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RESEARCH

Obesity and HIV: a compounding problem

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Objectives: A cross-sectional study was undertaken at Lancers Road Clinic, Durban, South Africa to determine body composition, haemoglobin, serum albumin and serum high sensitivity C-reactive protein (hs-CRP) levels in asymptomatic ART-naive HIV positive adults. Methods: All eligible adults attending the clinic were sampled. Body composition was assessed using deuterium dilution. Descriptive statistics, Wilcoxon rank-sum test, chi-square test, Fisher's exact test and Spearman's rank correlation coefficient were used for data analysis.Results: A total of 84 participants (CD4 count: 542.5 ± 145 cell/mm^3) enrolled. The mean body mass index (BMI) was 29.5 (± 6.4) kg/m^2 and the mean fat mass percentage was 44.9 (± 18.7). The prevalence of overweight (26.2%, 22/84) and obesity (46.4%, 39/84) was high. Mean haemoglobin (Hb) levels were 12.0 ± 1.6 g/dl. Mild, moderate and severe anaemia was present in 21.4% (18/84), 20.2% (17/84) and 1.2% (1/84) of patients, respectively. Mean albumin levels (36.2 ± 3.8 g/l) were on the borderline low range of normal with mildly depleted albumin levels being present in a third (32.1%, 27/84) of patients. The mean hs-CRP levels (5.5 ± 7.2 mg/l) were high.Conclusion: In this cohort of patients, wasting was not associated with HIV as the prevalence of overweight/obesity was high and followed the population trend in SA. This seemingly well, asymptomatic population of people living with HIV was at an increased risk of morbidity, progression and death due to the compounding factors of overweight/obesity, hypoalbuminemia, raised hs-CRP levels and anaemia.

Keywords: HIV, ART-naive, obesity, albumin, C-reactive protein

Introduction

South Africa (SA) is currently facing three devastating epidemics, that of HIV/AIDS,[1] obesity[2] and non-communicable diseases (NCDs).[1,3] HIV/AIDS remains the leading single cause of mortality in SA, despite the number of HIV-related deaths having almost halved from 1997 to 2012.[1] The obesity epidemic has been a major factor associated with the rise in NCDs,[4–6] which have become the leading group of causes of mortality in SA.[1]

Historically, HIV/AIDs was described as the 'wasting' disease as weight loss was universally accepted as a prognostic marker of disease progression of HIV.[7] This perception is so strong that it has shaped cultural beliefs amongst black South Africans. Higher body weights have been valued as they symbolise health and beauty, in contrast to weight loss or thinness which symbolises unhappiness and someone living with HIV/AIDS.[8–10]

Weight loss and wasting, as an inevitable outcome of HIV infection, has been challenged in developed countries as the rates of overweight and obesity are high amongst treatment-naive HIV-infected people. Rates appear to mimic that of the general population.[11–14] Although this trend has scarcely been investigated,[14] preliminary data from developing nations support this hypothesis. In these studies, high rates of overweight (38.4%) and obesity (21.5%) have been reported amongst treatment-naive Nigerian adults[15] as well as amongst treatment-naive black SA females where rates of overweight ranged from 28%[16] to 32%[8] and obesity from 20%[8] to 37%.[16, 17]

Obesity potentially exacerbates the metabolic abnormalities associated with HIV and antiretroviral therapy (ART).[18] In accordance with the WHO recommendations, the SA Department of Health (DOH) implemented the 'Universal Test and Treat' (UTT) guidelines from September 2016.[19] Any individual, therefore, who tests positive for HIV, regardless of CD4 count, qualifies for ART. The initiation of ART results in further weight gain[12,20,21] and a higher prevalence of hypertension and metabolic syndrome.[22] In SA, statistics from HIV clinics show a high prevalence of both overweight and obesity[13,23] with a significant proportion of those initiating ART becoming overweight/obese within one year.[8] As obesity contributes to the incidence of NCD, and those on ART are more susceptible to a range of NCDs,[20,24–28] the synergistic effect is potentially devastating as both overweight and obesity is associated with an increase in multimorbidity in those receiving ART.[29]

With the implementation of UTT, the prevalence of overweight and obesity in treatment-naive individuals in SA needs to be determined as the combination of ART and obesity may lower life expectancy further.[29]

Methods

Study design and sample size determination

A data-set from a double-blind randomised controlled trial that investigated the effect of inulin supplementation on HIV progression was analysed.[30] During 2013,[31] 100 HIV-infected ART-naive black male and female adults attending the eThekwini Lancers Road Clinic, in Durban, South Africa were enrolled in the trial. Complete data are available for 84 participants (74%). Fourteen adults were not eligible due to the exclusion criteria: pregnancy or lactation; WHO AIDS stage 2 to 4; isoniazid (INH) prophylaxis; or statin use due to the impact on hs-CRP.[32] A clinician conducted the medical examination to ensure compliance with the exclusion criteria and to calculate the Karnofsky performance scale/score as a measure of health.

The Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BFC145/010) as well as the eThekwini Health, Social Services Health Unit gave permission for this study. Written

informed consent was obtained from all participants who volunteered to be included in the study. Their anonymity was protected. They received their standard medical care during the study and were free to withdraw consent without consequences at any stage.

Data collection

Anthropometric measurements used the standardised methods of the International Society for the Advancement of Kinanthropometry (ISAK). Participants were weighed in a fasted state after urination and in minimal clothing (underwear) to the nearest 0.01 kg using a calibrated Masskot scale (50 g to 150 kg) (MultiPark, Columbine Place, Industrial Place, Durban). Height was measured to the nearest 0.1 cm using a stadiometer (Seca 213, Hamburg, Germany). All measurements were done in duplicate and averaged.

Body composition (fat and fat-free mass) was determined using the technique of deuterium dilution where participants drink a deuterium oxide solution and give saliva samples in accordance with the standard operating procedures (SOP) of the International Atomic Energy Agency.[33] The calculations in the SOP were used to calculate fat-free mass (kg), fat-free mass percentage, fat mass (kg) and fat mass percentage.[33]

Body mass index was calculated as weight in kilograms divided by height in meters squared and interpreted using the WHO classification.[34] Body fat mass index was calculated as body fat mass in kilograms divided by the height in metres squared. Body fat-free mass index was calculated as fat-free mass in kilograms divided by the height in metres squared. As there are no reference tables for people living with HIV, the NHANES-1 tables for healthy adults were used to interpret the ratios.[35] As many of the published studies had not reported the fat mass or fat-free mass index this was calculated from the data in the publication.[16, 36, 37]

Biochemical parameters included CD4 counts, high sensitivity C-reactive protein (hs-CRP), albumin and haemoglobin (Table 1). For CD4 counts, four millilitres (ml) of whole blood was drawn into an ethylenediaminetetraacetic acid (EDTA) containing endotoxin free tube (BD Biosciences, San Jose, CA, USA) by venepuncture. For albumin and hs-CRP 4 ml of whole blood was drawn into a serum separator tube (BD Biosciences) by venepuncture. The samples were analysed by a SANAS accredited laboratory according to international standards.

Haemoglobin was analysed using the HemoCue© Hb201 (HemoCue AB, Ängelholm, Sweden) according to the manufacturer's instructions.[38] If the Hb level was below 10 g/dl, the test was repeated using another HemoCue© Hb201 to confirm the reading. Anaemia was defined as follows: mild anaemia 11–11.9 g/dl, moderate anaemia 8–10.9 g/dl and severe anaemia < 8 g/dl.[39]

Table 1: Summary of the methods and equipment used

Variable	Method	Equipment
Body composition	Deuterium dilution	Fourier-transform infrared spectroscopy
CD4	Flow cytometry	BD FACSCalibur
hs-CRP	Latex immunoturbidimetric assay	Abbott Architect ci8200
Albumin	Bromcresol purple assay	Abbott Architect ci8200
Haemoglobin	Cyanmethemoglobin	HemoCue© Hb201

Statistical analysis

Statistical analysis software (SAS) version 9.2 (SAS Institute, Cary, NC, USA) was used. Quantitative variables were examined for departure from normality using the skewness statistic and its standard error. Normally distributed quantitative variables were described using means, standard deviations (SD) and ranges. Groups were compared using independent sample t-tests in the case of two unmatched groups. Where the data are non-normally distributed the Wilcoxon rank-sum test was used. Categorical variables were described using frequency and relative frequency tables. Where the assumption of the chi-square test of large-cell frequencies had been violated, Fisher's exact test was used. Spearman's rank correlation coefficient was used for nonparametric data to assess the relationship between two variables, whether continuous or discrete; $p < 0.05$ indicated a significant difference.

Results

Characteristics of the participants

Of the 84 participants, most were female (77/84, 92%) with a mean age of 34.9 ± 9.2 years and a CD4 count of 548 ± 147 cells/mm^3 compared with males (7/84, 8%; 38.2 ± 10.9 years; 485 ± 104 cells/mm^3) (Table 2). Approximately half (44/84, 52.4%) had a CD4 count of > 500 cell/mm^3. All were asymptomatic as reflected by a Karnofsky score of 100 (81/84, 96%) or 90 (3/84, 4%).

