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ORIGINAL RESEARCH

Metabolic Control and Determinants Among HIV-Infected Type 2 Diabetes Mellitus Patients Attending a Tertiary Clinic in Botswana

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Purpose: We primarily aimed at determining the prevalence of metabolic syndrome and abnormal individual metabolic control variables in HIV-infected participants as compared to HIV-uninfected participants given current concerns. Our secondary objective was to determine the predictors of metabolic syndrome and individual metabolic control variables among the study participants to guide future management.

Patients and Methods: A descriptive, case-matched cross-sectional study for four months from 15th June 2019 to 15th October 2019 at Block 6 Diabetes Reference Clinic in Gaborone, Botswana. We compared the proportions of metabolic syndrome and individual metabolic control variables based on gender and HIV status by means of bivariate analysis (Chi-squared test or Fisher's exact test) to determine factors associated with metabolic control. A p-value of less than 0.05 was considered statistically significant.

Results: Overall, 86% of the study participants were found to have metabolic syndrome by International Diabetes Federation (IDF) criteria with 79.8% among HIV-infected and 89.1% among HIV-negative participants (p-value = 0.018). Older age was significantly associated with metabolic syndrome (p-value = 0.008). Female gender was significantly associated with metabolic syndrome as compared to male gender (P-value < 0.001), and with a statistically significant higher proportion of low HDL-C compared to males (P-value < 0.001). Female participants were significantly more likely to be obese as compared to males (P-value < 0.001). High triglycerides were more common in HIV-infected compared to HIV-negative participants (P-value = 0.004). HIV-negative participants were more likely to be obese as compared to HIV-infected participants (P-value = 0.003).

Conclusion: Metabolic syndrome is an appreciable problem in this tertiary clinic in Botswana for both HIV-infected and HIV-negative participants. Future prospective studies are warranted in our setting and similar sub-Saharan settings to enhance understanding of the role played by HAART in causing the metabolic syndrome, and the implications for future patient management.

Keywords: human immunodeficiency virus infection, HIV, diabetes mellitus, metabolic syndrome, sub-Saharan Africa, Botswana

Introduction

Diabetes Mellitus (DM) is a major public health concern worldwide and is rapidly increasing in sub-Saharan Africa, where it is projected to affect approximately 47 million people by 2045, almost three times the number in 2015.[1,2] In Botswana, diabetes is also an emerging problem, and even when the real prevalence is currently unknown, current estimates indicate that at least 4.8% of adults aged 20–79 years were affected by DM in 2017, rising to 5.8% in 2019;[3] an appreciable increase from 0.47%

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reported in 2004 by the International Diabetes Federation (IDF).[4,5] This reflects growing concerns with the increased prevalence of DM across sub-Saharan Africa (SSA) increasing mortality rates, with an appreciable number of patients undiagnosed as well as sub-optimally managed.[6,7] The care of patients with diabetes is multifaceted involving more than just glycemic control. Randomized controlled trials have demonstrated benefits from intensive control of blood pressure and lipids in patients with diabetes, leading to the formation of American Diabetic Association (ADA) goals for blood pressure and lipids.[8,9]

An interaction between infectious and non-communicable diseases (NCDs) has become an emergent problem across SSA given the high prevalence rates of both and is creating additional challenges for health systems in SSA.[10–12] The combination of DM and HIV infection represents a collision of two chronic conditions adversely affecting patients and healthcare systems in SSA and wider.[13] Studies have shown an increase in poor glycemic control among DM patients who are HIV-infected with only 50–54% of them meeting the ADA HbA1c goal.[13–16] Similarly, Davies found that only 46% of patients with both DM and HIV achieved the ADA HbA1c goal of 7%.[17] According to Satlin's cross-sectional study where 33% of diabetic HIV-infected patients had inadequate glycemic control, factors associated with inadequate glycemic control included a more recent diagnosis of HIV, use of insulin or any diabetes medication, and higher triglyceride levels.[9] Protease inhibitors (PI) use was associated with lower rates of meeting the ADA goal for HDL cholesterol among patients attending HIV clinics in New York, USA, whereas being male or not of African American ethnicity and use of an older Nucleoside Reverse Transcriptase Inhibitor (NRTI) were associated with lower rates of meeting the ADA goal for triglycerides.[9] Previous global and regional studies have also shown that metabolic control among diabetic HIV-infected patients to be determined by both socio-demographic and economic factors; with age, body mass index, waist–hip ratio, central obesity and smoking being independently associated with metabolic disorders.[5,18–20]

