Accuracy of Neck Circumference as a Screening Test for Cardiovascular Disease Risk.

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Abstract

Background

The risk of cardiovascular disease (CVD) among people living with HIV (PLWH) is 2.0 times higher than in the general population. Neck circumference (NC) is a simple and inexpensive measurement and correlates well with the CVD risk in studies done outside sub-Saharan Africa. We determined the accuracy of neck circumference and the NC cut-off indicative of increased CVD risk in PLWH.

Methodology

In this cross-sectional study, we enrolled PLWHIV ≥ 30 years from urban clinics in Uganda in 2019. Medical history, physical examination (including NC), lipid profile, and HbA1C were obtained. CVD risk was computed using the Framingham Risk Score (FRS). Receiver operator curves (ROC) were constructed for different values of NC with FRS as the gold standard, whence to determine the accuracy of NC as a screening tool and the cut-off indicative of CVD risk. Factors associated with increased NC above the cutoff were determined using the Poisson regression model

Results

Of the 384 enrolled participants, 74% were females, the median age was 42 years (IQR 34-39 years) and median NC 33 cm (IQR 31-35 cm), meantime from HIV diagnosis 8.9 years. The area under the ROC was 0.63 and the optimum NC cut-off was 35 cm (sensitivity 43.9%, specificity 75.1%). Factors associated with a neck circumference ≥ 35 cm were male gender (Adjusted Poisson ratio (APR): 2.7, CI: 2.15 - 3.4; P<0.001), increased body mass index (overweight APR 2.4, CI: 1.24 - 4.47, P:0.009; obese APR: 3.2, CI: 1.67 - 6.24, P < 0.001), waist circumference, (1.7, CI: 1.26 - 2.21<0.001). Having HDL ≥ 1.50 was found to be negatively associated with large NC (0.7, CI: 0.55 – CI: 0.87 P: 0.002)

Conclusion

NC measurement is an easy tool that can be used accurately at cut off values of 35 cm to screen HIV individuals for risk of CVD

Introduction

Non-communicable diseases including cardiovascular diseases (CVDs) are rapidly increasing in low and medium-income countries including sub-Saharan Africa (SSA) (2–4). This rise is mainly due to the increase of modifiable risk factors like physical inactivity, poor dietary habits, smoking, alcohol consumption, hypertension, diabetes, hyperlipidemia, and obesity following rapid urbanization (5, 6).

People living with HIV (PLWH) are estimated to be at a 1.5–2 fold risk of death from cardiovascular diseases (CVDs) as compared to the HIV-negative population(1). This increased risk may be as a result of

an alteration of the traditional cardiovascular risk factors by chronic inflammation due to chronic HIV infection, long-term exposure to Anti-Retroviral Therapy (ART), or both (7,8).

While in the early years of ART scale-up high rates of mortality and morbidity were mostly attributed to the occurrence of opportunistic infection (OIs) (9), this trend has changed with the emergence of non-HIV related causes of morbidity and mortality with cardiovascular disease accounting for 11% of these deaths (10–12). A study from Uganda found 18% sub-clinical atherosclerosis, an indicator of cardiovascular disease, in HIV-positive patients(13). Risk prediction tools are developed to identify patients at risk and can be used to motivate patients and their health care providers to start an early lifestyle, pharmacological, and other healthcare interventions to reduce the risk of subsequent disease (14).

Cardiovascular risk prediction is largely dependent on algorithms and calculators, of which the best known and probably the most widely used globally is the Framingham Risk Score (14), which requires laboratory tests that are not easily accessible and affordable in SSA. These laboratory tests also involve long turnaround times and multiple visits, which may not be feasible in settings like Uganda. Other non-laboratory-based risk factors including BMI, waist-hip ratio (WHR) correlate relatively well with the laboratory-based risk factors for predicting cardiovascular events (15, 16) but it may be challenging to implement in a typically large HIV clinic in SSA.

Neck circumference (NC) is an indicator of upper body adiposity with a high positive correlation with factors of metabolic syndrome (17) and it independently contributes to the prediction of cardiometabolic risk factors beyond traditional anthropometric indices in adults (18–22), and therefore it could be adopted as a simple screening measure in these settings. This study aimed to determine the accuracy of neck circumference in determining CVD risk in people living with HIV under the care and the NC cut-off indicative of increased CVD risk.