Body composition characteristics of the participants

In general, females were overweight (BMI 29.9 ± 6.4 kg/m^2, fat percent 47.0 ± 17.8%) compared with normal-weighted males (BMI 24.2 ± 4.3 kg/m^2, fat percent 25.1 ± 16.3%) (see Table 2). The mean BMI ($p = 0.02$) and fat mass percentage ($p = 0.03$) of the males was significantly lower. Females were mostly overweight (19/77, 24.7%) or obese (39/77, 50.7%) with only a quarter being of normal body weight (18/77, 23.4%) (Table 3). Males were of normal weight (3/7, 43.8%) or overweight (3/7, 43.8%). The mean fat mass index was significantly higher for females (15.0 kg/m^2) ($p = 0.04$) when compared with males (5.83 kg/m^2) while the mean fat-free mass index was significantly lower for females versus males (15.5 kg/m^2 versus 18.7 kg/m^2) ($p = 0.03$). One female was severely malnourished and one male had mild malnutrition—both were unable to find employment and had no money for food.

Biochemical characteristics of the participants

The mean CRP (5.5 ± 7.2 mg/dl) was high (see Table 2). There was a weak negative correlation using the Spearman rank correlation test between the levels of albumin and CRP (rho (ρ) = –0.204; $p = 0.64$) although this did not reach significance.

The mean albumin levels (36.2 ± 3.8 g/l) were on the borderline low range of normal (35–50 g/l) (see Table 2) with mildly depleted albumin levels (25 to < 35 g/l) being present in a third (27/84, 32.1%), two (2/27, 7.4%) of which were males. Using the Spearman rank correlation test there was a weak positive correlation between the CD4 count and the albumin levels (rho (ρ) = +0.175; $p = 0.114$) although this did not reach significance.

The mean Hb levels (12.0 ± 1.6 g/dl) (see Table 2) were in the low range of normal (12.1–15.1 g/dl). Mild anaemia was present in 21.4% (18/84), moderate anaemia in 20.2% (17/84) and severe anaemia in 1.2% (1/84) of participants, respectively. Using the Wilcoxon rank-sum test there was no significant correlation between CRP and Hb levels ($p = 0.596$) or in mean CD4 count and Hb levels ($p = 0.542$).

Table 2: Participant demographics and clinical characteristics at baseline

	Total	Male	Female	
	(*n* = 84)	(*n* = 7)	(*n* = 77)	
	Mean (±SD) [min, max]	Mean (±SD) [min, max]	Mean (±SD) [min, max]	*p*-value*
Age (years)	35.2 (±9.3) [19.3, 60.2]	38.2 (±10.9) [27.3, 60.2]	34.9 (±9.2) [19.3, 59.4]	0.471
Height (cm)	164.0 (±6.2) [147.0, 172.8]	168.9 (±3.6) [162.4, 172.8]	159.2 (±5.7) [147.0, 172.1]	0.000[a]
Weight (kg)	75.2 (±15.9) [41.8, 128.3]	68.6 (±10.9) [53.9, 84.9]	75.8 (±16.2) [41.8, 128.3]	0.25
BMI (kg/m^2)	29.5 (±6.4) [15.7, 51.9]	24.2 (±4.3) [18.1, 29.1]	29.9 (±6.4) [15.7, 51.9]	0.02[a]
Fat-free mass (kg)	40.1 (±10.6) [18.4, 67.7]	51.8 (±14.3) [22.7, 67.7]	39.0 (±9.5) [18.4, 60.8]	0.002[a]
Fat-free mass (%)	55.1 (±18.7) [15.4, 97.2]	74.9 (±16.3) [42.2, 92.6]	53.0 (±17.8) [15.4, 97.2]	0.00 [a]
Fat mass (kg)	36.5 (±21.2) [1.5, 108.5]	16.7 (±8.8) [4.3, 31.1]	38.6 (±21.1) [15, 108,8]	0.01[a]
Fat mass (%)	44.9 (±18.7) [2.8, 84.6]	25.1 (±16.3) [7.4, 57.8]	47.0 (±17.8) [2.8, 84.6]	0.0 [a]
Albumin (g/l)	36.2 (±3.8) [28.0, 46.0]	37.86 (±5.7) [28.0, 45.0]	36.0 (±3.6) [28, 46]	0.437
Hb (g/dl)	12.0 (±1.6) [7.7, 15.3]	13.2 (±2.4) [8, 15]	11.9 (±1.5) [7.7, 15.3]	0.203
CD4 (cells/mm^3)	542.5 (±145) [350.0, 948.0]	485 (±104) [367, 681]	548 (±147) [348, 948]	0.275
Hs-CRP (mg/l)	5.5 (±7.2) [0.2, 36.9]	11.1, (±15.3) [0.5, 36.9]	4.9, (±5.9) [0.2, 36.0]	0.029[a]

*The *p*-value was calculated using Student's t-test to compare means and the chi-squared test to compare proportions. When an important assumption of the chi-squared test had been violated, Fisher's exact test was used; $p < 0.05$ indicates a significant difference between the males and females.
[a]Denotes a significant difference although the very small number of males versus females could impact on the accuracy of the analysis.

