOMA-IR), glucose tolerance, and severity of chronic liver disease determined by Child Pugh's score.

2. Subjects, materials and methods

This cross sectional analytical study was carried out in the Gastroenterology Outpatients Clinic of a tertiary hospital in South West, Nigeria between August and November 2016. Study approval was granted by the hospital's Ethics and Research Committee (IRB/IEC/0004553).

A total of 100 patients with CLD who consented after being informed about the study were consecutively recruited for this study. Subjects previously diagnosed with Diabetes mellitus or receiving treatment for Diabetes mellitus were excluded from this study.

The participants had a detailed history and clinical examination done, and this was documented in a pre-designed structured proforma. The amount of alcohol consumed was calculated based on the average concentration (weight/volume) of alcohol in the common brands sold in the Nigerian market (i.e. 2% for palm wine, 5% for beer/stout, 15% for wine and 40% for gin/whisky) and alcohol consumption was considered significant if a subject ingested more than 50g of alcohol per day for at least 10 years [19].

Laboratory investigations included fasting blood glucose and 2 h post prandial after 75g of anhydrous glucose, fasting serum insulin, serum bilirubin, serum albumin, serum alpha fetoprotein, and prothrombin time. Impaired fasting glucose, impaired glucose tolerance and Diabetes mellitus were diagnosed according to World Health Organisation criteria [20]. Insulin concentrations were measured using the enzyme linked immunosorbent assay (ELISA) (Accu-bind, Monobind Inc. USA). Bilirubin was measured using a commercially manufactured kit based on colorimetric method (Randox Laboratories limited, United Kingdom).

All subjects had abdominal ultrasonography. Severity of Chronic liver disease was based on Child Pugh score which was calculated by the summation of five factors (grades of hepatic encephalopathy and ascites, serum bilirubin, albumin, and prothrombin time), to classify patients into Child-Pugh class A [5,6], B [7–9] or C (10 or more) [21].

2.1. Chronic liver disease – definition of terms

Diagnosis of CLD was made using either clinical, ultrasonographic, biochemical, serological, histological or a combination of some or all of these criteria. Diagnosis of chronic hepatitis B infection was based on the presence of hepatitis B surface antigen (HB_sAg) for greater than six months, or presence of Anti HB_C I_gG antibody and absence of Anti HB_C I_gM antibody [6]. Subjects with liver cirrhosis had unequivocal signs and symptoms of chronic liver disease, impaired liver function tests (elevated serum bilirubin, elevated liver transaminases, aspartate transaminase: alanine transaminase ratio greater than two, reduced serum albumin and reversal of albumin: globulin ratio), and ultrasonographic features consistent with liver cirrhosis (shrunken liver, wavy outline, diffuse alteration and nodular transformation of liver parenchyma, and signs of portal hypertension). Diagnosis of hepatocellular carcinoma was based on clinical features of weight loss, right upper abdominal pain, serum alpha-fetoprotein levels greater than 400 ng/ml and the presence of a focal liver lesion or nodular transformation of liver parenchyma [22]. Diagnosis of alcoholic liver disease (ALD) was made if, in addition to significant alcohol consumption (>50g alcohol per day for at least 10 years), aspartate transaminase (AST): alanine transaminase (ALT) ratio was greater than two, and subjects were serologically negative for hepatitis B and C virus [23,24]. Subjects with non-alcoholic fatty liver disease had ultrasonographic evidence of hepatic steatosis (presence of a bright hepatic echo pattern), in the absence of significant alcohol ingestion [25].

2.2. Statistical analysis

Data from the study was processed and analysed using Statistical Package for Social Sciences version 20.0 (IBM, Armonk, NY, USA). Data was reported as mean and standard deviation (mean ± SD) for continuous variables and as frequencies and percentages (n, %) for categorical variables. Student's t-test was used for comparison of means for continuous variables and chi-square test was used to evaluate associations between categorical variables. Correlation was done to determine the relationship between insulin resistance and other factors. Multivariate regression analysis was applied to determine the relationship between insulin resistance, glucose tolerance abnormalities, and severity of chronic liver disease. The level of statistical significance was set at p values < 0.05.