The past few decades have resulted in appreciable improvements in the clinical outcomes of HIV-infected patients, mostly due to highly active antiretroviral therapy (HAART). Benefits of HAART include suppression of the viral load, improvement in CD4 count, decrease in opportunistic infections, reduction of length of hospital stay, and a reduction in mortality.[21] However, the use of HAART has also resulted in an increase in metabolic dysfunction, including insulin resistance, diabetes, dyslipidemia and lipodystrophy.[22,23] Even before the availability of HAART, Grunfeld et al and others found that patients with AIDS had elevated plasma triglyceride and free fatty acid levels.[24,25]

Several studies have evaluated the lipid profile in diabetic HIV-infected patients and most of these have shown that less than 50% of patients achieve the goal of ADA related to HDL-cholesterol and triglycerides.[9,15–17] Diabetic HIV-infected patients have unique potential cofactors for inadequate metabolic control including the use of specific antiretroviral medications such as nucleoside reverse transcriptase inhibitors (NRTIs) and Protease inhibitors (PIs).[9,26,27] Although the prevalence of inadequate metabolic control in the general diabetic population has been estimated in a large number of studies,[28–33] only a few studies have estimated this prevalence in HIV-infected patients and most of them have assessed the achievement of ADA goal for glycemic control rather than comparing the metabolic control variables among groups of diabetic, HIV-infected and HIV-negative patients.[9,14–17,28]

According to the UNAIDS report of 2016, Botswana has the third highest HIV prevalence in the world with the latest reports estimating prevalence rates of 22.2% for the general population and 24% for 15 years and above age group.[34] Botswana was the first African country to establish a National HIV Treatment Program and it has developed substantially over the last decade.[27] The key characteristic is that care is universal and free, making antiretroviral treatment available to all eligible citizens. It was estimated that in 2015 approximately 264,000 adults living with HIV were receiving antiretroviral treatment in Botswana, a coverage of 78%, up from 69% in 2013.[34] With access to treatment, HIV-related mortality in Botswana has declined from 6% in 2003 to 1% in 2011, which is encouraging.[34,35]

However, in Botswana, where DM is a significant and growing health problem along with a known high burden of HIV infection,[34] we are unaware of any documented research reporting prevalence and predictors of metabolic control among diabetic HIV-infected patients. We believe a better understanding will improve awareness of dual comorbidities and hence tailor scarce resources to the better management of patients with both diabetes and HIV infection in Botswana and among similar SSA countries with a double burden of DM and HIV-infection. This is

particularly important at this time as the COVID-19 pandemic with various lockdown and other measures has negatively impacted on the care of patients with both infectious and non-infectious diseases across Africa and wider.[36–38] Consequently, in the first instance, we principally sought to determine the prevalence of metabolic syndrome and abnormal individual metabolic control variables among HIV-infected patients in Botswana compared to HIV-negative patients. Our secondary objective was to determine the socio-demographic and clinical predictors of metabolic syndrome and individual metabolic control variables among study participants to guide future management.

Patients and Methods

Study Design, Setting and Subjects

A descriptive case-matched cross-sectional study was conducted from 15th June 2019 to 15th October 2019 at Block 6 Diabetes Reference clinic in Gaborone, Botswana. This is a leading clinic in Botswana offering various services to an estimated 3000 diabetic patients. Services include physician consultations, dietician, diabetes self-management, health education, eye and foot screening, laboratory services and the issuing of medicines. Within this population, cases were identified among patients with Type 2 DM who were confirmed to be HIV-infected and on treatment and matched to similar cases in terms of gender but HIV-negative. Cases and matches were enrolled at a ratio of 1:2. The sample size was calculated by OpenEpi, Version 3, an open source calculator, by using Fleiss Statistical Methods for rates and proportion.[39] The assumption used in the sample size calculation was a prevalence of 76.3% of glucose metabolic disorders among cases[12] and a prevalence of 61.8% among the controls.[40]

With the intention of two-sided confidence-level (1-alpha) of 95% and power of 80% with a ratio of cases to control of 1:2, we estimated a minimum sample size for cases of HIV of 119 patients and 238 for control matches; with an estimated total sample size of 357 patients. The majority of enrolled participants were those who visited the clinic for physician consultations. Some patients were also recruited from the other services such as dietitians, eye clinic and nurse educators. Enrollment was undertaken on a daily basis from Monday to Friday. Routinely at block 6 clinic, physicians complete attendance sheets which include recent HIV status. Consequently, physicians consecutively identified patients who were HIV-infected and subsequently introduced the study and asked for their willingness to participate. Patients who agreed were subsequently directed to the research assistants for consenting and enrollment into the study.

For each identified case, each doctor identified two matches by gender and also referred them to the research assistants for consenting and enrollment. Inclusion criteria for this study involved having a documented diagnosis of type 2 DM and documented results of HIV status in the past year. On the other hand, patients with type 1 DM, confirmed pregnancy, and those who did not consent were excluded from the study.

