PREVALENCE AND DETERMINANTS OF GLUCOSE INTOLERANCE AMONG HIV/AIDS PATIENTS IN NORTH-CENTRAL NIGERIA

Running title: Glucose intolerance in HIV/AIDS patients from North-Central Nigeria

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ABSTRACT

BACKGROUND
The advent of potent antiviral drugs has revolutionalised the clinical course of HIV / AIDS resulting in increased survival and improved quality of life. Metabolic derangements in HIV infected patients are becoming more common probably due to this increased survival from the use of HAART. There is limited data on the occurrence of glucose intolerance among HIV patients in Nigeria.

OBJECTIVE
To determine the prevalence of glucose intolerance and associated risk factors in HIV/AIDS patients.

METHODS
Consenting adult HIV patients at the HIV clinic of the Jos University Teaching Hospital (JUTH), Jos , Nigeria were evaluated were evaluated for the presence of glucose intolerance using a 75g oral glucose tolerance test (OGTT). There clinical characteristics, anthropometry, CD4 cell counts and viral load were determined using appropriate standard techniques. Impaired Fasting Glucose (IFG), Impaired Glucose Tolerance (IGT), and Diabetes Mellitus (DM) were defined based on the American Diabetes Association (ADA) cut-off values.

RESULTS
Of the 584 patients studied, 384 (130 males and 251 females) with mean±SD age of 38±15 years were HAART-treated; while 200 (61 males and 139 females) with mean±SD age of 33±17 years were HAART-naive. Overall, the prevalence of GI was 40.4% (IFG) 19.5%, IGT 11.5% and DM 9.4%. The prevalence of IFG (27.1%) and DM (11.2%) in HAART - treated patients were observed and those in HAART-naive patients were (IFG 5.0%, DM 6.0%), $p<0.005$. IGT was more prevalent in HAART-naive than in HAART-treated patients (19.5%, and 7.3% respectively), $p<0.05$. The proportions of patients with GI were higher in overweight and obese HAART-treated patients with moderate CD4 cell count (200-500 $x10^6$ cell/L); while in the HAART-naive patients, GI was more prevalent in underweight subjects with CD4 cell count (<200 x 10^6 cell/L). The Determinants of GI were age, increasing BMI, low CD4 cell count, metabolic syndrome and HAART treatment duration. The independent predictors of glucose intolerance in HIV / AIDS patients were low CD4 cell count and prolonged HAART treatment duration.

CONCLUSION:
The prevalence of GI among HIV/AIDS patients in North-Central Nigeria is high. Treatment with HAART and low CD4 cell count are strong determinants of glucose intolerance in our HIV / AIDS patients. Regular screening for glucose intolerance among our HIV / AIDS patients is recommended.

KEYWORDS: HIV, Glucose Intolerance, Prevalence, North-Central Nigeria

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INTRODUCTION

Glucose intolerance (GI) is a state of abnormal glucose metabolism in which Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are intermediate stages in the natural history of diabetes mellitus.[1] Impaired glucose tolerance is defined as two-hour glucose levels of 140-199mg/dl (7.8-11.0mmol/l) on the 75-g oral glucose tolerance test (OGTT), and Impaired fasting glucose is defined as glucose levels of 100-125mg/dl (5.6-6.9mmol/l) in fasting patients. Patients with IGT and IFG have a significant risk of developing diabetes and cardiovascular morbidity and mortality, thus are an important target group for primary prevention.[2]

In published data from North America and Western European populations, between 10 and 20% of adults (25 years and above) have IGT based on OGTT with a quarter to a third of older adults (55 years and above)

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having the condition.[3] There is a wide variation in the prevalence of IGT among different population in Africa. In Tanzania, the prevalence was found to be about 10% in rural Bantu and 20% in Dar-es-Salam. Ohwovoriole et al[4] found a prevalence of 29.5% in a hospital based study from pooled data from two Diabetes clinics in Lagos.

