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Brain-derived neurotrophic factor is associated with cardiometabolic risk factors in HIV patients on combination antiretroviral therapy in Ghana

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Abstract

Background Brain-derived neurotrophic factor (BDNF) has been implicated in the development of cardiometabolic risk factors in some populations. However, few studies have investigated the role of BDNF and cardiometabolic risk factors in HIV patients despite the plethora of evidence linking HIV infection with the dysregulation of circulating BDNF levels. We investigated the association between serum BDNF and cardiometabolic risk factors in HIV patients in a primary hospital in Ghana. We recruited 450 participants, comprising 150 combination antiretroviral (cART)-treated HIV patients, 150 cART-naïve HIV patients, and 150 non-HIV controls. Data on sociodemographic parameters and medical history were collected using a structured questionnaire. Fasting venous blood samples were collected to measure plasma glucose levels, lipid profiles, and BDNF. Metabolic syndrome (MetS) was defined using the joint interim statement criteria.

Results Compared to untreated HIV patients and uninfected controls, the proportion of participants having MetS was high in cART-exposed HIV patients (26.8% vs 21.1% vs 52.1%, respectively, $p < 0.001$). Generally, BDNF levels were higher in uninfected controls compared with untreated and cART-exposed HIV patients [7.1 (3.4–13.3) vs 4.9 (2.7–9.6) vs 5.6 (2.9–8.9) ng/ml, $p = 0.025$]. In participants without MetS, square root-transformed serum BDNF was lowest in cART-exposed HIV patients, followed by untreated HIV patients, with uninfected controls having the highest (1.8 ± 0.8 vs 2.4 ± 1.2 vs 2.9 ± 1.2 ng/ml, $p < 0.001$). MetS was associated with serum BDNF levels in only the cART-exposed HIV patients [OR (95% CI) = 2.98 (1.64–5.41), $p < 0.001$]. In cART-exposed HIV patients, an increase in BDNF was associated with increased likelihood of having impaired fasting glucose [2.49 (1.51–4.11), $p < 0.001$], high systolic blood pressure [1.64 (1.1–2.46), $p = 0.016$], and hypertriglyceridemia [2.73 (1.65–4.52), $p < 0.001$], as well as decreased likelihood of having low HDL cholesterol levels [0.32 (0.19–0.56), $p < 0.001$].

Conclusion In our study population, MetS was higher in cART-exposed HIV patients. HIV patients have low levels of serum BDNF, especially those without MetS. BDNF was associated with MetS and its components in HIV patients on cART management.

Keywords Brain-derived neurotrophic factor, Metabolic syndrome, Cardiometabolic risk factors, HIV, cART

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Background

Brain-derived neurotrophic factor (BDNF) is a neuropeptide that influences the development and functional processes of neuronal tissues in the central and peripheral nervous system. BDNF exerts its physiological action by binding to its receptor, TrkB [1, 2]. BDNF and its receptors have been reported to be present on adult endothelial cells, pancreatic islets, and skeletal muscles [1] as well as playing important roles in cardiovascular function and metabolism in peripheral tissues [1, 3, 4]. Therefore, abnormal circulating BDNF levels and functions may be associated with cardiometabolic risk factors [5] and the development of CVDs [6]. In non-HIV populations, abnormal BDNF levels have been reported in heart diseases like myocardial infarction or unstable angina pectoris [7]. In addition, studies have reported that HIV infection, via the viral envelope proteins, affects the synthesis, release, and functioning of BDNF [8–11].

The introduction and widespread accessibility of combination antiretroviral therapy (cART), even in developing countries in the sub-Saharan Africa region has reduced deaths associated with AIDS [12, 13]. However, as the worldwide infection rate of the human immunodeficiency virus (HIV) has been reducing for years now, the sub-Saharan Africa region has been experiencing rising infections and it is estimated that about 70% of new infections occur in this region [14]. This means that HIV patients now can live longer to experience the chronic effects of HIV infections and medication. It has been reported that the burden of non-communicable diseases such as diabetes, hypertension, cancers, and cardiovascular disease (CVDs) in HIV patients far exceeds that of the general population [13, 15]. HIV replication and cART are associated with increased systemic subclinical inflammation [16, 17] which may lead to the development and constellation of cardiometabolic risk factors to form what is called metabolic syndrome (MetS). MetS has been associated with the future occurrence of diabetes, CVDs, and other chronic diseases in HIV and the general population [18].

HIV infection dysregulates the immune system which is very important in the regulation of BDNF synthesis. CD11a is important for normal lymphocyte development [19]. Cytokines secreted by type 2 helper T lymphocytes promote the synthesis of BDNF and downregulate interferon and IL-22 secretion by type 1 helper T cells with secretion of IL-10 remaining unaffected [20]. Other infections also affect the expression of BDNF through the activation of the Toll-like receptors from the host immune defense [21] to activate the NFκB, which is necessary to increase BDNF expression [22]. In HIV patients, most of the studies investigating the functions of BDNF focused on neuroplasticity and neuropsychiatric disorders [8–11]. However, BDNF also regulates the metabolic process in the body and has been implicated in the pathogenesis of CVDs [23]. For instance, BDNF decreases inflammation by attenuating IL-1β induction of ICAM-1 mRNA expression and secretion in human microvascular endothelial cells [24]. Also, sVCAM-1 has been reported to inversely correlate with serum BDNF in healthy men [24]. From our literature search, we did not find any study that has associated levels of circulating BDNF with cardiometabolic risk factors in HIV patients. In addition, there is a paucity of data about BDNF in the sub-Saharan African population. We, therefore, compared the levels of serum BDNF in HIV patients, with or without cART treatment, to that of non-HIV controls. We also investigated the association between serum levels of BDNF and cardiometabolic risk factors in HIV patients. We hypothesized that HIV infection would reduce circulating BDNF levels and this may be associated with cardiometabolic disorders.