Data Collection

After signing an informed consent form, patients were interviewed by trained research assistants. A semi-structured questionnaire was used with components adopted from the WHO STEPs questionnaire.[41] Additional variables were subsequently included in the questionnaire. These included patients' demographic characteristics (age, gender, marital status and educational level) as well as clinical variables (durations of both diseases, ie, diabetes mellitus and HIV, modality of treatment for DM and antiretroviral (ARV) medication regimen (s) and duration).

All recruited patients had their blood pressure taken on the day of the interview using a digital blood pressure device while in a sitting position after a 10-minute rest period. This was performed before consultations. Anthropometric measurements including weight and height were also performed in order to calculate the body mass index (BMI) of patients using the following formula: weight (in Kilograms) divided by height squared (m^2). Waist and hip circumference were also measured to enable calculations of waist/hip ratio for categorizing their central obesity status. Research assistants involved in measuring weight, height, waist/hip circumference were oriented on standard measurement procedures before data collection was initiated.

Laboratory Investigations

Laboratory tests are undertaken routinely at block 6 clinic as a standard of care; consequently, patients did not incur any additional co-payment costs for these tests. These tests are usually performed in a non-fasting state at 3–6-month intervals. If patients' results of lipid profile {total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides} and glycated hemoglobin

(HbA1c) were available and within 3 months prior to data collection, they were recorded as current results; otherwise, patients were referred to the laboratory for venesection on the same day of the interview. Blood was collected at the block 6 clinic laboratory under aseptic techniques to obtain 5–10 ml in plain tubes for the tests. The result of recent CD4 counts and viral load (for cases) were obtained from the electronic medical records and all the results were within 6 months of the day of the interview. Patients attending doctors' consultation were usually tested for either fasting blood glucose or post-prandial blood glucose (finger prick capillary blood test) routinely before they were attended; hence, these results were routinely available.

Study Definitions

The body mass index (BMI) was classified as either non-obese (<30 kg/m^2) or obese (≥30 kg/m^2) according to the WHO classification.[42] The WHO STEPS protocol was adhered to with the waist circumference measurement made at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest whereas the hip circumference measurement was taken around the widest portion of the buttocks.[43,44] According to the WHO classification, central obesity was defined as waist/hip ratio of ≥0.85 for women and ≥0.90 for men.[45]

Metabolic syndrome was categorized according to the new IDF criteria[46] which included waist circumference of ≥80cm for women/≥94cm for men plus at least two of the following:

Triglycerides ≥ 1.7 or HDL < 1.3 for women/1.0 for men

OR

Systolic blood pressure (SBP) ≥130mmHg or Diastolic blood pressure (DBP) ≥85mmHg or being on treatment for hypertension

OR

Fasting blood glucose >5.6 mmol/l or previous diagnosis of type 2 diabetes mellitus.

Individual metabolic control variables were defined according to American Diabetes Standard of Care 2019/ SEMDSA 2017 guidelines.[47,48] The following indicated poor metabolic control: HbA1c >7.0%, LDL-C >1.8 mmol/l, HDL-C <1.0 for male and <1.3 mmol/l for female, Triglycerides>1.7 mmol/l, total cholesterol >4.5 mmol/l, fasting blood glucose >7.2 mmol/l, postprandial glucose >10.0 mmol/l, Systolic blood pressure (SBP) >140mmHg, diastolic blood pressure (DBP) >90mmHg.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) software version 21 was used for data entry, cleaning and analysis. Frequency and percentages were used to describe the data. We compared the proportions of metabolic syndrome and individual metabolic control variables based on gender and HIV status by means of Chi-squared test or Fisher's exact test using bivariate analysis to determine factors associated with metabolic control. A p-value of less than 0.05 was considered statistically significant.

Ethical Considerations

Ethical clearance was obtained from the University of Botswana, Ministry of Health and Princess Marina Hospital Institutional Review Boards. The study adhered to the principles of the Declaration of Helsinki.[49] The purpose of the study was fully explained to participants and they individually signed a written informed consent form administered in either Setswana or English, depending on which language the participant was comfortable with, prior to enrolment into the study. Patients received the standard of care and the study did not incur any costs to study participants. All participants were free to withdraw from the study at any time they wished to do so and this would not result in them receiving substandard care. To ensure patient confidentiality, the study participants were identified with unique identification numbers. Study information was stored in a secure cabinet at the University of Botswana and this was only accessible to the Principal Investigator.