3. Results

The sample population consisted of 77(77%) male and 23(23%) female, and overall mean age was 51.9 ± 11.9 years, with range of 19–80 years. Mean duration of CLD among the subjects was 15.9 ± 5.8 months from the time of diagnosis. There was significant alcohol intake in 7 (7%) of the subjects. Table 1 shows the mean laboratory measurements of the study population.

Hepatitis B virus was the aetiology in majority (89%) of the cases of CLD, alcohol in 7%, non-alcoholic fatty liver disease in 2% and the cause was unknown in 2% of participants. Liver cirrhosis was the most common type; occurring among 46% participants, 31% had chronic hepatitis and 23% had hepatocellular carcinoma.

Assessing severity of CLD using the Child-Pugh scoring scheme showed that 31%, 49% and 20% of the participants were in Child-Pugh A, B and C class respectively. All the participants ($n = 31$) with Child Pugh Class A had chronic hepatitis; Class B consisted of 41(83.7%) subjects with liver cirrhosis and 8(16.3%) subjects with

Table 1
Mean clinical and laboratory values among study participants.

Variables	Value
Liver span(cm)	9.7 ± 3.6
USS liver span (cm)	14.3 ± 4.8
Fasting blood glucose (mmol/L)	4.9 ± 1.3
2-Hour post-prandial (mmol/L)	8.9 ± 5.0
Fasting serum insulin (μU/L)	14.2 ± 14.1
Fasting serum insulin *Median (IQR)*	10.5 (5.8–16.2)
HOMA-IR	3.1 ± 2.9
Serum Bilirubin (μmol/L)	28.4 ± 14.8
Serum Albumin (g/L)	33.5 ± 4.8
Prothrombin time (seconds > normal)	2.5 ± 1.7
Serum α- fetoprotein (ng/ml)	763.7 ± 1624.6
α-FP *Median (IQR)*	12.0 (3.0–223.0)

BMI – Body mass index; IQR- Inter quartile range; α-FP – Alpha-fetoprotein.

hepatocellular carcinoma; Class C consisted of 5(25.0%) subjects with liver cirrhosis and 15(75.0%) subjects with hepatocellular carcinoma.

Glucose tolerance abnormalities occurred in 66% of the study participants: diabetes mellitus was found in 17% of subjects and IFG and/or IGT in 49% of subjects. None of the subjects had isolated impaired fasting glucose, forty four (44) subjects had isolated impaired glucose tolerance and five [5] had combination of impaired fasting glucose and impaired glucose tolerance.

Duration of CLD from the time of diagnosis was 17.7 ± 5.4 months in the study subjects with GTA compared to 12.4 ± 4.8 months in those without GTA ($p < 0.001$). A higher proportion of those on medications for CLD (85.2%) had GTA compared to those who were not on medications (35.9%) [$\chi 2 = 25.818$, $df = 1$; $p < 0.001$]. Proportion of people with glucose tolerance abnormalities increased with Child-Pugh scoring from 16.1% in class A, to 87.8% in class B, and 90% in class C.

Glucose tolerance abnormalities increased across age groups from 40.0% (DM = 13.3%; IGT = 26.7%) to 60.4% (DM = 17.5%; IGT = 42.9%) to 100.0% (DM = 18.2%; IGT = 81.8%) among participants in age groups 19–40 years, 41–60 years and 61–80 years respectively. Comparison of type of CLD with glucose tolerance abnormalities among study participants showed that GTA occurred in 91.3% (IGT = 60.9%; DM = 30.4%) participants with HCC, 87.0% with LC (IGT = 65.3%; DM = 21.7%) and 16.1% (IGT only) with chronic hepatitis (16.1%) ($p < 0.001$).

Result of independent sample *t*-test to compare mean biochemical parameters of the study subjects with the presence or absence of glucose tolerance abnormalities is presented in Table 2. Subjects with GTA had significantly higher fasting blood glucose, 2 h post prandial glucose, fasting serum insulin, HOMA-IR, serum bilirubin, prothrombin time and serum α-fetoprotein compared with subjects without GTA. Serum albumin was significantly lower in the subjects with glucose tolerance abnormalities in this study.

