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DIABETES MELLITUS/HIV INTERPHASE: A SERIES OF 10 CASES.
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DIABETES MELLITUS/HIV INTERPHASE: A SERIES OF 10 CASES.

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ABSTRACT

***Background*: Evidence shows that the use of protease inhibitors (PIs) in HIV/AIDS patients leads to the development of diabetes mellitus. Some degree of insulin resistance has also been noted in HIV infected patients not on protease inhibitor therapy and this may cause glucose intolerance and overt diabetes mellitus.**
***Objective*: To describe the epidemiological and laboratory characteristics associated with diabetes mellitus in HIV positive patients who are HAART naïve.**
***Design*: Cross-sectional, cohort analysis of patients with HIV infection on HIV care programme.**
***Setting*: Kisumu District Hospital and Mater Hospital.**
***Subjects*: Ten adult patients with HIV infection at initial presentation to the clinic.**
***Main Outcome Measures*: Blood Sugar, CD4+ Cell Count, body mass index (BMI) , alanine transaminase (ALT), aspartate transaminase (AST), serum lipase and amylase levels.**
***Results*: One hundred and three patients (60 males and 43 females) were screened. Ninety one (57 males, 34 females) patients were excluded because they had normal blood sugars. Twelve patients were excluded and out of these, two were further excluded due to pancreatitis. Ten patients (three males and seven females) were included in the study. The mean age and body mass index was 48.9 years (27-68) and 22.6 kg/M^2 (16.8-28.8) respectively. All patients were HAART naive. Mean fasting blood sugar was 17.8 mmol/L (15.4-27.1), mean CD4+ cell count was 236.9 cells/μl (12-885). There was no family history of diabetes mellitus. Mean ALT, AST, serum amylase and lipase levels were all normal at 34 IU/L, 28.4 IU/L, 76.7 IU/L and 34.96 IU/L respectively. The patients were not on diabetogenic drugs or steroids.**
***Conclusion*: Diabetes mellitus is recognised in patients having HIV/AIDS who are HAART naïve. They had low mean CD4+ cell count. The body mass indices (BMIs) were all normal and all were type II diabetics (T2DM). Adequate screening should be done to detect this metabolic syndrome early enough, escpecially where a family history of diabetes and other risk factors occur.**

INTRODUCTION

While the bulk of evidence suggest that diabetes mellitus in HIV/AIDS is associated with protease inhibitor (PI) use, there may also be an HIV disease-associated component in highly active anti-retroviral therapy (HAART) naïve HIV positive patients (1-3). There is a degree of insulin resistance in patients infected with HIV, who are not on PI therapy (4).

The incidence of overt diabetes mellitus in HIV population ranges from as low as 1-2% to as high as 6-7% (2,3,8), diagnosed on a two hour post-prandial blood glucose values > 200 mg/dl (11.1 mmol/L), after oral glucose tolerance test (OGTT) (5-7).

Pancreatic beta cell function or insulin secretion might also be affected by HIV infection or its treatment. This causes decreased beta cell responsiveness to glucose and subsequent development of overt diabetes mellitus (8, 9). HIV infection itself may be associated with insulin resistance and truncal obesity. Drugs other than PIs which are commonly used in the treatment of patients with HIV and may alter

glucose metabolism include (4):

Agent	Mechanism of action
Glucocorticoid	Insulin resistance
Human growth hormone	Insulin resistance
Megasterol acetate	Insulin resistance
Androgenic steroid	Insulin resistance
Pentamidine	β cell dysfunction
Didanosine	β cell dysfunction

The association of diabetes mellitus and HIV has received little attention hence the reason of this study.

Inclusion criteria: Patients who presented with signs and symptoms suggestive of diabetes mellitus and hyperglycaemia in a cohort of HIV positive HAART naïve patients.

Exclusion criteria: Patients who were symptomatic for diabetes mellitus, were HIV positive, HAART naïve and had normal blood sugar levels.