Methods

Setting and participants

The study utilized a case–control design with the cases being already diagnosed HIV patients and the controls being non-HIV individuals, recruited conveniently during their visit to the HIV clinic for voluntary testing of their HIV status. For HIV patients, systematic random sampling was employed as every third patient attending the clinic was invited to participate in the study. We intentionally recruited similar numbers of non-HIV controls, HIV patients as newly diagnosed patients who are yet to be placed on cART (cART-naïve) and those already on cART (cART exposed patients). Participants who have been diagnosed and/or treated for diabetes, CVDs, clinical depression, sleep problems, and other clinical neuropsychiatric conditions were excluded from the study. These conditions can activate platelets and mean platelet volume [25]. Serum BDNF levels are reported to be higher in T2DM patients with increased platelet activation compared to those with normal platelet activation [26]. The study was carried out at Atua Government Hospital, which is a 150-bed primary healthcare facility, located in Agormanya, a peri-urban town in the Eastern region of Ghana.

We conducted the study following the ethical principles set up in the Helsinki Declaration on Human Experimentation, 1964, with subsequent revisions, latest Seoul, October 2008. The study proposal was approved by the Ethics and Protocol Review Committee of the College of Health Sciences of the University of Ghana (Protocol ID number: CHS-Et/M.6–5.17/2018–2019), and all the participants provided written voluntary informed consent before enrolling into the study.

Data collection

We collected data on basic personal and lifestyle using a structured questionnaire. Anthropometric characteristics such as body weight, height, waist, and hip circumferences were measured with appropriate instruments. Blood pressures were measured with an Omron blood pressure monitor (BF- 508, Omron Healthcare, Inc.).

Biochemical analysis

Using an aseptic technique, 5 ml of fasting venous blood samples were drawn from each participant and the serum/plasma extract was stored at − 80 °C for analysis. A semi-automated chemical analyzer (Contec BC 400, China) was used to measure the levels of plasma glucose and lipid profiles. A FACScan flow cytometer (Becton–Dickinson, NJ, USA) was used to assay CD4 + lymphocyte levels.

We applied the joint interim statement criteria [18] to define metabolic syndrome as participants meeting three or more of the following: "(1) abdominal obesity (waist circumference ≥ 94 cm for men and ≥ 80 cm for women), (2) high triglycerides ≥ 1.7 mmol/L, (3) low HDL cholesterol: men < 1.0 mmol/L or women < 1.3 mmol/L, (4) high BP (systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg), and (5) fasting plasma glucose (FPG) ≥ 5.6 mmol/l".

Serum BDNF levels were assayed using commercial ELISA kits (DuoSet, R&D Systems, Minneapolis, MN, USA) and following the manufacturer's instructions. All samples were assayed in triplicate, and the technician did not know the HIV status of the samples. The lower detection limit was 5 pg/ml, and the inter- and intra-assay coefficients of variation were less than 5%. The concentrations are expressed as nanograms per milliliter.

Sample size and data analysis

Since no study has reported serum levels of BDNF in sub-Saharan African HIV patients, we used data from a closely related racial group, the African-American HIV patients [27]. A minimum of 144 participants were required in each group to detect an effect size (f-type) ≥ 0.3, with a power of 90% and a significance level of 95%. We, therefore, recruited 150 participants for each group.

Data were analyzed using the Jamovi 2.3.13 software. The differences in the mean values of anthropometric indices, biochemical analytes, sociodemographic, and clinical variables were analyzed using ANOVA for continuous variables and Pearson's χ^2 test for categorical variables. Analysis of the distribution of serum BDNF values using the Shapiro-Wilks test showed that they were positively skewed, and therefore, square root transformation was applied to normalize the data, and the transformed values were used for analysis (Figure S1, supplementary file). We performed a correlational analysis between BDNF and the characteristics of the study participants and presented the degree of association using the Pearson correlation coefficient (Table S1, supplementary file). Multiple linear regression analyses were used to identify the main predictors of variability in BDNF (Table S2, supplementary file), and multivariable logistic regression analyses were used to determine the association between serum BDNF and metabolic syndrome. $p < 0.05$ was considered statistically significant.

Results

General characteristics of study participants

The various study groups were similar in terms of mean age, BMI, systolic and mean BPs, HDL cholesterol, CD4 cell count, marital status, and hypertension. In comparison to other study groups, cART-exposed HIV patients had higher mean levels of waist circumference, waist-hip ratio, percentage of body fat, mean and diastolic blood pressure, heart rate, FPG, triglycerides, total, and LDL cholesterol. Serum levels of BDNF were higher in non-HIV controls compared to untreated and cART-treated HIV patients, with the latter groups being similar in serum BDNF levels (Table 1).

The duration of HIV infection in cART-exposed HIV patients was 7.8 (3.7–12.1) years with the mean duration on cART management being 7.5 (4–11.7) years. For the cART exposure, 86 (57.3%) patients were on TDF-based regimens, 52 (34.7%) patients were on AZT-based regimens, and 12 (8%) patients were on LPV/r-based regimens.

MetS and BDNF levels among study participants

HIV patients on cART had a higher prevalence of MetS compared to untreated HIV patients and uninfected controls (Fig. 1; $\chi^2 = 52.6$, $p < 0.001$). In uninfected controls, those with MetS had higher levels of serum BNDF when compared to those without MetS. In the cART-naïve HIV patients, those having MetS had similar levels of serum BDNF as those without MetS. In the cART-exposed HIV patients, those with MetS had higher levels of serum BDNF compared to those without MetS. In participants without MetS, non-HIV controls had the highest levels of serum BDNF, followed by cART-naïve HIV patients, with the cART-exposed HIV patients having the lowest levels of serum BDNF. Among participants with MetS, BNDF levels were similar irrespective of HIV status (Fig. 2). In cART-exposed HIV patients, BDNF levels were similar among participants on various cART regimens (Fig. 3).