Table 3 is a comparison of clinical and biochemical parameters across subsets of GTA (DM, IGT and normal glucose tolerance) using one way analysis of variance (ANOVA). Appropriate post hoc analysis was used to detect where the significant inter-group differences were located. The age of the subjects and the duration of CLD differed significantly among those with DM and IGT compared to those with normal glucose tolerance. However, there was no statistical difference in the age of the subjects or duration of CLD between the IGT and DM subsets.

In Table 4, one way analysis of variance (ANOVA) was used to compare the study subjects' clinical and laboratory findings with the severity of CLD using Child Pugh's class. This is followed by the appropriate post hoc analysis to detect the location of the significant inter-group differences. The age of the subjects was statistically different across all the Child Pugh classes. The duration of CLD differed significantly in class A compared to class B and class B compared to C. There was no statistical difference in the FBG among the 3 Child Pugh classes, but the 2HPP was significantly lower in class A compared to class B and C.

Multivariate analysis using logistic regression was used to ascertain the odds of having GTA in the presence of relevant variables. Variables that were significantly associated with the presence of glucose tolerance abnormality at the bivariate analysis level were entered into a logistic regression model analysis to determine independent factors associated with the presence of glucose tolerance abnormality. Increasing age, presence of Hepatocellular carcinoma, Child Pugh's Class B and Class C were factors independently associated with glucose tolerance abnormalities (Table 5).

The Pearson correlation (r) analysis was used to evaluate linear relationship between normally distributed numerical patient variables and HOMA-IR. The Spearman correlation was used with non-normally distributed numerical variable. HOMA -IR was significantly correlated with age ($r = 0.311$, $p = 0.002$), BMI ($r = 0.389$, $p < 0.001$), duration of CLD ($r = 0.286$, $p = 0.004$), FBG ($r = 0.254$, $p = 0.011$), 2HPP ($r = 0.303$, $p = 0.002$) and severity of CLD ($rho = 0.500$, $p < 0.001$). There was a negative and significant correlation between HOMA IR and liver span ($r = -0.289$, $p = 0.004$).

4. Discussion

Diabetes Mellitus (DM) leads to several complications, including micro and macro vascular disease. The continuum of glucose intolerance is mostly associated with cardiovascular diseases, and this association results in increased morbidity and mortality. Occurrence of abnormal glucose tolerance may also lead to increase morbidity in people with chronic liver disease and have negative

Table 2
Comparison of some biochemical parameters in subjects with and without glucose tolerance abnormalities.

Variables	Glucose tolerance abnormality		t	p value
	Present	Absent		
	(n = 66)	(n = 34)		
Fasting blood glucose (mmol/L)	5.2 ± 1.3	4.3 ± 0.9	4.214	< **0.001***
2 h post-prandial (mmol/L)	10.6 ± 5.3	5.7 ± 1.1	7.312	< **0.001***
Fasting serum insulin (μU/L)	18.7 ± 15.6	5.6 ± 2.0	6.689	< **0.001***
HOMA-IR	4.2 ± 3.1	1.0 ± 0.5	8.334	< **0.001***
Serum Bilirubin (μmol/L)	33.6 ± 12.5	18.4 ± 13.9	5.541	< **0.001***
Serum Albumin (g/L)	32.4 ± 4.7	35.5 ± 4.3	−3.228	**0.002***
Prothrombin time (sec > normal)	3.0 ± 1.9	1.5 ± 0.5	6.222	< **0.001***
Serum α- fetoprotein (ng/ml)	1047.6 ± 1850.9	212.7 ± 834.3	3.103	**0.003***
α-FP *Median (IQR)* (ng/ml)	41.6 (6.9–778.8)	3.5 (1.7–9.1)		

*t = t-test statistic; * - p value statistically significant; IQR-inter quartile range.*

Table 3
Comparison of means of subjects' clinical and biochemical parameters with subsets of glucose tolerance abnormalities.