Results

Studied socio-demographic and clinical characteristics including marital status, diabetes duration and history of hypertension and the use of lipid-lowering drugs were similar between HIV-infected and HIV-negative participants. There was though a significant difference in age categories between HIV-infected and HIV-negative participants (P-value = 0.011). There was also a significant difference in the regimen of antidiabetic treatment with HIV-infected participants more likely to be on combined oral hypoglycemic medications and insulin therapy regimen as compared to HIV-negative participants (37.0% versus 23.9%, P-value= 0.020) [Appendix Table 1].

Over half of the HIV-infected participants were diagnosed more than 10 years prior to the study (56.3%). Almost all the HIV-infected participants, 118/119

(99.2%), were on HAART with 88.6% and 98.2% having CD4 counts of ≥350umol/l and undetectable viral loads, respectively. The rest of the characteristics of studied HIV-infected participants are depicted in [Table 1].

Overall, 86% of the study participants were found to have metabolic syndrome by IDF criteria. The difference in proportions of metabolic syndrome between HIV-infected (79.8%) and HIV negative (89.1%) participants was statistically significant (P-value = 0.018) [Table 2].

Age was significantly associated with metabolic syndrome (P-value = 0.008) with proportions with metabolic syndrome for age group ≥40 years ranging between 87.4% −89.7% compared to 67.6% for the age group <40 years. Female gender was significantly associated with metabolic syndrome as compared to males (95.2% versus 69.0%) (P-value <0.001). Marital status, level of education, and diabetes duration were similar between participants with/without the metabolic syndrome. HIV-infected participants with a shorter duration since HIV diagnosis (0–9 years) were more likely to have the metabolic syndrome (88.9%–92.3%) compared to those with a longer duration since HIV diagnosis of ≥10 years (67.9%–76.7%). However, the duration since HIV diagnosis was not statistically associated with metabolic syndrome (P-value = 0.056). Other HIV-infection characteristics including the duration of HIV treatment, CD4 count, and viral load count, as well as the use of protease inhibitors, integrase inhibitors and NNRTIs, were similar between participants with/without the metabolic syndrome [Table 3].

Female gender showed a significantly higher proportion of low HDL-C compared to males (76.6% versus 50.5%) (P-value <0.001). Female participants were significantly more likely to be obese as compared to males (60.8% versus 19.4%, P-value <0.001). On the other hand, male gender was associated with a higher proportion of participants with elevated diastolic blood pressure compared to females (25.6% versus 11.7%, P-value = 0.001). As for glycemic control using HbA1c, 53.2% and 60.6% of male and female participants, respectively, had poor control with the difference not statistically significant. Central obesity was one of the commonest findings in both males and females accounting for 76.8% and 82.8%, respectively. The rest of the analyzed individual metabolic control variables including LDL-C, triglycerides, total cholesterol, and systolic blood pressure were similar between male and female participants [Table 4].

High triglyceride levels were more common in HIV-infected compared to HIV-negative participants (68.9% versus 51.4%, P-value = 0.004). On the other hand, HIV-negative participants (52.5%) were more likely to be obese (high body mass index) as compared to HIV-infected participants (34.9%, P-value = 0.003). HIV-infected participants had higher proportions of central obesity (87.4%) as compared to HIV-negative participants (77.3%). The difference was however not statistically significant (p-value = 0.057). The HIV-infected group had higher proportions of participants with both high fasting blood glucose and postprandial blood glucose compared to the HIV-negative group; however, the difference was not statistically significant. The rest of the individual metabolic control variables were similar between HIV-infected and HIV-negative participants [Table 5].

Discussion

We believe this is one of the first studies that has evaluated the prevalence and factors associated with metabolic syndrome in diabetic patients with HIV-infection in a country with a high prevalence of both HIV and diabetes. The published literature is rich with studies of either metabolic syndrome in HIV-infected participants or metabolic syndrome in diabetic participants; however, not the combination. We found a very high overall prevalence of metabolic syndrome of 86% in our participants regardless of their HIV status. In addition, the prevalence of metabolic syndrome was significantly higher in HIV-negative participants (89.1%) as compared to HIV-infected participants (79.8%). Previous studies in Africa have estimated a prevalence of metabolic syndrome among HIV-infected participants ranging from 13% to 58%.[50,51] We did not find studies on the prevalence of metabolic syndrome among diabetic patients in Africa; however, studies in India revealed a prevalence of metabolic syndrome ranging from 71.9% to 73.85%.[52,53] Due to the fact that both HIV-infection and DM are pro-inflammatory conditions associated with metabolic disturbances including but not limited to insulin resistance and lipoprotein disturbances, a high prevalence of metabolic syndrome was expected. The fact that metabolic syndrome was highest among HIV-negative diabetic participants emphasizes the need to look closely at individual factors that impact on metabolic syndrome in this group.