Table 1 General characteristics of study participants

	All participants	Non-HIV controls	cART-naïve HIV	cART-exposed HIV	*p*
N	450	150	150	150	
Age, years	38.6 ± 11.5	37.4 ± 13.5	37.8 ± 12.2	39.4 ± 10.6	0.109
Females, *n* (%)	301 (66.9)	101 (67.3)	82 (54.7)	118 (78.7)	< 0.001
Married, *n* (%)	158 (42.7)	55 (44.4)	56 (41.8)	47 (42)	0.79
Current smoking, *n* (%)	18 (4)	2 (1.3)	4 (2.7)	12 (8)	0.008
Alcohol intake, *n* (%)	92 (20.4)	35 (23.3)	41 (27.3)	16 (10.7)	< 0.001
Waist circumference, cm	87 ± 12	85 ± 11	84 ± 11	89 ± 12$^{\#*}$	0.002
Hip circumference, cm	102 ± 11	104 ± 10	100 ± 11*	102 ± 11	0.028
Waist-hip ratio	0.86 ± 0.07	0.83 ± 0.05	0.85 ± 0.08*	0.89 ± 0.07$^{*\#}$	< 0.001
Body height, cm	164 ± 8	163 ± 7	165 ± 4	161 ± 9	0.194
Body weight, kg	60 ± 13.2	67.8 ± 12.8	64.9 ± 12.1	64.7 ± 12.8	0.204
BMI, kg/m^2	24.8 ± 5	25.4 ± 4.6	23.9 ± 4.4*	24.6 ± 4.8	0.061
BMI categories, *n* (%)					< 0.001
Underweight	36 (8.1)	5 (3.4)	18 (12)	13 (8.7)	
Normal	221 (49.4)	63 (42.9)	89 (59.3)	69 (46)	
Overweight	125 (28)	51 (29.8)	20 (13.3)	54 (36)	
Obese	65 (14.5)	28 (19)	23 (15.3)	14 (9.3)	
Systolic BP, mmHg	133 ± 17	131 ± 14	132 ± 20	134 ± 20	0.184
Diastolic BP, mmHg	82 ± 12	79 ± 9	82 ± 13	84 ± 14$^{*\#}$	0.008
Mean BP, mmHg	101 ± 13	97 ± 11	98 ± 15	105 ± 15$^{*\#}$	0.007
Pulse BP, mmHg	52 ± 12	51 ± 14	51 ± 11	52 ± 10	0.672
Heart rate, bpm	75 ± 10	73 ± 7	74 ± 8	81 ± 9$^{*\#}$	< 0.001
Hypertension, *n* (%)	147 (32.7)	47 (31.3)	41 (27.3)	59 (39.3)	0.078
FPG, mmol/l	5.3 ± 0.9	5.1 ± 0.8	5.3 ± 0.7	5.8 ± 0.5*	< 0.001
Triglycerides, mmol/l	1.4 ± 0.4	1.4 ± 0.3	1.4 ± 0.4	1.6 ± 0.4*	< 0.001
Total cholesterol, mmol/l	5.1 ± 1.2	4.8 ± 1.3	5 ± 1.1	5.4 ± 1.1*	< 0.001
HDL cholesterol, mmol/l	1.5 ± 0.4	1.6 ± 0.4	1.4 ± 0.4	1.4 ± 0.5	0.128
LDL cholesterol mmol/l	3 ± 0.9	2.6 ± 0.9	3 ± 0.8*	3.2 ± 0.7$^{*\#}$	< 0.001
Current CD4 count, cells/mm^2	405 (273–562)		430 (327–534)	403 (253–583)	0.804
BDNF, ng/ml	6 (3–10.2)	7.1 (3.4–13.3)*	4.9 (2.7–9.6)	5.6 (2.9–8.9)	0.025
Sqrt BDNF, ng/ml	2.6 ± 1.2	2.8 ± 1.3*	2.4 ± 1.1	2.4 ± 1	0.004

BMI Body mass index, *HDL* High-density lipoprotein, *LDL* Low-density lipoprotein, *BDNF* Brain-derived neurotrophic factor; *sqrt*, square root transformation

* $p < 0.05$ compared to non-HIV; $^{\#}p < 0.05$ compared to treatment naïve HIV patients

Association between levels of serum BDNF and MetS

In the entire study participants and cART-naïve HIV patients, there was no association between MetS and serum BDNF. In controls without HIV, a unit increase in serum BDNF was associated with a 0.65 decrease in MetS odds in the unadjusted model, but no association in the fully adjusted model. In cART-exposed HIV patients, a unit increase in the serum BDNF was associated with a 2.84 and 2.98 increase in the prevalence rate ratio of MetS in the unadjusted and adjusted models respectively (Table 2). The prevalence of components of MetS among various categories of study participants is shown in Figure S2 (supplementary information). In all participants, a unit increase in BDNF was associated with an increase in the odds of high systolic BP and hypertriglyceridemia and a decrease in the odds of low HDL cholesterol in the unadjusted and adjusted models. In non-HIV controls, a unit increase in serum BDNF was associated with increased odds of high systolic BP in the unadjusted model, but no association in the adjusted model. In cART-exposed HIV patients, a unit increase in serum BDNF was associated with an increase in the odds of IFG, high systolic BP, high triglycerides, and a decrease in the odds of low HDL cholesterol in the unadjusted and adjusted models. There was no association between components of MetS and serum levels of BDNF in cART-naïve HIV patients (Table 3).