Table 3: Nutritional status classified according to body mass index (kg/m^2)

BMI (kg/m^2)	Total *n* (%)	Male *n* (%)	Females *n* (%)	Interpretation
< 16	1 (1.2)	0	1 (1.3)	Severe malnutrition
16–< 17	0 (0.0)	0	0	Moderate malnutrition
17–< 18.5	1 (1.2)	1 (14.3)	0	Mild malnutrition
18.5–< 25	21 (25.0)	3 (42.9)	18 (23.4)	Normal weight
25–< 30	22 (26.2)	3 (42.9)	19 (24.7)	Overweight
30–< 35	22 (26.2)	0	22 (28.6)	Obese Class I
35–40	14 (16.7)	0	14 (18.2)	Obese Class II
> 40	3 (3.5)	0	3 (3.9)	Obese Class III
Total	84 (100.0)	7	77 (100)	

Discussion

Prevalence of overweight/obesity

These results challenge the long-standing belief that involuntary weight loss/wasting is an integral part of the progression of HIV, and supports the conclusion of both Tate *et al*. (2012) and Crum-Cianflone *et al*. (2010) , who proposed that the prevalence of obesity of people who are HIV-infected and ART-naive mirrored that of the general population of the nation in which they resided.[11,14] The most recent SA population survey, the SANHANES-1, reported that in KZN the prevalence of overweight and obesity amongst black SA females was 25% and 44% respectively.[40] This correlated with the findings of this study amongst HIV-infected ART-naive black SA females in KZN where the prevalence of overweight and obesity was 25% and 51% respectively. The prevalence of overweight and obesity, even in less developed countries, appears to follow or exceed the national population trends, with weight loss and wasting no longer an inevitable consequence of the progression of HIV.

Body composition

Studies in SA using advanced methods of body composition determination, such as deuterium dilution and dual-energy X-ray absorptiometry (DXA), are limited. These study participants' fat-free mass index (15.5 kg/m^2) was similar to that of HIV-infected ART-naive black SA breastfeeding mothers (15.7 kg/m^2)[36] and black SA HIV-infected ART-naive females (15.9 kg/m^2).[41] Their fat-free mass, however, was lower than that of HIV-uninfected black SA females (17.05 kg/m^2).[37] This was in agreement with the findings of international studies, which concluded that the fat-free mass of asymptomatic adults living with HIV was lower than that of healthy controls.[42–45] This has important clinical ramifications as diminishing fat-free mass has been linked to an increased progression of HIV,[46] an impairment in strength and functional status,[47] low bone mineral density[48] and increased mortality.[49]

When compared with other SA studies, these study participants displayed substantially higher levels of body fat as represented by the higher fat mass index (15.0 kg/m^2), BMI (29.5 kg/m^2) and fat mass percentage (44.9%) than that of HIV-infected ART-naive black South African breastfeeding mothers living in a rural area of KZN (10.5 kg/m^2: 26.2 kg/m^2; 39.2%) and black African HIV-infected ART-naive females in Soweto (10.1 kg/m^2: 26.5 kg/m^2; 39.5%).[16, 36] Although it is well established that excess body fat results in adverse health outcomes in the HIV-uninfected population,[50] the consequences of the superimposition of HIV infection have not been investigated extensively.[14] As both ART and obesity are independently related to increased rates of cardiovascular disease, hyperlipidaemia, hypertension and insulin resistance,[26, 28, 51] and obesity in HIV is associated with a greater likelihood of multimorbidity, it is feasible to conclude that ART in combination with obesity may lower life expectancy further.[29] The implementation of the UTT guidelines, which will expose many more obese individuals to ART and the related complications, further raise the urgency of addressing the obesity epidemic in South Africa.