Study: On going prospective, longitudinal, descriptive, consecutive entry of patients included in the study.

MATERIALS AND METHODS

The patients who were HIV positive gave signed informed consent for fasting blood sugar test to be done. The other parameters assessed included height (Cm), weight (Kg), (body mass index Kg/M^2), urinalysis, Serum amylase and lipase (to rule out pancreatitis seen in HIV patients with or without HAART causing glucose metabolism abnormalities) and CD4+ cell counts. Alanine transaminase (ALT) and aspartate transaminase (AST) were analysed to assess any non-alcoholic fatty liver disease (NAFLD) correlation which is associated with a degree of glucose intolerance.

Also included was family history of diabetes mellitus, concomitant/chronic drug use which are potentially diabetogenic (steroids), history of fatigue, blurred vision, weight loss, polyuria and polydipsia. Further counselling was done and sustained to ensure compliance with HAART and oral hypoglycaemic agents (OHAs) and advised to be followed up in the diabetes outpatient clinic.

Under aseptic condition, 10 mls whole blood was drawn from the cubital vein for analyses of complete blood count (CBC), fasting blood sugar and CD4+ cell counts, serum amylase and lipase levels and AST, ALT levels. Body weight (Kg) was taken using the Salter weighing machine, height (Cm) was taken using the tape measure. Alanine transaminase (ALT) and aspartate transaminase (AST) were analysed using the reverse passive haemaglutination test assay (RPHA), fasting blood sugar (FBS) was analysed using a glucometer and complete blood count was done using coulter counter machine. CD4+ cell count was analysed by fluorescent activated cell sorter (FACS) flow cytometry method with a sensitivity of 1-2000 cells/μl.

Urine was also tested by dipstick method.

The patients who had fasting blood sugars done were those who had polyuria, polydipsia, and oral candidiasis as pointers to diabetes mellitus.

One hundred and one (60 males and 41 females) were screened, 80 (57 males and 23 females) were excluded; they did not have polyuria and polydipsia. Twenty one patients were enrolled out of whom nine (four males, five females) had normal blood sugars and were also excluded. The twelve patients included (four males and eight females) had hyperglycaemia.

Intervention: HAART was promptly initiated in all the patients (self-purchased and some sent to Nairobi Rheumatology Clinic (for free HAART). Oral hypoglycaemic agents glibenclamide and or metformin was initiated and the dose adjusted to adequate controlling levels. One patient was admitted for rehydration; Herpes simplex virus was treated with acyclovir, Oral candidiasis was treated with oral fluconazole and all the patients are on follow up at the diabetes out patient clinic (Kisumu District Hospital, Nairobi Rheumatology Clinic).

RESULTS

The results are summarised in Table 1. All patients were HIV positive and had type II diabetes mellitus. The mean fasting blood glucose was 17.8 mmol/L (range 15.4 – 27.1) and the normal range is 2.5-6.1 mmol/l. From the 12 patients with hyperglycaemia, two were excluded from the study because they had pancreatitis. Their serum amylase and lipase levels were 341 IU/L and 500 IU/L and 117 IU/L, and 190 IU/L respectively (normal range amylase 35-118 IU/L and lipase 2.3-50.0 IU/L). One patient

had florid angular stomatitis. All the urinalysis tests were normal.

The M:F ratio was 3:7 and mean age was 48.9 years . The mean fasting blood sugar and CD4+ cell count was 17.8 mmol/L (15.4-27.1) and 236.9 cells/μl (12-885) respectively. Two patients had CD4+ cell counts > 350 cells/μl and eight patients had CD4+ cell counts < 350 cells/μl.

The co-morbidities were herpes zoster virus 1, oral candidiasis 10, hypertension 1 and deep venous thrombosis (DVT) 1. One patient used commercial herbal/vitamin supplements (GNLD) "to boost the immunity" while other patients did not have any concomitant drug use. No deaths occurred and the patients are on follow up at the diabetic outpatient clinic.