Variables	Glucose tolerance abnormalities			F	P value
	DM	IGT	Normal		
	(n = 17)	(n = 49)	(n = 34)		
[a]Age (year)	54.9 ± 9.3	57.8 ± 9.7	42.0 ± 9.4	28.492	< **0.001***
[b]Duration of CLD (months)	16.4 ± 6.2	18.2 ± 5.1	12.4 ± 4.8	12.123	<**0.001***
BMI (kg/m^2)	23.79 ± 1.73	24.45 ± 2.90	23.27 ± 2.34	2.178	0.119
Liver span (cm)	9.5 ± 4.9	9.6 ± 4.1	9.9 ± 1.6	0.081	0.922
USS liver span (cm)	15.4 ± 5.7	14.7 ± 5.2	13.2 ± 3.4	1.566	0.214
[c]FBG (mmol/L)	6.4 ± 1.6	4.8 ± 0.9	4.3 ± 0.9	24.160	< **0.001***
[d]2 HPP (mmol/L)	15.4 ± 8.9	9.0 ± 0.9	5.7 ± 1.1	38.342	< **0.001***
[e]Fasting serum insulin (μU/L)	17.6 ± 10.8	19.1 ± 17.0	5.6 ± 2.0	11.732	< **0.001***
[f]HOMA-IR	4.8 ± 2.6	4.0 ± 3.2	1.0 ± 0.5	18.988	< **0.001***
[g]Serum Bilirubin (μmol/L)	39.9 ± 15.9	31.4 ± 10.4	18.4 ± 13.9	18.948	< **0.001***
[h]Serum Albumin (g/L)	32.6 ± 6.8	32.3 ± 3.8	35.5 ± 4.3	5.188	**0.007***
[i]Prothrombin time (sec > normal)	3.0 ± 1.1	3.0 ± 2.1	1.5 ± 0.5	10.781	< **0.001***
[j]Serum α-fetoprotein (ng/ml)	1207.9 ± 1949.8	991.9 ± 1833.0	212.7 ± 834.3	3.212	**0.045***

F = One-way analysis of variance (ANOVA) statistic; *- p value significant.
DM – Diabetes mellitus IGT – Impaired glucose tolerance.
[a] Post hoc tamhane – significance between DM vs normal and IGT vs normal.
[b] Post hoc tamhane – significance between DM vs normal and between IGT vs normal.
[c] Post hoc tamhane – significance across all subsets of GTA.
[d] Post hoc tamhane – significance across all subsets of GTA.
[e] Post hoc tamhane - significance between DM vs normal and IGT vs normal.
[f] Post hoc tamhane - significance between DM vs normal and IGT vs normal.
[g] Post hoc tamhane - significance between DM vs normal and IGT vs normal.
[h] Post hoc tamhane - significance between IGT vs normal.
[i] Post hoc tamhane - significance between DM vs normal and IGT vs normal.
[j] Post hoc tamhane - significance between IGT vs normal.

Table 4
Comparison of means of subjects' clinical and biochemical parameters with severity of chronic liver disease.

Variables	Severity of CLD (Child Pugh's)			F	P value
	Class A	Class B	Class C		
	(n = 31)	(n = 49)	(n = 20)		
[a]Age (years)	41.4 ± 10.4	58.4 ± 9.5	52.4 ± 7.0	31.711	< **0.001***
[b]Duration of CLD (months)	11.9 ± 4.6	19.3 ± 4.5	13.8 ± 5.4	26.105	<**0.001***
BMI (kg/m^2)	24.55 ± 2.93	23.64 ± 2.60	23.69 ± 1.78	1.310	0.275
[c]Liver span (cm)	10.1 ± 1.0	8.3 ± 3.6	12.2 ± 4.6	9.843	< **0.001***
[d]USS span of liver (cm)	12.7 ± 1.2	13.1 ± 4.3	20.0 ± 5.4	25.952	< **0.001***
FBG (mmol/L)	4.6 ± 0.7	4.9 ± 1.3	5.4 ± 1.7	2.502	0.087
[e]2 HPP (mmol/L)	6.3 ± 1.3	9.0 ± 2.4	13.0 ± 9.1	13.876	< **0.001***
[f]Fasting serum insulin (μU/L)	6.5 ± 3.7	17.3 ± 17.2	18.9 ± 11.3	7.841	**0.001***
[g]HOMA-IR	1.3 ± 0.9	3.8 ± 3.3	4.4 ± 2.8	10.429	< **0.001***
[h]Serum Bilirubin (μmol/L)	14.6 ± 7.3	29.2 ± 9.4	48.0 ± 10.7	82.479	< **0.001***
[i]Serum Albumin (g/L)	37.2 ± 2.4	33.0 ± 4.9	28.9 ± 2.0	30.370	< **0.001***
[j]Prothrombin time (sec > normal)	1.3 ± 0.4	2.4 ± 1.2	4.5 ± 2.1	39.059	< **0.001***
[k]Serum α-fetoprotein (ng/ml)	5.9 ± 6.9	537.7 ± 1433.5	2492.0 ± 2085.1	21.420	< **0.001***

