The Relationship Between Glycaemic Control and Non-Alcoholic Fatty Liver Disease in Nigerian Type 2 Diabetic Patients

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Abstract: Background: Metabolic risk factors associated with non-alcoholic fatty liver disease (NAFLD) include Type 2 diabetes mellitus (T2DM), obesity and dyslipidaemia. Prevention or management of these risk factors with glycaemic control, weight reduction and low serum lipid levels respectively have been reported to reduce the risk of NAFLD or slow its progression. Since ultrasound (USS) is a safe and reliable method of identifying fatty changes in the liver, this study was done to determine the relationship between glycaemic control and ultrasound diagnosed NAFLD in T2DM.

Methodology: : Demographic data, anthropometric measurements and laboratory tests including glycated haemoglobin (HbA1c), fasting blood glucose (FBG) and serum lipids of 80 T2DM subjects aged 40-80 years were taken. Their livers were evaluated using B-mode ultrasound, and the data obtained were statistically analysed using SPSS version 20.

Results: Fifty-five of all participants (68.8%) were diagnosed with NAFLD sonographic grades 1, 2 and 3 made up of 13 (16.3%), 26 (32.5%) and 16 (20.0%), respectively while 25 (37.2%) had grade 0. The prevalence of NAFLD in T2DM varied significantly with BMI ($p = 0.001$) and glycaemic control ($p = 0.048$) while the USS grades of NAFLD varied significantly with age ($p = 0.043$) and BMI ($p = 0.006$). The independent strong predictors of NAFLD were overweight ($r = 0.409$, $p = 0.012$, OR = 6.626) and obesity ($r = 0.411$ $p = 0.009$, OR = 11.508), while poor glycaemic control ($r = 0.270$, $p = 0.015$, OR = 3.473) was a moderate independent predictor.

Conclusion: The prevalence of NAFLD increases with increasing BMI and HBA1c in T2DM, while its ultrasound grade varies with BMI. Overweight, obesity and poor glycaemic control are independent predictors of NAFLD.

Keywords: Diabetes mellitus■Non-alcoholic fatty liver disease■Obesity■Glycaemic control■Body mass index■Lipids

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INTRODUCTION

About 347 million people worldwide have been diagnosed with diabetes mellitus (DM), while the World Health Organization (WHO) projects that it will be the seventh leading cause of death by 2030.[1] It is a metabolic disorder characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action or both.[1] High insulin resistance and/or deficit in insulin secretion that is associated with DM increases the activity of the enzyme lipase.[2] This gradual development of impairment in free fatty acid (FFA) metabolism leads to increased levels of FFA in excess of what the liver can oxidize. These are consequently deposited in the liver, a condition known as non-alcoholic fatty liver disease (NAFLD). Simple NAFLD can become non-alcoholic steatohepatitis when the liver cells get inflamed, progressing into fibrosis and eventually cirrhosis and/or hepatocellular carcinoma. Eventually, this greatly impairs the quality of life of a diabetic, culminating in end stage liver disease. Therefore, early detection and prompt management of NAFLD can greatly improve the quality of life of diabetics.[3]

Liver biopsy is the gold standard for diagnosing NAFLD but this method is invasive and cannot be used for screening purposes.[4] Ultrasound (USS) has been shown to be sensitive in detecting fatty liver, and since it is safe, available, affordable, and does not require the use of ionizing radiation, it is the preferred method of choice for screening patients for NAFLD.[5] Computerized Tomography (CT), Magnetic Resonance Imaging (MRI) and Spectroscopy are other alternative imaging techniques for the detection of fatty liver. They have however failed to show better accuracy than ultrasonography,[5] and their high cost and other disadvantages such as radiation in CT and claustrophobic effects in MRI, limit their usefulness as screening tools.[5]

NAFLD in T2DM subjects has been well studied among Asians, Indians and Caucasians.[4,6–11] However, the few African studies on the subject matter majorly addressed its prevalence and some associated risk factors.[12,13] The present study aimed to determine the relationship between NAFLD and glycaemic control levels in Nigerian T2DM subjects.