Older age was significantly associated with metabolic syndrome similar to several previous studies.[54–58] Female HIV-infected diabetic participants were significantly more likely to have metabolic syndrome compared with their male counterparts; a finding that has been consistently

Table 1 Clinical Characteristics of HIV-Infected Participants

Variables	Frequency, n (%)
HIV duration in years	
0–4	26 (21.8%)
5–9	26 (21.8%)
10–14	37 (31.1%)
15+	30 (25.2%)
HIV treatment duration in years	
0–4	39 (32.8%)
5–9	29 (24.4%)
10–14	25 (21.0)
15+	26 (21.8%)
HAART treatment status	
Yes	118 (99.2%)
No	1 (0.8%)
Initial HAART regimen	
Truvada + Efavirenz	51 (43.6%)
Combivir + Efavirenz	30 (25.6%)
Combivir + Nevirapine	18 (15.4%)
Truvada + Dolutegravir	12 (10.3%)
Others*	6 (5.3%)
Current HAART regimen	
Truvada + Efavirenz	48 (41.0%)
Combivir + Efavirenz	23 (19.7%)
Combivir + Nevirapine	12 (10.3%)
Truvada + Dolutegravir	20 (17.1%)
Abacavir + Lamivudine + Dolutegravir	9 (7.7%)
Others*	5 (4.4%)
CD4 count	
<350	13 (11.4%)
350–500	23 (20.2%)
>500	78 (68.4%)
Viral Load	
Suppressed	111 (98.2%)
Not Suppressed	2 (1.8%)
Protease inhibitor use	
Yes	2 (1.7%)
No	113 (98.3%)
Integrase inhibitor (DTG) use	
Yes	27 (23.5%)
No	88 (76.5%)
NNRTI (Efavirenz or Nevirapine) use	
Yes	87 (74.4%)
No	30 (25.6%)

Note: Others*, refers to Truvada+ Nevirapine; Truvada+ Lopinavir/Ritonavir; Truvada+ Dolutegravir; Abacavir+ Lamivudine+ Nevirapine; Abacavir+Lamivudine + Efavirenz; Abacavir+Lamivudine+ Dolutegravir.

found in previous studies.[52,56–58] HIV-infected participants had a significantly lower prevalence of obesity as compared to HIV-negative participants, a finding similar to a study by Mondy et al in the US.[54]

Table 2 Metabolic Syndrome Using IDF Criteria According to HIV Status

Variables	Metabolic Syndrome		p-value
	Yes	No	
HIV status			
Positive	95 (79.8%)	24 (20.2%)	**0.018**
Negative	212 (89.1%)	26 (10.9%)	
Total	**307 (86.0%)**	50 (14.0%)	

Note: Bold indicates statistical significance.

We found the prevalence of the metabolic syndrome to be highest during the early years of HIV diagnosis compared to later years. The difference did not reach statistical significance. Given the limitation of our study design, it is difficult to explain whether the metabolic syndrome was present before the initiation of HAART. It is possible that HAART played a part in the development of the metabolic syndrome as most patients are initiated on HAART at diagnosis, and we will be looking at this more closely in future prospective projects. Our results are similar to findings of other studies in SSA that revealed a higher prevalence of metabolic disorders after HAART initiation.[59,60]

Different classes of HAART including nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) have been shown to cause the metabolic syndrome through mechanisms such as increasing insulin resistance, reducing insulin secretion, interfering with glucose transporter type 4-mediated glucose transport, lipodystrophy, alteration in leptin/adiponectin dynamics and mitochondrial dysfunction.[27,61] The PIs have also been shown to interfere with cellular retinoic acid-binding protein type 1 (CRAB-1) which in turn inhibits peroxisomal proliferator-activated receptor γ (PPARγ). The inhibition of PPARγ leads to insulin resistance and the release of free fatty acids.[27] The prescribing of PIs was not though associated with the metabolic syndrome in our study, similar to a previous study.[12] We believe this can be explained by the small sample size as only 2/116 (1.7%) of our participants were on PIs. On the other hand, the majority of our HIV-infected participants had been on NRTI regimens containing tenofovir as it is currently part of first-line treatment for HIV patients in Botswana.[62] This may partly explain the lack of association between metabolic syndrome and NRTIs for patients who had been exposed to HAART for