F = Oneway analysis of variance (ANOVA) statistic, * - p value significant.
[a] Post hoc tamhane - significance across all Child Pugh classes.
[b] Post hoc tamhane – significance between Child Pugh class A vs B and B vs C.
[c] Post hoc tamhane - significance between Child Pugh class A vs B and class B vs C.
[d] Post hoc tamhane - significance between Child Pugh class A vs C and class B vs C.
[e] Post hoc tamhane - significance between Child Pugh class A vs B and class A vs C.
[f] Post hoc tamhane - significance between Child Pugh class A vs B and class A vs C.
[g] Post hoc tamhane - significance between Child Pugh class A vs B and class A vs C.
[h] Post hoc tamhane - significance across all Child Pugh classes.
[i] Post hoc tamhane - significance across all Child Pugh classes.
[j] Post hoc tamhane - significance across all Child Pugh classes.
[k] Post hoc tamhane - significance across all Child Pugh classes.

impact on the survival of subjects with chronic liver disease compared with those with normal glucose tolerance [26]. The occurrence of glucose tolerance abnormalities in chronic liver disease has been documented in studies within and outside Nigeria [11,12,27,28]. However the relationship between chronic liver disease and glucose tolerance abnormalities, determinants of glucose tolerance abnormalities and possible impact of glucose tolerance abnormalities on chronic liver disease outcome remains largely unknown in Nigeria. This study assessed insulin and plasma glucose tolerance abnormalities in CLD and their relationship with severity of CLD in Nigerian adults with chronic liver disease.

The overall prevalence of glucose tolerance abnormalities in CLD in this study was 66% (DM- 17%, IFG and or IGT- 49%). The prevalence of DM in CLD has been reported to range from 10% to 60% and

Table 5
Logistic regression analysis of factors associated with glucose tolerance abnormalities in study participants.

Variables	OR (95% CI)	P value
Age (years)	1.188 (1.076–1.360)	**0.002***
Marital Status		
Single	1	
Married	0.117 (0.008–4.098)	0.280
Duration of CLD (months)	1.137 (0.952–1.357)	0.156
Medications for CLD		
No	1	
Yes	4.186 (0.730–24.000)	0.108
Type of CLD		
Chronic hepatitis	1	
Liver cirrhosis	1.652 (0.226–12.059)	0.621
Hepatocellular carcinoma	22.847 (2.551–204.647)	**0.005***
Severity of CLD (Child Pugh's class)		
Class A	1	
Class B	5.048 (1.014–25.135)	**0.048***
Class C	29.582 (4.200–208.361)	**0.001***

*- *p value statistically significant; OR- Odds ratio.*

IGT ranged between 25% and 70% [12,13,29,30]. The wide range of frequency of glucose abnormalities in these studies reflects the different population studied and diagnostic criteria used. The frequency of DM obtained in our study is similar to 14.0% obtained by Mukherjee et al. [29] among patients with CLD. This study contrasts with the frequency of 71.0% obtained by Holstein [30], where only people with liver cirrhosis were examined compared to our study where we considered all people with CLD (and not liver cirrhosis alone). The prevalence of DM obtained in this study is about threefold of the national prevalence of 5.77% of DM in Nigeria [31].