Human immunodeficiency virus (HIV) / Acquired immune deficiency Syndrome (AIDS) is a major health concern and cause of death in many parts of Africa. The continent is home to about 15.2% of the world's population,[5] sub-saharan Africa alone accounted for an estimated 69% of all people living with HIV(2)4new) and 70% 0f allAIDS deaths in 2011.[6] A 2013 special report issued by joint United Nation Programme on HIV/AIDS (UNAIDS) noted that the prevalence of HIV positive people in Africa receiving anti-retroviral treatment in 2012 was over seven times the number receieving treatment in 2005.[7] The 2011 prevalence rate in Nigeria was 3.7% within the Ages 15-49 years. It has been documented that along with improvement in well being and survival, patients with HIV/AIDS on HAART develop metabolic imbalances (IFG, IGT, DM and dyslipdeamia) more readily than the normal population.[8] In this study, we aimed to determine the prevalence of glucose intolerance and associated risk factors in HIV/AIDS patients in a specialist HIV / AIDS treatment centre. We also intend to add to the growing literature on the subject thus improving the paucity of data in Nigeria.

METHODS

This is a cross-sectional study carried out at the AIDS Prevention Initiative in Nigeria (APIN) clinic of the Jos University Teaching Hospital, Jos over an eleven month period. After obtaining ethical approval from the JUTH Research Ethics Committee, three hundred and eighty four consenting subjects (HIV sero-positive HAART treated), aged 15-70years were consecutively recruited. An age and sex matched control population of HIV sero-positive individuals (HAART naive) were selected from the same clinic after obtaining an informed consent. We obtained basic patient data such as age, gender, duration of HIV/AIDS, type and duration of treatment at the clinic and documented these in an interviewer-administered profoma.

Physical examination carried out for all study participants included blood pressure, height, weight and waist circumference measurements. Body mass index (BMI) classified based on WHO guidelines.[9] The waist circumference (WC) was determined for each subject using a non-stretchable tailor's tape rule placed in a horizontal plane along the line of the umbilicus with the subject standing erect without upper clothing. The WHO guideline was used to classify waist circumference based on gender.[10] Blood pressure was measured using appropriate cuff sizes on both upper arms, one at a time under a calm and conducive environment with phase I and V Korotcoff recordings. The arm with the highest recording was taken as the subject's BP recording. The BP was defined by WHO/ISH guidelines.[11] Blood samples were taken in the morning after an overnight (8 – 12 hours) fast into appropriate specimen bottles for plasma glucose and lipid estimation. Each subject was prepared for an Oral Glucose Tolerance Test (OGTT) using 75g glucose based on standard laboratory procedures. Plasma glucose estimation was done using the glucose oxidase method of Trinder[12], while plasma lipids were determined using reagents contained in a kit (BIOLABO S. A. France). Plasma lipids determined include total cholesterol, HDL cholesterol and Triglycerides. The low density lipoprotein (LDL) cholesterol was calculated using Firedwald's formula.[13] The diagnosis of IGT was made based on ADA diagnostic criteria for DM and intermediate glucose abnormalities.1 HIV testing, CD4 cell counts and viral load were determined using appropriate methods.

Statistical Analysis

Collated data was analyzed using EPI – INFO (version 3.3.2). The student T-test was used for comparison of mean, while the Chi-squared test was used compare proportions. Multivariate analysis using logistic regression statistics was deployed to determine the independent risk factors for glucose intolerance. Statistical significance was defined as p value < 0.05.

RESULTS

Of the 584 patients studied, 384 (130 males and 254 females) with mean±SD age of 38±15 years were HAART-treated (subjects); while 200 (61 males and 139 females) with mean±SD age of 33±17 years were HAART-Naive (controls). Table 1 shows the details of age and gender distribution of both subjects and controls.

Table 1: Age and Gender Distribution of Study Subjects and Controls

Age Group (years)	Subjects n(%)			Controls n(%)		
	Males	Females	Total	Males	Females	Total
15 – 24	0 (0)	11(2.9)	11(2.9)	0(0)	32(16.0)	32(16.0)
25 – 34	25(6.5)	112(29.3)	137(35.7)	23(11.5)	70(35.0)	93(46.5)
35 – 44	57(14.8)	91(23.7)	148(38.5)	22(11.0)	31(15.5)	53(26.5)
45 – 54	36(9.4)	36(9.4)	72(18.8)	10(5.0)	6(3.0)	16(8.0)
55 – 64	12(3.2)	3(0.8)	15(3.9)	6(3.0)	0(0)	6(3.0)
Total	130(33.9)	254(66.1)	384(100)	61(30.5)	139(69.5)	200(100)