Table 3 Predictors of Metabolic Syndrome (IDF Criteria) Among Study Participants

Variables	Metabolic Syndrome		p-value
	Yes	No	
Age			
21–40	25 (67.6%)	12 (32.4%)	**0.008**
41–50	70 (89.7%)	8 (10.3%)	
51–60	104 (87.4%)	15 (12.6%)	
60+	108 (87.8%)	15 (12.2%)	
Gender			
Male	87 (69.0%)	39 (31.0%)	**<0.001**
Female	220 (95.2%)	11 (4.8%)	
Level of education			
No formal school	36 (87.8%)	5 (12.2%)	0.717
Less than primary education	35 (79.5%)	9 (20.5%)	
Primary school completed	71 (86.6%)	11 (13.4%)	
Secondary school completed	109 (87.9%)	15 (12.1%)	
College/University/Post-graduate degree	56 (84.8%)	10 (15.2%)	
Marital status			
Never married	126 (86.9%)	19 (13.1%)	0.771
Currently married	127 (83.6%)	25 (16.4%)	
Separated	1 (100.0%)	0 (0.0%)	
Divorced	8 (88.9%)	1 (11.1%)	
Widowed	39 (90.7%)	4 (9.3%)	
Cohabiting	4 (100.0%)	0 (0.0%)	
Diabetes duration in years			
Less than 2	60 (77.9%)	17 (22.1%)	0.118
2–5	92 (86.8%)	14 (13.2%)	
6–10	78 (90.7%)	8 (9.3%)	
11 or more	75 (87.2%)	11 (12.8%)	
HIV duration in years			
0–4	24 (88.9%)	3 (11.1%)	0.056
5–9	24 (92.3%)	2 (7.7%)	
10–14	25 (67.9%)	12 (32.4%)	
15+	23 (76.7%)	7 (23.2%)	
HIV treatment duration in years			
0–4	34 (85.0%)	6 (15.0%)	0.650
5–9	23 (79.3%)	6 (20.7%)	
10–14	18 (72.0%)	7 (28.0%)	
15+	21 (80.8%)	5 (19.2%)	
CD4 count			
<350	8 (61.5%)	5 (38.5%)	0.189
350–500	18 (78.3%)	5 (21.7%)	
>500	65 (83.3%)	13 (16.7%)	
Protease inhibitor use			
Yes	2 (100.0%)	0 (0.0%)	0.466
No	90 (78.9%)	24 (21.1%)	

(*Continued*)

Table 3 (Continued).

Variables	Metabolic Syndrome		p-value
	Yes	No	
Integrase inhibitor (DTG) use			
Yes	19 (70.4%)	8 (29.6%)	0.190
No	73 (82.0%)	16 (18.0%)	
NNRTI (Efavirenz or Nevirapine) use			
Yes	71 (81.6%)	16 (18.4%)	0.378
No	23 (74.2%)	8 (25.8%)	

Note: Bold indicates statistical significance.

a longer duration in our study. Previous studies have also associated older regimens of NRTIs such as stavudine, zidovudine and didanosine with the prevalence of the metabolic syndrome;[61] with the effect noticeably after a longer exposure. However, this is not the case in Botswana as the guideline stipulates patients should be initiated on tenofovir-containing regimens unless there are contraindications. We did not find any association between the use of NNRTIs and the occurrence of the metabolic syndrome; similar to a previous study in the US.[54] Dolutegravir (DTG) which is an integrase inhibitor was introduced to HIV treatment guidelines in Botswana in 2016.[62] Previous studies comparing DTG to NNRTIs and PIs revealed that the former has more of a neutral effect on causing lipid abnormalities and it was only associated with more weight gain.[15,63] About a quarter of our HIV-infected participants were on DTG-containing regimen and we did not find an association between the use of DTG and the metabolic syndrome. However, this finding needs to be interpreted with caution given the shorter duration of its use in Botswana. Future studies are needed to fully assess the effect of DTG on metabolic control after a longer exposure period to establish whether the previous established weight gain effect has a role to play in the development of the metabolic syndrome in patients with HIV, and we will be following this up in future studies.

We did not find any difference in the level of glycemic control between HIV-infected and HIV-negative participants, which was also observed in previous studies in SSA;[18,64] however, 57.1% of the HIV-infected diabetic participants had poor glycemic control in our study as compared to 33% and 46% from studies in Tanzania and Nigeria, respectively.[18,64] We found that 58.1% of HIV-negative diabetic participants had poor glycemic control, in contrast to findings of US studies that had 44% and 24% of patients with poor glycemic control.[65] This variation may be explained by differences in patients' characteristics and differences in cut-off points for glycemic control with the Tanzania study using a 7.5% cut-off point while we used the ADA cut-off point of 7%. On the other hand, there was a significant difference among HIV-infected and HIV-negative participants on types of antidiabetic treatment prescribed, with the former group having a large number of patients on combination therapy of oral hypoglycemic agents together with insulin therapy. It is possible that HIV-infected participants had presented with poorer glycemic control levels necessitating insulin initiation, which ultimately resulted in seemingly similar levels of glycemic control with HIV-negative participants. This though remains to be shown.