Frequency of IGT in our study contrasts with values of 11.4%, 58.1% and 38.5% obtained by Alavian et al. [12], Garcia-Compean et al. [27], and Mukherjee et al. [29] where the American Diabetes Association (ADA) criteria was used for the diagnosis of IGT compared with the WHO criteria used in our study. The ADA criteria states values of fasting blood glucose of between 5.6 and 6.9 mmol/l for impaired fasting, and hence will inadvertently include more subjects into the category of impaired glucose than the World Health Organization criteria.

Another reason for the wide range in prevalence of GTA in different studies may be due to the different aetiologies and types of the CLD implicated. Chronic liver disease is a broad term which encompasses different types of liver disease with various aetiologies. Non-alcoholic fatty liver disease (NAFLD), alcohol, hepatitis C virus (HCV) and haemochromatosis are more frequently associated with diabetes [32–34]. The commonest aetiology implicated in this study was hepatitis B virus (89%), while alcohol was the commonest aetiology (74.3% and 50.7%) implicated by Garcia-Compean et al. [27] and Mukherjee et al. [29].

This study showed that patients with GTA (IGT and DM) were older compared with those without GTA. These findings are similar to that observed in other studies. Alavian et al. [12], Mukherjee et al. [29] and Garcia- Compean et al. [26,27] reported that the prevalence of GTA was significantly associated with older age. In the general population, diabetes occurs in the middle aged and elderly and thus, it was expected to be associated with glucose tolerance abnormalities in CLD. In addition, most of the advanced forms of CLD occurred in older subjects in this study. This was probably due to HBV infections acquired in childhood which were undetected and untreated [6]. Advanced chronic liver disease in adulthood further increases the risk of glucose tolerance abnormalities in old age.

A significant association was also found between glucose tolerance abnormalities and the severity of CLD measured using Child Pugh score in this study. The prevalence of GTA increased significantly from 16.1% in Child Pugh's Class A, to 87.8% in class B and to 90.0% in Class C. This is similar to what was reported by Alavian et al. [12] and Garcia-Compean et al. [26] where DM was significantly more in subjects in Child Pugh class B than class A. There were no subjects in Child Pugh class C in these studies.

Insulin resistance, measured using the HOMA-IR paralleled increasing age, obesity, plasma glucose, and severity of CLD. Association of insulin resistance with severity of CLD, earlier reported by Braganca et al. [13] and Grancini et al. [35] suggests a detrimental effect of liver dysfunction on the pancreatic islets cells. Although the underlying reason why insulin resistance increases in tandem with the severity of CLD has not been fully elucidated; IR has been shown to parallel liver fibrosis. In viral hepatitides, this association is presumably caused by viral induced liver damage and subsequent inflammatory activities [36,37].

Insulin resistance is an important feature of Type 2 diabetes mellitus and is also associated with metabolic syndrome. Likewise, in chronic liver disease, insulin resistance in muscle, liver and adipose tissues are the pathophysiologic bases of GTA [16]. Impairment of hepatic insulin degradation and porto-systemic shunting are important mechanisms of hyperinsulinemia in chronic liver disease [38], and may be responsible for higher levels of HOMA-IR in CLD.

We were unable to use the glucose clamp method which is regarded as the gold standard in assessing insulin resistance, due to its time-consuming and expensive nature. The cross-sectional method of this study may preclude concluding that the relationship between insulin resistance and glucose tolerance abnormalities in the population of interest is causal.

5. Conclusion

Glucose tolerance abnormalities are common among adult Nigerians with chronic liver disease and are associated with increasing age, advanced CLD and presence of hepatocellular carcinoma. Insulin resistance is associated with increasing age, obesity, plasma glucose, and severity of CLD. We advise that patients with CLD should be informed and educated about glucose tolerance abnormalities. There should be close monitoring of people with chronic liver disease for early detection of glucose tolerance abnormalities and prompt intervention.

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Conflicts of interest

We confirm that there are no known conflicts of interest with this manuscript.

Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.05.014.

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