Methods

Study settings and participants

This study was conducted in the HIV clinics of the Kampala Capital City Authority (KCCA) supported by the Infectious Disease Institute (IDI), College of Health Sciences, Makerere University. These clinics receive 80 to 350 adult patients per day, 3 days a week.

In this cross-sectional study we enrolled participants living with HIV aged ≥ 30 years consecutively selected from those coming in for care between Feb and Aug 2019. Patients with confirmed CVD (prior history of stroke, heart attack, peripheral artery disease, aortic dissection, chest pains worsening with exercise, hemiparesis, limb claudication, and transient ischemic attack) were excluded. In addition, we excluded patients with distortions and masses in the neck.

Assessments

A pre-tested questionnaire was used to obtain detailed clinical assessment including relevant CVD familial history, HIV and ART history, drug history related to CVD risk (anti-diabetic and anti-hypertensive drugs), and lifestyle (smoking, alcohol consumptions, exercise habits). We calculated the body mass index (BMI) and we measured blood pressure, waist circumference, and hip circumference with an inextensible tape measure.

The neck circumference was measured between midway cervical spine prominences and midway of the anterior neck with the shoulders relaxed and the patient standing upright looking straight ahead. In patients with laryngeal prominence, the neck circumference was measured just below the prominence anteriorly (28, 29).

Laboratory testing was performed at the SANAS accredited Rakai Health Sciences Program laboratory. Lipid profile and HB A1C % were performed using the Roche Cobas C111 instrument. HB A1C% was categorized as: <5.7% - normal, 5.7% – 6.4%- pre-diabetic, and ≥ 6.5% - diabetic. For lipid profile, non-fasting lipid profile was determined in mmol/L, and results were categorized according to the score ranges in the Framingham CVD risk score calculator (https://reference.medscape.com/calculator/252/framingham-risk-score-2008)

Cardiovascular disease risk was measured using the Framingham Cardiovascular Score (FRS) risk calculator, with a score of ≥ 10 considered to be an increased risk for cardiovascular disease.

Data analysis

Data was entered in Epidata 3.1 and exported into STATA 12 for analysis. Accuracy of neck circumference in determining cardiovascular disease risk in all participants stratified by gender was determined by generating area under the receiver operator curves (ROC) drawn from the respective sensitivities and specificities of the different neck circumferences using FRS as the gold standard. The thresholds of neck circumferences indicative of increased cardiovascular were obtained from the respective receiver operator curves of the different risk scores. Perpendicular lines to the ROCs from the point of maximum sensitivity and specificity (red lines on Fig. 1) were drawn from which the corresponding sensitivities and specificities were read off from the graphs (Black lines on Fig. 1). These respective sensitivities and specificities obtained above were then identified in the tables of sensitivities and specificities to read off the corresponding neck circumference cut-off indicative of increased CVD risk. Factors associated with an increased neck circumference above the established cutoff were determined using the Poisson regression model.

Ethical approval

Ethical approval was obtained from the Department of Medicine, School of Medicine Research and Ethics Committee (REC REF 2018-181) and the Uganda National Council for Science and Technology (Ref number HS353ES). All patients provided written consent to participate in the study. The study was done by the rules and regulations of the ethics bodies that approved the study.

Results

Characteristics of the study participants

We screened 430 participants, 3 of these were HIV negative, 10 were < 30 years, and 17 had a history suggestive of CVD. Of the remaining 400 participants enrolled in the study, 16 had incomplete laboratory results (HBA1C and/or lipid profile) and were excluded from the analysis. Of the 384 participants included in the analysis, the majority were females (285, 74.2 %), the median age was 41 years (IQR 35 - 48 years). The median neck circumference was 33 cm (IQR 31-35 cm). One hundred seventy-nine participants (63.0%) had been on ART for >5 years. Three hundred sixty-two (94.3%) had viral load <40 copies/ml, 144 participants (37.5%) were on dolutegravir based regimen,207 participants (53.9%) on NNRTI based regimen, and 29 (7.6%) on protease inhibitor-based regimen.