Our results showing higher proportions of elevated fasting blood glucose (FBG) and post-prandial blood glucose (PPBG) are similar to the results of a prospective study by Zannou et al which showed similar trends after 24 months of follow up.[59] Similar trends have been observed in cross-sectional studies undertaken in the United States of America.[66,67] The results of this study are similar to those of Maganga et al in Tanzania[18] but differ from similar studies in other SSA countries which showed no differences in glucose measurements between HIV-infected and HIV-negative participants.[16,68,69] The possible reasons for the discrepancies between the various studies include differences in patients' characteristics and methods used for assessing glucose levels. The higher proportions of higher FBG and PPBG in our HIV-infected group may be related to immune reconstitution from the use of HAART as there was a trend of increasing metabolic syndrome (FBG being a component) with higher CD4

Table 4 Characteristics of Individual Metabolic Control Variables Classified from ADA Criteria According to Gender

Characteristics	Male	Female	p-value
Glycemic control (HbA1c)			
Good control (≤7%)	59 (46.8%)	91 (39.4%)	0.174
Poor control (>7%)	67 (53.2%)	140 (60.6%	
Central obesity			
Yes	96 (76.8%)	188 (82.8%)	0.159
No	29 (23.2%)	39 (17.2%)	
LDL-C			
Normal	15 (18.5%)	23 (15.9%)	0.609
High	66 (81.5%)	122 (84.1%)	
HDL-C			
Low	48 (50.5%)	141 (76.6%)	**<0.001**
Normal	47 (49.5%)	43 (23.4%)	
Triglycerides			
Normal	43 (42.2%)	75 (42.1%)	0.997
High	59 (57.8%)	103 (57.9%)	
Total cholesterol			
Normal	84 (68.3%)	146 (64.6%)	0.487
High	39 (31.7%)	80 (35.4%)	
Fasting Blood Glucose			
Normal	5 (62.5%)	5 (62.5%)	1.000
High	3 (37.5%)	3 (37.5%)	
Post-prandial blood glucose			
Normal	73 (62.9%)	139 (64.4%)	0.797
High	43 (37.1%)	77 (35.6%)	
Systolic blood pressure			
Normal	70 (56.0%)	142 (61.5%)	0.315
High	55 (44.0%)	89 (38.5%)	
Diastolic blood pressure			
Normal	93 (74.4)	204 (88.3%)	**0.001**
High	32 (25.6%)	27 (11.7%)	
Body mass index (BMI)			
Non-obese	87 (80.6%)	78 (39.2%)	**<0.001**
Obese	21 (19.4%)	121 (60.8%)	

Note: Bold indicates statistical significance.

counts though this did not reach statistical significance (p-value = 0.189). With our HIV-infected participants being largely HAART experienced, the role of HAART cannot be excluded and needs to be investigated in future prospective studies in Botswana.

Diabetes mellitus (DM) and HIV-infection are both known to be pro-inflammatory conditions with metabolic disturbances such as defective lipoprotein metabolism resulting in hypertriglyceridemia, hypercholesterolemia and low serum high-density lipoprotein.

(HDL) cholesterol.[8,24] The same observation was made in our study whereby HIV-infected participants were found to have high degrees of dyslipidemia of 39.3%, 67.7% and 68.9% for hypercholesterolemia, low serum high-density lipoprotein (HDL) cholesterol, and hypertriglyceridemia, respectively, according to ADA criteria. These findings are similar to those of Maganga et al in Tanzania.[18] A very small proportion of our participants achieved target levels of low-density lipoprotein cholesterol (LDL-C) with 14.4% and 18.4% in HIV-infected and HIV-negative

Table 5 Characteristics of Individual Metabolic Control Variables Classified from ADA Criteria According to HIV Status

Characteristics	HIV-Infected	HIV-Negative	p-value
Glycemic control (HbA1c)			
Good control (≤7%)	51 (42.9%)	99 (41.6%)	0.820
Poor control (>7%)	68 (57.1%)	139 (58.4%)	
Central obesity			
Yes	104 (87.4%)	180 (77.3%)	0.057
No	15 (12.6%)	53 (22.7%)	
LDL-C			
Normal	13 (14.4%)	25 (18.4%)	0.438
High	77 (85.6%)	111 (81.6%)	
HDL-C			
Low	65 (67.7%)	124 (67.8%)	0.993
Normal	31 (32.3%)	59 (32.2%)	
Triglycerides			
Normal	32 (31.1%)	86 (48.6%)	**0.004**
High	71 (68.9%)	91 (51.4%)	
Total cholesterol			
Normal	71 (60.7%)	159 (68.5%)	0.144
High	46 (39.3%)	73 (31.5%)	
Fasting Blood Glucose			
Normal	3 (50.0%)	7 (70.0%)	0.424
High	3 (50.0%)	3 (30.0%)	
Post-prandial blood glucose			
Normal	63 (56.8%)	149 (67.4%)	0.056
High	48 (43.2%)	72 (32.6%)	
Systolic blood pressure			
Normal	69 (58.5%)	143 (60.1%)	0.771
High	49 (41.5%)	95 (39.9%)	
Diastolic blood pressure			
Normal	100 (84.7%)	197 (82.8%)	0.638
High	18 (15.3%)	41 (17.2%)	
Body mass index (BMI)			
Non-obese	71 (65.1%)	94 (47.5%)	**0.003**
Obese	38 (34.9%)	104 (52.5%)	