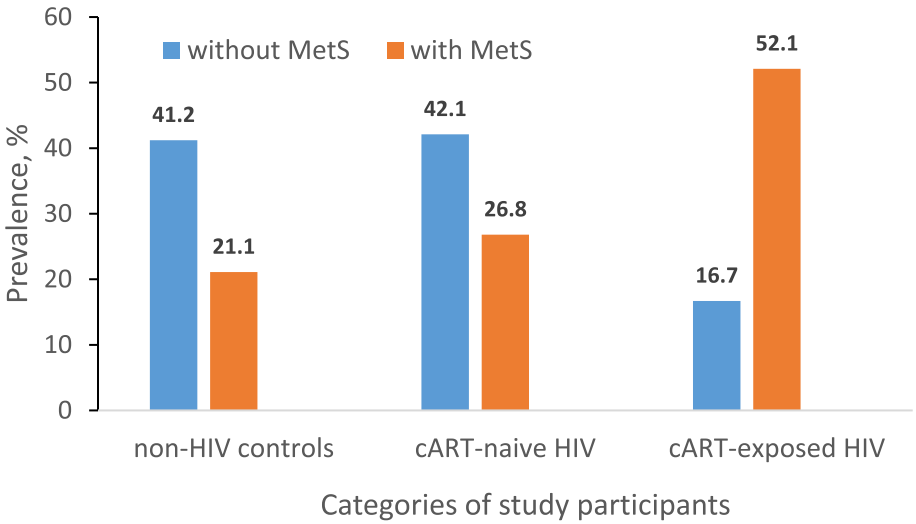

Fig. 1 Prevalence of metabolic syndrome among study participants

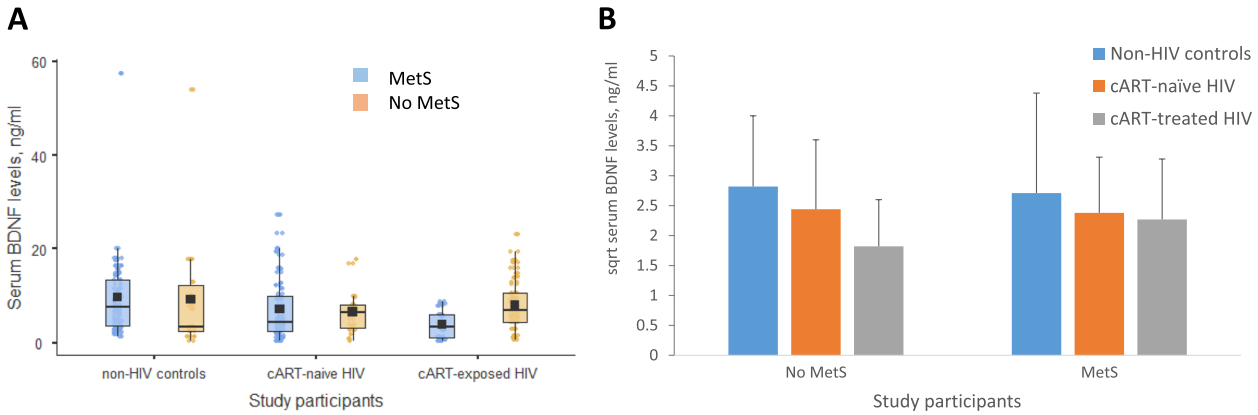

Fig. 2 Comparison of serum BDNF levels by **A** HIV status and **B** metabolic syndrome status

Discussion

The main outcomes of this study were (1) HIV patients on cART had a high burden of MetS compared to untreated HIV patients and non-HIV controls, (2) serum levels of BDNF were reduced in HIV patients, and (3) a unit increase in serum BDNF was associated with increased odds of MetS in cART-exposed HIV patients.

The prevalence of MetS found in this study is consistent with the previous study in Ghanaian HIV patients which found that patients receiving cART treatment had higher MetS than cART-nave patients [15, 28]. On the other hand, a lower prevalence of MetS of 34% was reported in cART-exposed HIV patients in the USA [29]. Similar findings were obtained in a meta-analysis that reported a higher prevalence of MetS in HIV-infected Africans, 30.5%, compared to patients from Asia and South America, who had the prevalence of MetS to be 21.4% and 21.5% respectively [30]. There may be various reasons attributed to disparities in the prevalence of MetS including ethno-geographical and socio-cultural variations in lifestyle, leading to the different levels of exposure to various risk factors such as diet and physical activity [18].

In this study, the levels of serum BDNF were found to be lower in HIV patients compared to non-HIV controls, and this is consistent with a study in HIV patients from the USA [31]. Low levels of serum BDNF in HIV patients could be due to decreased synthesis in neuronal and non-neuronal cells. In neuronal cells, the interaction of HIV viral envelope glycoprotein 120 (gp120) with neurons in the dorsal striatum of rodents decreases the synthesis and release of BDNF [8]. Also, shed viral protein, a trans-activator of transcription (Tat), is reported to reduce the synthesis of BDNF in rat brains [10]. In non-neuronal