Ninety-eight participants (25.5%) had a BMI> 30, while using waist-hip ratio (WHR) (cut-offs: 0.85 in females and 0.90 in males), 46.7 % were considered obese. Eighty-three (21.6%) participants were at high CVD risk with FRS ≥ 10 (25% males and 20% females). The characteristics of participants by gender are presented in Table 1.

Accuracy and cut off of neck circumference to predict CVD risk

Receiver operator curves (ROCs) were generated using the respective specificities and sensitivities of the different neck circumferences using FRS as the gold standard and considering a score of ≥10 as being at risk of CVD (Supplemental Tables 3 in the appendix). For the overall population, the area under the ROC (AU-ROC) was 0.63 (95% CI-0.561-0.670) (Figure 1a). For the male-only, population AU-ROC was 0.612 (95% CI -0.469-0.756) (Figure 1b), and 0.648 (95% CI-0.565-0.73) in females (Figure 1b), indicating a fair performance of the neck circumference screening test.

We estimated a cut off of 35 cm for the overall study population with a sensitivity of 43.9% and specificity of 75.1% (Figure 1a, Table 3a), a cut off of 36.3 cm for males with a sensitivity of 45.83%, and specificity of 77.33% (Figure 1b and Table 3b), and a cut off of 33.5 for females with a sensitivity of 48.28% and specificity of 74.01% (Figure 1c and Table 3c)

Factors associated with a neck circumference greater than the cut off of 35cm

Males participants were 2.7 times (CI: 2.15 - 3.4; P<0.001) more likely to have a large neck circumference compared to females. Overweight (APR: 2.4, CI: 1.24 - 4.47, P: 0.009) or obese (APR: 3.2, CI1.67 - 6.24, P: 0.001) participants, participants with a large (> 120 cm in males or > 80 cm in females) waist circumference (APR: 1.7, CI:1.26 - 2.21, P<0.001) were 1.7 times more likely to be associated with a neck circumference above a cut off of 35cm (Table 2). Having HDL ≥ 1.50 mmol/l was negatively associated with large neck circumference (APR: 0.7, CI:0.55 - 0.87, P:0.002). Physical activity, HIV duration, systolic blood pressure, total cholesterol levels, triglyceride levels, LDL cholesterol levels, consumption of alcohol, familial history of hypertension, diabetes mellitus, and stroke were found not to be associated with a neck

circumference above the cut off of 35 cm. Table 2 presents the risk factors that were significantly associated with large neck circumference.

Discussion

This is the first study in sub-Saharan Africa to evaluate the accuracy of neck circumference compared to Framingham cardiovascular risk score to determine the optimum NC cut-off to screen for CVD risk. We assessed the accuracy of neck circumference using Framingham cardiovascular risk score as the gold standard and determined a cut-off of neck circumference that can be used to indicate increased CVD risk. Neck circumference is easy to perform, point of care, and an inexpensive examination which could potentially identify an important population at risk for CVD who may benefit from further intervention to prevent future disease.

Neck circumference performed relatively well against the FRS with the area under the receiver operator curve (AUC) overall at 0.6306. Using these receiver operator curves we estimated that a neck circumference ≥35 cm (33.5 cm for females and ≥36.3 cm for men) as screening for cardiovascular disease risk has a sensitivity of 43.9% and specificity of 75.2 %. While the sensitivity of NC is relatively low, its low cost and simple implementation could still result in a significant proportion of the population at risk of CVD being identified who might otherwise be completely missed. Using the neck circumference cut off of 35 cm, 28.6% of our study population would be at risk of cardiovascular disease.

The cut-offs of neck circumference in this study were lower than those done in other populations, for example, a study done in Brazil found neck circumference cut off values of 40.5 cm in males and 35.7 cm in females and one of 37 cm for males and ≥33 cm for females in the non-HIV population (25). These findings underline the importance of validating the optimum NC cut-off in different populations.

Framingham cardiovascular risk scores have been used with good accuracy in HIV patients in several studies (23), however, it is expensive and time-consuming; associated with increased waiting and turnaround time, and not suitable for resource-limited settings which have large volumes of patients. We found that in these settings neck circumference could be a reasonable tool in the screening path of cardiovascular risk in people living with HIV who have increased risk due to HIV itself, ART in addition to other traditional cardiovascular risk factors.