Table 1

Epidemiological and laboratory characteristics of the 10 patients, who are HAART naïve, with diabetes mellitus and HIV infection.

Parameter	Mean (Range)
Females	7
Males	3
Mean age (years)	48.9 (27-68)
Body mass index (Kg/M2)	22.6 (16.8-28.8)
Family history of diabetes mellitus	NIL
ART use	NIL
Fasting blood sugar (2.5-6.1 mmol/L)	17.8 (15.4-27.1)
Mean CD4+ cell counts(350-1600 cells/μl)	236.9 (12-885)
CD4+ cell counts > 350 cells/μl	716 (547 and 885)-2 patients.
CD4 + cell counts < 350 cells/μl	117.1 (12-300)-8 patients.
AST (5-37 IU/L)	28.4 (19-37)
ALT (5-40 IU/L)	34.0 (31-89)
Serum amylase (35-118 IU/L)	76.7 (50-93)
Serum Lipase (2.3-50.0 IU/L)	34.96 (15-48)
Urinalysis	Glycosuria ++++, and bacteria-Nil
Concomitant drugs used	9-Nil, 1-commercial herbs/multivitamin supplement.

ART-anti-retroviral therapy

DISCUSSION

Evidence shows that insulin resistance may be associated with HIV infection in patients not receiving anti-retroviral therapy (ARTs) or protease inhibitors (PIs). This case series shows type 2 diabetic patients with normal body mass indices (BMI), no family history of diabetes mellitus, a low CD4+ cell count mean of 236.9 cells/μl and preponderance of oral candidiasis as an opportunistic infection. Indeed, oral candidiasis has also been shown to be associated with low CD4+ cell counts < 200 cells/μl, in studies done at Kenyatta National Hospital and Moi Referral and Teaching Hospital respectively (10,11). This implies that the patients with oral candidiasis should be screened for diabetes mellitus and the fasting blood sugar level assessed will help elucidate the prevalence of diabetes mellitus in HIV/AIDS patients, which is currently unknown.

Evidence shows that regardless of causality, there is a high prevalence of insulin resistance in patients infected with HIV and a frequently co-existing dyslipideamia and abdominal obesity, which may increase the development of cardiovascular morbidity in this population (1, 2, 13, 14). A study done in Kenya showed that HIV-infected patients at the Kenyatta National Hospital Comprehensive Care Clinic demonstrated a high prevalence of dyslipidaemia with high levels of total low density lipoproteins (LDL) cholesterol and triglycerides

(15). As is the case in the general population, the prevalence of impaired glucose tolerance (IGT) and insulin resistance significantly exceeds the prevalence of overt fasting hyperglycaemia (4).

Frank diabetes mellitus could therefore be considered only the "tip of the iceberg" in the HIV infected and general population and must be actively looked for.

Deep venous thrombosis (DVT) in one patient and hypertension in two patients, could be complications of the diabetes mellitus. The deep vein thrombosis (DVT) could also be due to the hypercoagulable state due to the severe HIV itself as depicted by the low CD4+ cell counts in this cohort of patients (16).

Other factors which have been noted to interact in the development of diabetes mellitus in HIV infected patients include a higher body mass index (BMI > 30 Kg/M2), higher ALT > 66 IU/L and a strong family history of diabetes mellitus (2,3). In this cohort, the patients had normal BMI, ALT and AST (implying no liver injury) and no positive family history of diabetes mellitus. Study done in Kenya showed that most of the type 2 dibetics were lean (personal observation– C. F. Otieno).

It is noteworthy that HIV infection causes a general inflammatory process with the production of tumor necrosis factor α and interleukin (IL)-6. These may cause inflammation of the pancreas and lead to the development of diabetes mellitus. Studies should therefore be done to evaluate this plausible association. There could also be a direct HIV involvement of the pancreas leading to diabetes mellitus.

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