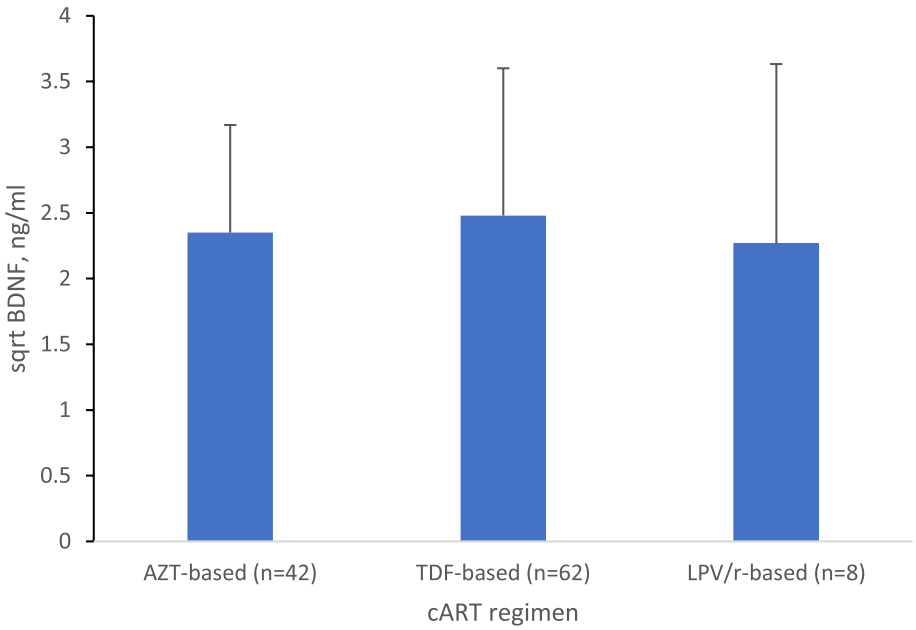

Fig. 3 Serum BDNF levels among participants based on the cART regimen

Table 2 Association between metabolic syndrome and serum BDNF levels from logistic regression analyses

	Unadjusted model		Adjusted model	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***
All participants	1.13 (0.94 -1.37)	0.193	1.18 (0.98–1.42)	0.077
Non-HIV controls	0.65 (0.43–0.98)	0.038	0.92 (0.63–1.34)	0.662
cART-naïve HIV patients	0.99 (0.71–1.37)	0.998	1.23 (0.79–1.91)	0.365
cART-exposed HIV patients	2.84 (1.83–4.4)	< 0.001	2.98 (1.64–5.41)	< 0.001

Adjusted for sex, age, plus alcohol intake, smoking status, educational level, marital status, employment status, CD4 cell count (only in cART-naïve and cART-exposed HIV patients), and cART regimen (only in cART-exposed patients). The duration of HIV infection and cART management were excluded from the model due to their low tolerance in model diagnostics

BDNF values were square-root transformed to reduce skewness before being incorporated into the model

cells, HIV infection downregulates the expression of BDNF in circulating T cells, leading to increased apoptosis and an immunocompromised state [32]. Furthermore, the inflammatory milieu created by HIV activity may be attributed to decreased levels of serum BNDF levels [17]. Our findings also indicate that the reduction in BDNF in HIV patients was only in patients without MetS (Fig. 1B). Therefore, it may be reasonable to hypothesize that the constellation of CVD risk factors may mask the effects of HIV on serum BNDF. This observation may be in collaboration with Fazeli et al., who reported similar levels of BDNF between HIV patients and non-HIV controls [27]. Their study population included a higher proportion of patients with cardiometabolic diseases (diabetes, hypercholesteremia), drug abuse, and depression; all these parameters can affect circulating BDNF levels.

Another interesting finding in our study was that, in the cART-exposed HIV patients, a unit increase in serum BDNF almost tripled the odds of MetS. This is consistent with studies that reported higher levels of serum BDNF in patients with cardiometabolic disorders such as diabetes [33, 34]. A similar observation of higher circulating levels of BDNF has been reported in adolescents with MetS [5]. It has been postulated that the increase in circulating BDNF levels in patients with MetS and other cardiometabolic disorders may be a compensatory response to oxidative stress and the pro-inflammatory environment associated with these conditions [35]. Another explanation may be the effect of HIV infection on BDNF biosynthesis; both gp120 [8, 11] and Tat [9] induce the synthesis and premature release of proBDNF protein instead of matured BDNF. The premature release

Table 3 Association between components of MetS and serum BDNF levels from logistic regression analyses

	Unadjusted model		Adjusted model	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***
All participants				
IFG	1.09 (0.93–1.28)	0.282		
High systolic BP	1.23 (1.04–1.45)	0.014	1.23 (1.02–1.47)	0.027
Abdominal obesity	1.15 (0.97–1.35)	0.106		
Low HDL	0.72 (0.59–0.86)	< 0.001	0.73 (0.6–0.9)	0.003
High triglycerides	1.2 (1.01–1.43)	0.035	1.25 (1.04–1.51)	0.017
Non-HIV controls				
IFG	0.78 (0.58–1.03)	0.081		
High systolic BP	1.34 (1.02–1.75)	0.033	1.01 (0.71–1.44)	0.941
Abdominal obesity	0.94 (0.73–1.2)	0.614		
Low HDL	0.95 (0.72–1.25)	0.716		
High triglycerides	1.19 (0.89–1.58)	0.241		
cART-naïve HIV patients				
IFG	1.04 (0.77–1.4)	0.805		
High systolic BP	0.99 (0.75–1.33)	0.992		
Abdominal obesity	1.2 (0.9–1.61)	0.219		
Low HDL	0.85 (0.61–1.17)	0.315		
High triglycerides	0.98 (0.67–1.43)	0.917		
cART-exposed HIV patients				
IFG	2.53 (1.69–3.78)	< 0.001	2.49 (1.51–4.11)	< 0.001
High systolic BP	1.46 (1.05–2.04)	0.026	1.64 (1.1–2.46)	0.016
Abdominal obesity	1.75 (1.19–2.58)	0.005	1.63 (0.98–2.72)	0.059
Low HDL	0.41 (0.28–0.61)	< 0.001	0.32 (0.19–0.56)	< 0.001
High triglycerides	2.06 (1.42–2.98)	< 0.001	2.73 (1.65–4.52)	< 0.001

Adjusted for sex, age, plus alcohol intake, smoking status, educational level, marital status, employment status, CD4 cell count (only in cART-naïve and cART-exposed HIV patients), and cART regimen (only in cART-exposed patients). The duration of HIV infection and cART management were excluded from the model due to their low tolerance in model diagnostics

IFG Impaired fasting glucose, *BP* Blood pressure, *HDL* High-density lipoprotein cholesterol

of proBDNF into the blood has opposite effects to BDNF, thus, increasing neurotoxicity and metabolic abnormalities [36]. Unfortunately, the Elisa method we employed in this study to assay BDNF levels has been reported to capture epitomes of both proBDNF and mature BDNF [37], and hence, the high levels of circulating BDNF may be due to increased premature release of proBDNF. It has also been demonstrated in adult male rhesus macaques infected with simian immunodeficiency virus that the alteration in BDNF secretion may even persist with cART suppression of viremia, reduction in neuroinflammation by HIV viral replication suppression, and normalizing CD4 + cell count [38].