As seen in prior studies (18,24-25), large neck circumference was associated with traditional cardiovascular risk factors, for example in our study overweight and obese participants had a 1.7-fold and 3.2 risks of having a large neck circumference, as well those with large (>120 cm in males and >80 cm in females) waist circumference. High HDL cholesterol was protective of a larger neck circumference. However, we did not find a significant relationship between large neck circumference and other traditional HIV non-related and HIV related risk factors like physical activity, systolic blood pressure, total cholesterol levels, triglyceride levels, LDL cholesterol levels, consumption of alcohol, familial history of hypertension, diabetes mellitus HIV duration, ART regimens, duration of ART.

Limitations

The average neck circumference of the general Ugandan population is not known. Also, the Framingham score has not been well validated in Uganda.

Conclusions

With the emergence of non-HIV-related causes of morbidity and mortality, HIV programs in resource-limited settings should start planning for screening and treatment of non-communicable diseases. Using a simple measurement of neck circumference, we were able to identify a proportion of individuals that could be further investigated for cardiovascular disease risk

List Of Abbreviations

AIC (HbA1C) Glycosylated hemoglobin

ART Anti-Retroviral therapy

ATP III Adult Treatment Panel III.

AUC Area under the curve

AU-ROC Area under receiver operator curve

BMI Body mass index.

CDC Centre for disease control.

CVD Cardiovascular disease

DAD study Data Collection on Adverse Events of Anti-HIV Drugs Study.

DM Diabetes mellitus

HDL High-density lipoprotein

HIV Human immunodeficiency virus

IDI Infectious Diseases Institute

KCCA Kampala Capital City Authority

LDL low-density lipoprotein.

NC Neck circumference

NCD Non-communicable diseases

NNRTI Non-nucleoside reverse transcriptase inhibitor

PIs Protease inhibitors

Pre-ART Pre-antiretroviral therapy

ROC Receiver operator curve

SDG Sustained development goal.

TG Triglycerides

WHO World Health Organisation

Declarations

Ethics approval and consent to participate

Permission and authorization were sought from Infectious Diseases Institute Scientific Research Committee (IDI SRC), Department of Medicine, School of Medicine Research and Ethics Committee (REC REF 2018-181), and Uganda National Council for Science and Technology (Ref number HS353ES). Administrative clearances from IDI were obtained. All these clearances were used to obtain administrative clearance from Kampala City Council Authority (KCCA) to carry out research in their clinics. All participants of this study had written informed consent before participation and to maintain confidentiality patients were identified by study numbers. All the study methods were done following the guidelines and regulations of the ethics bodies in handling human subjects.

Consent for publication

Not applicable.

Availability of data

All the data generated and analyzed during this study are available and attached as an excel sheet in the supplementary files (In name of Moses Kiwanuka Ssebuliba data NC screening test sheet).

Competing interests

No competing interests are held by the authors.

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Authors' contributions

All authors reviewed, discussed the results of this study, and contributed to writing the paper. Conceived and designed the idea; Moses Kiwanuka Ssebuliba, Isaac Ssinabulya, Harriet Mayanja-Kizza, performed the experiments; Moses Kiwanuka Ssebuliba. Analyzed the data; Moses Kiwanuka Ssebuliba, Isaac Ssinabulya, Harriet Mayanja-Kizza, Yusuf Mulumba. Made a significant contribution to patient care and management; Moses Kiwanuka Ssebuliba, Reynold Steven J, Barbara Castelnuovo, Isaac Ssinabulya.

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Tables

Table 1: Characteristics of participants.