Note: Bold indicates statistical significance.

participants, respectively. This is in contrast to previous studies which had targeted LDL-C levels in 50%-66% of their participants.[18,64,70–72] Hypertriglyceridemia was the only lipoprotein significantly different between HIV-infected and HIV-negative participants highlighting the possibility of diabetes mellitus playing a significant role in defective lipoprotein metabolism in both groups. The significantly high level of triglycerides among HIV-infected participants on HAART as compared to HIV-negative participants has also been observed in previous studies.[54] There is a possibility of HAART contributing selectively to hypertriglyceridemia; however, this remains to be substantiated with a prospective study given the cross-sectional nature of our study.

Despite having a high proportion of patients not reaching target LDL-C levels, only a quarter of our participants were on statins which is a concern. This compares to findings of Mwita et al in the same clinic in Botswana who found 45.5% of eligible diabetes patients were on statins.[73] Our findings are also worse than those of diabetic HIV-infected patients in Tanzania where approximately one-third of patients were on statins. Our results emphasize the need to remind physicians even in a tertiary care setting on the importance of prescribing statins to reduce LDL-C levels and subsequent cardiovascular events in eligible patients, and we will be following this up.

In our study, female gender was also significantly associated with not reaching target HDL-C levels by ADA criteria. This is similar to findings in some studies[19,53] but contradicts the findings of others which consistently showed a high likelihood of women being within target HDL-C compared to men.[64,72,74] We are not sure of the reasons behind these differences, but will be exploring this further.

Finally, our study also revealed that 34.2% of HIV-infected diabetic participants were obese. This is similar to the findings of a study in the USA which found 38.2% of HIV patients were obese.[75] HIV-negative diabetic participants had a significantly higher prevalence of obesity (52.5%). This is not surprising given that a previous study in Botswana using the same cut-off point for BMI in the same city found a prevalence of 65.5% among patients attending a private hospital medical clinic year 2005 to 2015.[76] However, our results indicate a higher prevalence of obesity compared to the general population in Botswana. According to the Botswana Demographic Survey of 2017, obesity accounted for 10.9% of the surveyed population.[77]

Strengths and Limitations

Our study has several strengths and limitations. It is the first study in Botswana to evaluate the prevalence of metabolic syndrome and individual metabolic control variables among a population of diabetic patients with HIV-infection. The study adds to the body of literature not well studied in SSA and provides an opportunity for future prospective and intervention studies in the area of

metabolic control and associated complications. However, the cross-sectional nature of this study cannot provide causal relationships rather only associations; similarly, the bivariate analysis in this study cannot control for confounding variables emphasizing the need for future prospective studies. The study was also conducted in a tertiary setting whose patients' characteristics may differ from those in the primary/secondary care settings. Despite these limitations, we believe this study has found valuable findings which we are taking forward in our clinic.

Conclusion

Overall, the metabolic syndrome is an appreciable problem in this leading tertiary diabetic clinic in Botswana among both HIV-infected and HIV-negative participants, with the presence of the metabolic syndrome significantly associated with older age and female gender. Future prospective studies are warranted in our setting and similar SSA settings to enhance the understanding of the role played by HAART in causing the metabolic syndrome. In the meantime interventions such as reminding physicians to regularly assess for individual metabolic control variables in their patients and act accordingly in a multidisciplinary approach involving pharmacotherapy is warranted including increasing use of statins as well as encouraging regular exercise and improved diet. There is also a need to devise programmes specific for diabetic HIV-infected and HIV-negative participants in Botswana to curb the worrying trend of obesity, and we will be following this up.

Data Sharing Statement

The data set generated and/or analyzed during this study are included in this submitted manuscript and is available from the corresponding author on reasonable request.

Ethical Approval

Ethical approval to conduct the study was obtained from the University of Botswana Institutional Review Board, Ministry of Health and Princess Marina Hospital Institutional Review Boards. The study adhered to the principles of Declaration of Helsinki.

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Disclosure

All authors declare no conflicts of interest for this work.

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