Subjects $X^2 = 44.5$, $p = 0.0001$. Controls $X^2 = 39.9$, $p < 0.001$

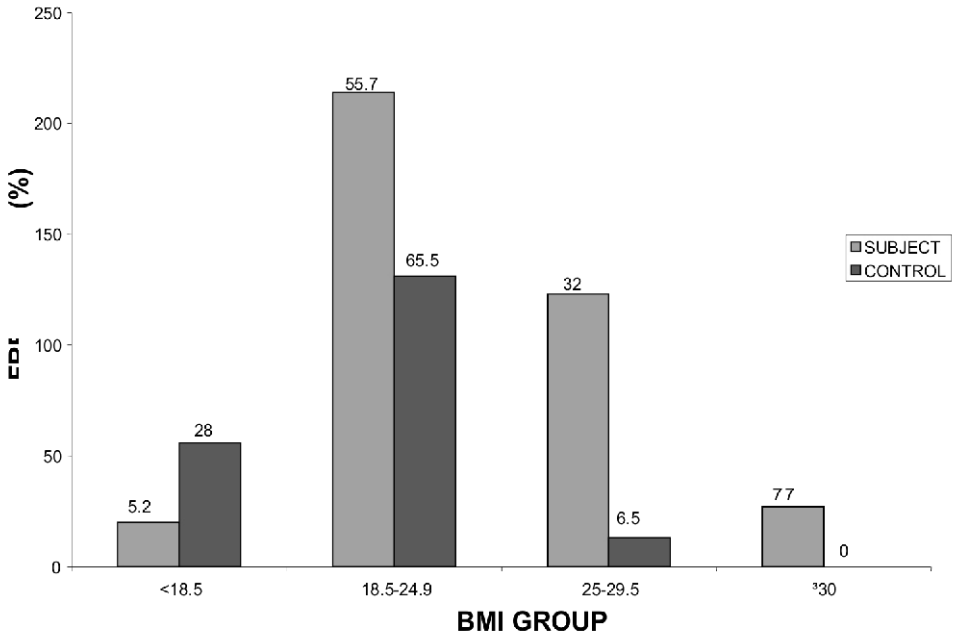

Figure 1: Body Mass Index (BMI) of Study Subjects Compared to Controls

The anthropometric parameters of the subjects and controls are presented in Figure 1. The study subjects that were overweight (32%) were higher than in control (6.5%), same was observed for obese (7.7%) in the study subject as compared to the control (0%) ($P<0.05$).

Table 2: Prevalence of Glucose Intolerance among Study and Control Subjects

Glucose Intolerance	Study n(%)	Control n(%)	Total n(%)	P
IGT	28(11.9)	39(16.5)	67(28.4)	0.01
IFG	104(44.1)	10(4.2)	114(48.3)	0.001
DM	43(18.2)	12(5.1)	55(23.3)	0.002
Total	175(74.2)	61(25.8)	236(100.0)	

IGT = Impaired Glucose Tolerance; IFG = Impaired Fasting Glucose; DM = Diabetes Mellitus

A total of 175 (45.6%) persons among the 384 HAART-treated subjects were glucose intolerant, while 61 (30.5%) of the 200 controls (HAART-naive) were glucose intolerant. The relative distribution of the various forms of glucose intolerance observed in this study is shown in table 2. The plasma glucose cut off values used, are based on the American Diabetes Association position statement (ADA)[1]

Table 3: Distribution of Glucose Intolerance in Study Subjects by CD4 Cell Count.

	Disease group by CD4 cell count (x10^6 cell/L)			
Glucose Intolerance	**>500(%)**	**200-499(%)**	**<200(%)**	**P**
IGT	4(14.3	15(53.6)	9(32.1)	0.27
IFG	13(12.5)	67(64.4)	24(23.1)	0.001
DM	4(9.3)	29(67.4)	10(23.3)	0.001

IGT = Impaired Glucose Tolerance; IFG = Impaired Fasting Glucose; DM = Diabetes Mellitus

Subjects with CD4 count 200 – 499 x 10^6cell/L had the highest proportion of IFG (64.4%), IGT (53.6%) and DM (67.4%) as depicted in Table 3.

Table 4 shows the distribution of glucose intolerance among control subjects based on CD4 cell count. The highest IFG (60%) was seen in the CD4 cell count range of 200 – 499x10^6 cell/L.