In cART-exposed HIV patients, a unit increase in serum BDNF was associated with increased odds of metabolic abnormalities such as IFG, high systolic BP, and hypertriglyceridemia and decreased odds of low HDL cholesterol. This is consistent with other studies that reported increased circulating BDNF levels in participants with cardiometabolic risk factors [3, 4]. Some studies have reported the mechanisms linking BDNF dysregulation to these metabolic abnormalities. For example, hyperglycemia and hyperinsulinemia, two conditions present in MetS and early stages of type 2 diabetes were shown to increase the expression of BDNF mRNA expression in the brain of female mice [39], and the high levels of BDNF expression and release had been demonstrated, using in vitro studies, to have a synergistic effect on hyperglycemia-induced insulin secretion in pancreatic islet cells [1]. These studies highlight the feed-forward loop involving high circulating BDNF levels and hyperinsulinemia in the early stages of metabolic syndrome, possibly as a compensatory response to insulin resistance [1, 40]. Concerning the association between BDNF and high blood pressure, it has been demonstrated in spontaneously hypertensive rats that oxidative stress upregulates BDNF synthesis before a rise in blood pressure

is observed [41]. Similarly, BDNF was associated with hypertrophic remodeling of the carotid artery in the SAPBA study [42]. BDNF is reported to have a role in cholesterol biosynthesis in the liver and adipose tissue. The adipose tissue expresses BDNF and its receptor, TrkB, but proinflammatory condition increases the expression of BDNF while reducing that of TrkB [43]. Additionally, in human neurons and astrocytes, BDNF has been reported to regulate HDL cholesterol by modulating the synthesis of apolipoprotein E synthesis [2]. However, since peripheral cholesterol biosynthesis is separated from central nervous cholesterol biosynthesis, more studies may be needed to investigate the role of BDNF in circulating cholesterol levels. Furthermore, all these effects of BDNF were studied in non-HIV participants or models, and hence further studies may be needed to clarify whether the same processes occur in HIV patients or models.

Strengths and limitations of the study

To our knowledge, this is the first study to report serum BDNF in HIV patients in the sub-Saharan African population and associate it with cardiometabolic risk factors. We employed an adequate sample size and included cART-naïve HIV patients in our design to compare the effect of HIV infection alone on BDNF levels. In addition, we excluded participants with drug abuse, clinical neuropsychiatric diseases, diabetes, and cardiovascular disease which may mask the association between BDNF and cardiometabolic risk factors. The limitations of this study include the one-time data collection which cannot be used to infer causality from the findings of the study. The findings of this study cannot indicate that low levels of BDNF cause alterations in cardiometabolic risk factors or vice versa. Furthermore, we did not measure other sources of BDNF, such as platelets or muscles, and we did not measure BDNF mRNA levels. The study was carried out in a single healthcare facility, and hence, the results cannot be generalized to other healthcare centers. Due to logistical constraints in peri-urban hospitals at the time of data collection, there were no viral load data for the HIV patients. Therefore, we could not assess the influence of viral load on MetS and BDNF levels. However, cART-treated HIV patients had undetectable viral load in their previous year's medical records. We also did not assess the levels of physical activity and dietary patterns, which are known to affect BDNF levels and cardiometabolic factors [6, 43]. Although we excluded those with diagnosed neuropsychiatric conditions and CVDs, some of our participants may have subclinical conditions that may have affected the outcome variables in this study. In addition, we did not measure the polymorphism of the BDNF gene, which has been reported to affect BDNF maturation and secretion [27, 44].

Conclusion

Despite the limitations, the findings of this study have shown that there is a high prevalence of MetS in cART-exposed HIV patients compared to cART-naïve HIV patients and non-HIV controls. Serum levels of BDNF were lower in HIV patients compared to non-HIV controls. A unit increase in serum BDNF levels almost triples the odds of MetS in cART-exposed HIV patients. Further studies could examine the effect of pharmacological and non-pharmacological interventions that improve serum BDNF levels in HIV patients and their effects on cardiometabolic health.

Abbreviations

BDNF	Brain-derived neurotrophic factor
HIV	Human immunodeficiency virus
cART	Combination antiretroviral therapy
MetS	Metabolic syndrome
CVD	Cardiovascular diseases
BMI	Body mass index
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
FPG	Fasting plasma glucose
BP	Blood pressure

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43162-023-00257-6.

Additional file 1: Fig. S1. Density plot of BDNF levels showing the distribution before (left) and after (right) squared root data transformation. **Figure S2.** Prevalence of the components of MetS by HIV status. **Table S1.** Correlation between BDNF and characteristics of study participants. **Table S2.** Determinants of BDNF from multivariate linear regression analyses in various study groups

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Authors' contributions

KY conceptualized the study, analyzed the data, and drafted the manuscript. FFO collected the data and revised the manuscript. JAA analyzed the data and made scientific contributions to the drafting of the manuscript. BD revised the manuscript and made scientific contributions to the manuscript. All authors approved the content of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