MATERIALS AND METHODS

Recruitment of study subjects

The study was approved by the Review Board of our institution and written informed consent was obtained from all study participants. Eighty consecutive T2DM patients aged 40-80 years old without history of significant alcohol intake (less than 20 g/day for females and 30 g/day for males[14]) were recruited from the Endocrinology clinic of the hospital. The sample size was calculated by Leslie formula (with 10% attrition rate factored in) using a reported prevalence rate of 4.7% in T2DM in a previous study in our locality.[15] Other exclusion criteria were protein calorie malnutrition, starvation, total parenteral nutrition, acute fatty liver of pregnancy, laboratory evidence of hepatitis B infection, history of jaundice, previous liver surgeries, inflammatory bowel disease, previous exposure to environmental hepatotoxins (phosphorus, toxic mushrooms), patients on chronic use of glucocorticoids, synthetic oestrogen, Tamoxifen, Methotrexate, Valproic acid, Fialuridine, Zidovudine and Didanosine, and those in diabetic coma, as well as those with abnormal level of serum lipids.

Clinical and laboratory assessment

The age, gender and duration of diabetes were recorded for each subject. Their body weight was measured to the nearest 0.1 kg using a weighing scale (Mechanical physician weighing scale attached with a height gauge, model ZT-160, China) while their height was measured to the nearest 0.1 m using a stadiometer (model ZT-160, China) in erect position without shoes. Their BMI was calculated by dividing their weight in kilograms by the square of their height in meters.[12,13]

Patients were screened for Hepatitis B surface antigen (HBsAg Elabscience^{R} II ELISA kit) and Hepatitis C virus (HCV Elabscience^{R} II ELISA kit) using enzyme-linked immuno-absorbent assays. Venous blood was taken from prospective participants after an overnight fast of at least 8 h for serum lipid profile [total cholesterol (TC), high density lipoproteins (HDL), low density lipoproteins (LDL), and Triglycerides (TG)]. These were estimated using standardised enzymatic kits on biochemical Mindray DS auto-analyser. Dyslipidaemia was defined as having one or more of the following: TC $\geq$5.2 mmol/L, LDL-C $\geq$3.4 mmol/L, HDL-C $\leq$1.0 mmol/L, or TG $\geq$1.70 mmol/L.[16]

Venous blood was obtained again from those free of HBsAg and HCV viruses with normal serum lipid level after an overnight fast of at least 8 h, and their blood glucose (FBG) concentration was measured using Finetest^{TM} glucometer (Model IGM-0005A) with Finetest^{TM} test strips (Infopia Co. Ltd) while their glycated haemoglobin (HBA1c) was assessed by chromatography using Glycated haemoglobin analyser (Model LTJL760, Beijing Share-sun OET. Co., Ltd, China). Good glycaemic control was taken as HBA1c $<$7.0% while poor glycaemic control was taken as HBA1c $\geq$7.0%, similar to other authors.[7] Abnormal FBG was taken as $\geq$7.0 mmol/L.[16]

Sonographic assessment/technique

All USS examinations were performed using the MINDRAY® real time ultrasound scanner model DC-7 (Shenzhen Mindray Bio-medical Electronics, Nanshan, Shenzhen, China), equipped with a curvilinear probe with frequency of 3.5-5.0 MHz. Each subject was positioned supine on the examination couch. For better access to the liver, patients were asked to place their hands behind their heads, with their shoulders abducted and elbows flexed, thus increasing the intercostal spaces and the distance between the costal margin and the iliac crest.[17] With coupling gel applied to the abdomen, the liver was scanned in both longitudinal and transverse planes.

Sonographic grading of fatty liver, as described by other authors,[18–21] was classified as given below:

- Grade 0: Homogenous liver parenchyma with echogenicity equal to or slightly greater than that of the renal cortex
- Grade 1: Increased echogenicity of the liver with normal visualization of the diaphragm and the intrahepatic vessel borders.
- Grade 2: Increased echogenicity of the liver with obscuration of the walls of the portal vein branches.
- Grade 3: Increased echogenicity of the liver with obscuration of the diaphragmatic outline.

Statistical analysis

Continuous variables are presented as mean ± SEM (standard error of mean) and categorical variables as percentages and frequencies. The significance of comparative difference was determined between the grades of NAFLD using One-Way Analysis of Variance (ANOVA), followed by Student–Neumann–Keuls *post-hoc* test. Also, independent samples t test was used for multiple comparisons between groups with and without NAFLD. Point biserial correlation analysis and logistic regression analysis was used to evaluate for participants' characteristics associated with NAFLD and its independent predictors, respectively. Statistical significance was set at $p \leq 0.05$.