Table 4: Distribution of Glucose Intolerance in Control Subjects by CD4 Cell Count

	Disease group by CD4 cell count (x10^6 cell/L)			
Glucose Intolerance	**>500(%)**	**200-499(%)**	**<200(%)**	**P**
IGT	0(0)	10(25.6)	29(32.1)	0.001
IFG	1(10)	6(60)	3(30)	0.001
DM	4(0)	0(0)	12(100)	0.47

IGT = Impaired Glucose Tolerance; IFG = Impaired Fasting Glucose; DM = Diabetes Mellitus

Table 5 shows the distribution of glucose intolerance among the subjects based on HIV treatment duration. It appears a longer duration (longer than 48 months) of treatment using anti-retrovirals was seen in subjects with IFG.

Table 5: Distribution of Glucose Intolerance in Subjects by Treatment Duration

	Treatment Duration (Months)			
Glucose Intolerance	**12-24**	**25-48**	**>48**	**P**
IGT	18(6.9)	5(7.4)	5(9)	0.51
IFG	60(23.0)	19(28)	25(44.6)	0.001
DM	20(7.7)	123(19.1)	10(17.8)	0.001

X^2= 52.0, p<0.001

DISCUSSION

Advances in the antiretroviral therapy has led to prolonged survival and improved quality of life of HIV/AIDS infected patients with the development of metabolic derengments.

The prevalence of glucose intolerance among HIV/AIDS patients on HAART in this study was (45.6%) with IFG (27%) being highest in the study subjects and IGT (19.5%), DM (19.6%) in the controls. This is comparable to previous reports by YaraSheski[14] who observed that up to 40% of HIV infected patients with lipodystrophy had impaired glucose tolerance or diabetes mellitus diagnosed on an oral glucose tolerance test (OGTT). The pathogenic mechanisms underlying the fat redistribution and metabolic alterations are multifactorial. The factors related to HIV/AIDS infection and its treatment, mitochondrial dysfunction, cytokine activation related to immune reconstitution and individual genetic predisposition are aetiological.

Grinspoon[15] observed that 35% of HIV subjects had impaired glucose tolerance and 7% had diabetes. The prevalence of metabolic syndrome observed in our study was 18.5% which was similar with the finding of Carlos et al[3] with a prevalence rate of 17% which is all attributable to the Lipodystrophic changes seen in HIV/AIDS patients with increased risks of cardiovascular disease. An increasing prevalence of glucose intolerance and metabolic syndrome with increasing BMI was observed in this study, a finding consistent with previous studies[3,16]. Obesity is strongly associated with insulin resistance and glucose tolerance.[17]

The proportion of patients with glucose intolerance were higher in HAART treated patients with moderate CD4 cell count (200 – 499 x 10^6 cells/L) while in HAART Naive patients glucose intolerance was more prevalent in patient with low CD4 cell count (< 200 x 10^6 cells/L), thus similar to the findings of Carlos J et al, who observed more risk of metabolic syndrome with reference to glucose homeostasis. El-Sadr et al[18], also noted that lower CD4 cell count confers increased risk of insulin resistance as an important marker in the development of DM. It is likely that the observed increase in prevalence of DM in this cohort of HIV-treated patients may result in increased occurrence of DM related complications similar to the non HIV DM population as reported in a recent Nigerian multicentre study by Uloko et al.[19] The HAART-experienced patient were also noted to have increased glucose intolerance and metabolic syndrome with prolonged treatment duration as observed by Justman et al[20] with a reported threefold increase incidence of self reported diabetes. Leow et al[21] also noted similar finding. Regular screening for diabetes is essential for all patients with HIV, especially those who are on HAART.[22]

CONCLUSION

The prevalence of glucose intolerance in the North-central region is high. Treatment with HAART and low CD4 cell count are strong determinants. The availability of free treatment programs in Nigeria has transformed HIV/AIDS to a chronic disease, thus leading to the development of metabolic derengements (IFG, IGT and DM). More frequent monitoring using fasting plasma glucose or 2-hour plasma glucose from oral glucose tolerance test (OGTT) may be reasonable for patients who are at highest risk because of their family history, and/or lipodystrophy ,with the view to treat early all patient with these metabolic sequelae.

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