We carried out the study following the Helsinki Declaration on Human Experimentation, 1964, with subsequent revisions, latest Seoul, October 2008. The study was approved by the Ethics and Protocol Review Committee of the College of Health Sciences of the University of Ghana (Protocol ID number: CHS-Et/M.6 – 5.19/2018–2019), and each study participant provided a written voluntary informed consent before inclusion to the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Fulgenzi G, Hong Z, Tomassoni-Ardori F, Barella LF, Becker J, Barrick C, Swing D, Yanpallewar S, Croix BS, Wess J et al (2020) Novel metabolic role for BDNF in pancreatic β-cell insulin secretion. Nat Commun 11(1):1950
2. Spagnuolo MS, Donizetti A, Iannotta L, Aliperti V, Cupidi C, Bruni AC, Cigliano L (2018) Brain-derived neurotrophic factor modulates cholesterol homeostasis and Apolipoprotein E synthesis in human cell models of astrocytes and neurons. J Cell Physiol 233(9):6925–6943
3. Golden E, Emiliano A, Maudsley S, Windham BG, Carlson OD, Egan JM, Driscoll I, Ferrucci L, Martin B, Mattson MP (2010) Circulating brain-derived neurotrophic factor and indices of metabolic and cardiovascular health: data from the Baltimore Longitudinal Study of Aging. PLoS ONE 5(4):e10099
4. Levinger I, Goodman C, Matthews V, Hare DL, Jerums G, Garnham A, Selig S (2008) BDNF, metabolic risk factors, and resistance training in middle-aged individuals. Med Sci Sports Exerc 40(3):535
5. Pedersen NH, Tarp J, Andersen LB, Gejl AK, Huang T, Peijs L, Bugge A (2017) The association between serum brain-derived neurotrophic factor and a cluster of cardiovascular risk factors in adolescents: the CHAMPS-study DK. PLoS ONE 12(10):e0186384
6. Pius-Sadowska E, Machaliński B (2017) BDNF - a key player in cardiovascular system. J Mol Cell Cardiol 110:54–60
7. Jin H, Chen Y, Wang B, Zhu Y, Chen L, Han X, Ma G, Liu N (2018) Association between brain-derived neurotrophic factor and von Willebrand factor levels in patients with stable coronary artery disease. BMC Cardiovasc Disord 18(1):23
8. Bachis A, Avdoshina V, Zecca L, Parsadanian M, Mocchetti I (2012) Human immunodeficiency virus type 1 alters brain-derived neurotrophic factor processing in neurons. J Neurosci 32(28):9477–9484
9. Carvallo L, Lopez L, Fajardo JE, Jaureguiberry-Bravo M, Fiser A, Berman JW (2017) HIV-Tat regulates macrophage gene expression in the context of neuroAIDS. PLoS ONE 12(6):e0179882
10. Liu Y, Zhou D, Feng J, Liu Z, Hu Y, Liu C, Kong X (2018) HIV-1 protein Tat1–72 impairs neuronal dendrites via activation of PP1 and regulation of the CREB/BDNF pathway. Virologica Sinica 33(3):261–269
11. Wang Y, Liao J, Tang S-J, Shu J, Zhang W (2017) HIV-1 gp120 upregulates brain-derived neurotrophic factor (BDNF) expression in BV2 cells via the Wnt/β-catenin signaling pathway. J Mol Neurosci 62(2):199–208
12. Defo AK, Chalati MD, Labos C, Fellows LK, Mayo NE, Daskalopoulou SS (2021) Association of HIV infection and antiretroviral therapy with arterial stiffness: a systematic review and meta-analysis. Hypertension 78(2):320–332
13. Bijker R, Jiamsakul A, Uy E, Kumarasamy N, Ditango R, Chaiwarith R, Wong W, Avihingsanon A, Sun L, Yunihastuti E et al (2019) Cardiovascular disease-related mortality and factors associated with cardiovascular events in the TREAT Asia HIV Observational Database (TAHOD). HIV Med 20(3):183–191
14. Joint United Nations Programme on HIV/AIDS. Global HIV & AIDS statistics — Fact sheet. Geneva, Switzerland: UNAIDS; 2021 [cited 2023 April 28]. Available from: https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf
15. Dzudzor B, Essel S, Musah L, Agyekum JA, Yeboah K (2023) Metabolic syndrome and combination antiretroviral therapy in HIV patients in periurban hospital in Ghana: a case-control study. AIDS Research and Treatment 2023:1566001
16. Fourie CMT, Schutte AE, Smith W, Kruger A, van Rooyen JM (2015) Endothelial activation and cardiometabolic profiles of treated and never-treated HIV infected Africans. Atherosclerosis 240(1):154–160
17. McArthur JC, Johnson TP (2020) Chronic inflammation mediates brain injury in HIV infection: relevance for cure strategies. Curr Opin Neurol 33(3):397
18. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart J-C, James WPT, Loria CM, Smith SC Jr (2009) Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study Of Obesity. Circulation 120(16):1640–1645
19. Abdel Hameed MR, Nafady HA, Mostafa MI, Sayed D, Obiedallah AA (2021) Possible role of CD11a in primary immune thrombocytopenia patients on immunosuppressive therapy. J Blood Med 12:197–205
20. Schulte-Herbrüggen O, Nassenstein C, Lommatzsch M, Quarcoo D, Renz H, Braun A (2005) Tumor necrosis factor-alpha and interleukin-6 regulate secretion of brain-derived neurotrophic factor in human monocytes. J Neuroimmunol 160(1–2):204–209
21. Abdel Hammed MR, Elgendy SG, El-Mokhtar MA, Sayed D, Mansour SM, Darwish AM (2022) T-lymphocytes expression of toll-like receptors 2 and 4 in acute myeloid leukemia patients with invasive fungal infections. Mediterr J Hematol Infect Dis 14(1):e2022022
22. Sochal M, Ditmer M, Gabryelska A, Białasiewicz P (2022) The role of brain-derived neurotrophic factor in immune-related diseases: a narrative review. J Clin Med 11(20):6023
23. Chang CC, Chang HA, Chen TY, Fang WH, Huang SY (2014) Brain-derived neurotrophic factor (BDNF) Val66Met polymorphism affects sympathetic tone in a gender-specific way. Psychoneuroendocrinology 47:17–25
24. Takeda K, Obinata Y, Konishi A, Kajiya M, Matsuda S, Mizuno N, Sasaki S, Fujita T, Kurihara H (2016) Brain-derived neurotrophic factor inhibits intercellular adhesion molecule-1 expression in interleukin-1β-treated endothelial cells. Cell Biochem Biophys 74(3):399–406
25. Abd El-Hameed MR, Abozied AM (2013) Mean platelet volume in impaired fasting glucose subjects and diabetic patients as a risk factor for thrombotic complications. J Am Sci 9(9):12–17. (ISSN: 15451003). http://www.jofamericanscience.org
26. Abdel Hammed MR, El-Amien HA, Asham MN, Elgendy SG (2022) Can platelets indices and blood neutrophil to lymphocyte ratio be used as predictors for diagnosis of spontaneous bacterial peritonitis in decompensated post hepatitis liver cirrhosis? Egypt J Immunol 29(4):12–24
27. Fazeli PL, Woods SP, Lambert CC, Li W, Hopkins CN, Vance DE (2022) Differential associations between BDNF and memory across older Black and White adults with HIV disease. JAIDS Journal of Acquired Immune Deficiency Syndromes 89(2):129–135
28. Obirikorang C, Quaye L, Osei-Yeboah J, Odame EA, Asare I (2016) Prevalence of metabolic syndrome among HIV-infected patients in Ghana: a cross-sectional study. Niger Med J 57(2):86–90
29. Sears S, Buendia JR, Odem S, Qobadi M, Wortley P, Mgbere O, Sanders J, Spencer EC, Barnes A (2019) Metabolic syndrome among people living with HIV receiving medical care in Southern United States: prevalence and risk factors. AIDS Behav 23(11):2916–2925
30. Naidu S, Ponnampalvanar S, Kamaruzzaman SB, Kamarulzaman A (2017) Prevalence of metabolic syndrome among people living with HIV in developing countries: a systematic review. AIDS Patient Care STDS 31(1):1–13