		Female n (%) N=285	Male n (%) N=99	Total n (%) N=384
Age, years	30 to 35	82 (28.8%)	32 (32.3%)	114 (29.7%)
	36 to 71	203 (71.2%)	67 (67.8%)	270 (70.3%)
		9.4 (6)	7.4 (5.6)	8.9 (6.0)
ART duration	< 6 months	15 (5.3%)	6 (6.0%)	21 (5.5%)
	6 -12 months	12 (4.2%)	8 (8.1%)	20 (5.2%)
	1 - 5 years	78 (27.5%)	38 (38.4%)	116 (30.3%)
	>5 years	179 (63.0%)	47 (47.5%)	226 (59.0%)
ART regimen	PI based	19 (6.7%)	10 (10.1%)	29 (7.6%)
	NNRTI based	166 (58.2%)	41 (41.4%)	207 (53.9%)
	DTG based	99 (34.7%	45 (45.5%)	144 (37.5%)
Smoking Habit	No	267 (93.7%)	74 (74.8%)	341 (88.8%)
	Current	7 (2.5%)	9 (9.1%)	16 (4.1%)
	Ex-smoker	11 (3.9%)	16 (16.2%)	27 (7.03%)
BMI Category kg/m^2	Under weight (< 18)	3 (1.1%)	7 (7.1%)	10 (2.6%)
	Normal (18.5 to 25)	88 (30.9%)	65 (65.7%)	153 (39.8%)
	Over weight (25.09 -30)	100 (35.1%)	23 (23.2%)	123 (32.0%25.5%)
	Obese (> 30)	94 (33.0%)	4 (4.0%)	98 (25.5%)
Waist circumference	Non-Obese	135 (47.4%)	93 (94%)	228 (59.4%)
	Obese	150 (52.6%)	6 (6%)	156 (40.6%)
WHR	Not obese	145 (50.9%)	61 (61.6%)	206 (55.7%)
	Obese	140 (49.1%)	38 (38.4%)	178 (46.3%)
Hypertension	Not Hypertensive	214 (75.1%)	83 (83.8%)	297 (77.3%)
	Hypertensive	71 (24.9%)	16 (16.2%)	87 (22.7%)
Hb A1C: g/dl (%)	< 5.7	232 (81.4%)	76 (76.8%)	308 (80.2%)
	5.7 to 6.4	44 (15.4%)	16 (16.1%)	60 (15.6%)
	≥ 6.5	9 (3.1%)	7 (7.1%)	16 (4.2%)

Total Cholesterol	< 5.1	203 (71.2%)	81 (81.8%)	284 (74.0%)
	5.1 to 6.1	64 (22.4%)	13 (13.1%)	77 (20.0%)
	≥ 6.2	18 (6.3%)	5 (5.1%)	23 (6.0%)
HDL Cholesterol Category	< 0.9	37 (13%)	20 (20.2%)	57 (14.8%)
	0.90 to 1.49	165 (57.9%)	59 (59.6%)	224 (58.3%)
	≥ 1.50	83 (29.1%)	20(20.2%)	103(26.8%)
LDL Cholesterol Category	0.48 to 3.34	217 (76.1%)	88 (88.9%)	305 (79.4%)
	3.35 to 4.14	48 (16.9%)	9 (9.1%)	57 (14.8%)
	4.15 to 5.83	20 (7.0%)	2 (2.0%)	22 (5.7%)
FRS Category	FRS ≥ 10	58(20 %)	25(25%)	83(21.6%)
	FRS < 10	227(80%)	74(75%)	301(78.4%)

BMI – body mass index; WHR- waist-hip ratio

LDL- low-density lipoprotein; HDL- high-density lipoprotein; Hb AIC – glycated hemoglobin.

ART- anti-retroviral treatment; PI: protease Inhibitor NNRTI: non-nucleoside reverse transcriptase inhibitor DTG-dolutegravir; HIV – human immunodeficiency syndrome; CVD- cardiovascular disease; FRS – Framingham cardiovascular risk score

Table 2: Factors associated with a neck circumference greater than the cut off of 35cm in PLHIV

Variable	CPR* (95%CI; P-Value)	APR (95%CI; P-Value)
Gender		
Female	1	1
Male	1.6 (1.44 - 1.8;<0.001)	2.7 (2.15 - 3.4;<0.001)
On the treatment of hypertension		
No		1
Yes	1.3 (1.1 - 1.61;0.003)	1.1 (0.77 - 1.6;0.566)
Unknown	1.5 (1.4 - 1.62;<0.001)	2 (1.31 - 2.98;0.001)
Smoking habit		
No	1	1
Current	0.7 (0.46 - 1.23;0.251)	0.8 (0.56 - 1.19;0.292)
Ex-Smoker	1.3 (1.07 - 1.52;0.006)	1.2 (0.98 - 1.47;0.074)
BMI group		
Under weight (15 to 18.49)	1	1
Normal (18.5 to 25)	1.4 (0.63 - 2.94;0.440)	1.7 (0.93 - 3.12;0.086)
Over weight (25.09 to 30)	1.7 (0.77 - 3.6;0.194)	2.4 (1.24 - 4.47;0.009)
Obese (30.02 to 83)	2.3 (1.07 - 4.92;0.033)	3.2 (1.67 - 6.24;0.001)
Waist circumference		
≤ 120 cm in males or ≤ 80 cm in females	1	1
> 120 cm in males or > 80 cm in females	1.5 (1.33 - 1.74;<0.001)	1.7 (1.26 - 2.21<0.001)
HDL cholesterol group		
less 0.9 mmol/l	1	1
0.90 to 1.49 mmol/l	0.9 (0.76 - 1.02;0.099)	0.9 (0.76 - 1.05;0.181)
greater or equal 1.50 mmol/l	0.6 (0.52 - 0.81;<0.001)	0.7 (0.55 - 0.87;0.002)

* only factors that were significantly associated (or expected to be significantly associated) are included in the table

CPR-crude poison ratio; APR- adjusted poison ratio; HIV – human immunodeficiency syndrome; CVD-cardiovascular disease; FRS – Framingham cardiovascular risk score; LDL- low-density lipoprotein; HDL-high-density lipoprotein; BMI – body mass index.

Figures

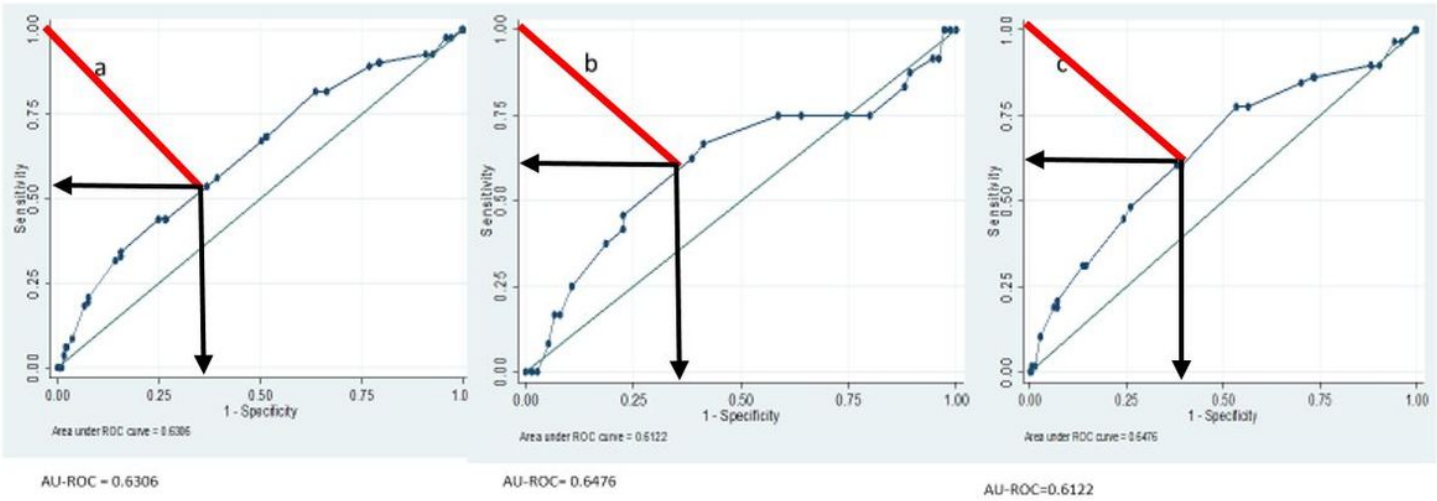

Figure 1

Receiver operator curves for neck circumference using the Framingham cardiovascular risk score and determination of the neck circumference cut-offs in the overall population (a), males (b) and female (c) participants

Supplementary Files

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- Appendix3tablesshowinghowcutoffisgot..docx
- MosesKiwanukaSsebulibadataNCscreeningtestsheet.xls