31. Woods SP, Babicz M, Shahani L, Colpo GD, Morgan EE, Teixeira AL (2021) Brain-derived neurotrophic factor (BDNF) is associated with depressive symptoms in older adults with HIV disease. J Neurovirol 27(1):70–79
32. Avdoshina V, Garzino-Demo A, Bachis A, Monaco MCG, Maki PM, Tractenberg RE, Liu C, Young MA, Mocchetti I (2011) HIV-1 decreases the levels of neurotrophins in human lymphocytes. AIDS 25(8):1126–1128
33. Berton O, McClung CA, DiLeone RJ, Krishnan V, Renthal W, Russo SJ, Graham D, Tsankova NM, Bolanos CA, Rios M (2006) Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. Science 311(5762):864–868
34. Boyuk B, Degirmencioglu S, Atalay H, Guzel S, Acar A, Celebi A, Ekizoglu I, Simsek C (2014) Relationship between levels of brain-derived neurotrophic factor and metabolic parameters in patients with type 2 diabetes mellitus. J Diabetes Res 2014:978143
35. Civelek S, Konukoglu D, Erdenen F, Uzun H (2013) Serum neurotrophic factor levels in patients with type 2 diabetes mellitus: relationship to metabolic syndrome components. Clin Lab 59(3–4):369–374
36. Teng HK, Teng KK, Lee R, Wright S, Tevar S, Almeida RD, Kermani P, Torkin R, Chen Z-Y, Lee FS et al (2005) ProBDNF induces neuronal apoptosis via activation of a receptor complex of p75NTR and sortilin. J Neurosci 25(22):5455–5463
37. Michalski B, Fahnestock M (2003) Pro-brain-derived neurotrophic factor is decreased in parietal cortex in Alzheimer's disease. Mol Brain Res 111(1):148–154
38. Maxi JK, Foret BL, Amedee AM, McDaniel LS, Nelson S, Simon L, Edwards S, Molina PE (2021) Antiretroviral therapy administration reduces neuroinflammation without restoring brain-derived neurotrophic factor signaling in alcohol-administered simian immunodeficiency virus-infected macaques. AIDS 35(9):1343–1353
39. Negrón AL, Beymer M, Yu G, Warren KA, Acosta-Martínez M (2015) Prolonged hyperglycemia & hyperinsulinemia increases BDNF mRNA expression in the posterior ventromedial hypothalamus and the dorsomedial hypothalamus of fed female rats. Neuroscience 303:422–432
40. Duan W, Guo Z, Jiang H, Ware M, Mattson MP (2003) Reversal of behavioral and metabolic abnormalities, and insulin resistance syndrome, by dietary restriction in mice deficient in brain-derived neurotrophic factor. Endocrinology 144(6):2446–2453
41. Amoureux S, Lorgis L, Sicard P, Girard C, Rochette L, Vergely C (2012) Vascular BDNF expression and oxidative stress during aging and the development of chronic hypertension. Fundam Clin Pharmacol 26(2):227–234
42. Smith AJ, Malan L, Uys AS, Malan NT, Harvey BH, Ziemssen T (2015) Attenuated brain-derived neurotrophic factor and hypertrophic remodelling: the SABPA study. J Hum Hypertens 29(1):33–39
43. Nakagomi A, Okada S, Yokoyama M, Yoshida Y, Shimizu I, Miki T, Kobayashi Y, Minamino T (2015) Role of the central nervous system and adipose tissue BDNF/TrkB axes in metabolic regulation. NPJ Aging Mech Dis 1:15009
44. Mizoguchi Y, Yao H, Imamura Y, Hashimoto M, Monji A (2020) Lower brain-derived neurotrophic factor levels are associated with age-related memory impairment in community-dwelling older adults: the Sefuri study. Sci Rep 10(1):16442

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