High-sensitivity C-reactive protein

The mean hs-CRP levels were high (> 5 mg/l) with 12% being above 10 mg/l. Raised CRP levels are an important predictor of all-cause mortality in HIV-infected ART-naive adults independent of anthropometry, CD4 count and viral load.[52–55] Adults with a CD4 count of > 500 cells/mm^3 and a CRP level > 3 mg/l had a 2.7-fold

higher adjusted odds of death when compared with those whose CRP was < 1 mg/l.[55] Based on these parameters, 39% of this apparently well, asymptomatic population was at higher risk of death. Raised levels of hs-CRP in those with HIV is associated with a markedly increased relative risk of an acute myocardial infarction[56] and cardiovascular disease[57] and hs-CRP levels may be important in the assessment of cardiovascular risk in this population. As CRP is an important inflammatory marker in obesity, and tends to be increased in the presence of excessive adiposity,[58–60] the raised CRP levels could in part be attributed to the high prevalence of obesity. Weight-loss strategies therefore could perceivably reduce the risk and improve the outcome, reinforcing the urgency to address obesity in people living with HIV in SA. Although the Nutritional Guidelines for HIV-infected Adults and Children in Southern African (2008) are clear that overweight, asymptomatic adults need to lose weight sensibly,[61] the SA guidelines briefly refer to obesity as being undesirable when on ART but primarily focus on preventing weight loss and the importance of regaining the lost weight.[62] To shift the perception amongst the SA black African population that 'big is beautiful', the stigma that weight loss and thinness is associated with HIV/AIDS[9, 63] needs to be actively addressed as the beliefs, traditions and attitudes of black women in South Africa promote obesity.[10, 40] One of the key challenges that SA as a nation faces regarding the control and prevention of obesity is the cultural discrepancy that highlights the preference for larger body sizes[64] and the satisfaction with their body size as many perceive themselves to be a smaller body shape than they actually are, resulting in them being unable to identify themselves as being obese.[63]

Albumin

Lower mean albumin levels and a higher prevalence of hypoalbuminemia than expected were found. The borderline low (36.2 g/l) mean albumin levels, although similar to that found in HIV-infected ART-naive individuals in Rwanda (36 g/l)[65] and Kenya (38.5 g/l),[66] were well below those described in SA by Hattingh et al. (41.3 g/l) and Oosthuizen *et al*. (40.9 g/l).[67, 68] The prevalence of hypoalbuminemia (32.1%) was two- to fourfold higher than that previously reported in Kenya[66] and in SA.[67]

Hypoalbuminemia, a strong predictor of mortality,[69–71] is associated with increased progression of HIV.[71] The United States Women's Interagency HIV Study (WIHS) demonstrated that the three-year mortality for those with albumin levels < 35 g/l was 48% versus 11% in those with levels > 42 g/l and that the relative hazard of death was five times greater regardless of CD4 count.[69] Pre-ART albumin levels of < 35 g/l in Tanzania were associated with a 4.52 times greater risk of death at the initiation of ART.[72] Although asymptomatic and not wasted, a third (32.4%) of this study population were at an increased risk of disease progression and death, which may be further increased with the initiation of ART, and this is especially significant in light of the recent implementation of the UTT guidelines.

Anaemia

Nearly one in two (42%) were mildly anaemic, a prevalence which was 10% above that found by the SANHANES-1 general population survey of KZN females (33%).[40] To our knowledge, this is the only study in SA that has investigated the Hb levels of asymptomatic HIV-infected adults (CD4 542.5 cells/mm^3) prior to the initiation of ART (CD4 counts ≤ 200 cells/mm^3).[73, 74] Mild anaemia (Hb 8–14 g/dl men, Hb 8–12 g/dl women) has been shown to have a relative hazard ratio of disease progression of 2.2 when compared with those without anaemia.[75] Anaemia is a strong independent risk factor for disease progression, mortality and a loss of quality of life independent of both viral load and CD4 count.[74, 76–79] Shah *et al*. (2007) suggested that it might be useful to consider albumin levels in relation to the Hb levels to identify high-risk individuals.[79]

Limitations of the study were that this was a relatively small observational study performed on a single cohort of mainly female patients in a specific location, which may have impacted on the findings and may therefore not be applicable to a larger population group.

Conclusions

The high prevalence of both overweight and obesity amongst ART-naive people living with HIV in SA follows the general population trend, exposing them to the well-documented risks of obesity in addition to those associated with HIV. The recent implementation of the UTT will expose many overweight/obese individuals to ART, potentially complicating their outcome. This apparently well, asymptomatic population of people living with HIV was at an increased risk of morbidity, progression and death due to the high prevalence of hypoalbuminemia, raised hs-CRP levels and iron deficiency anaemia. These adults look deceptively well and in the overloaded clinic system would not be identified as being at high risk and in need of additional care. Ironically, overnutrition in the form of an excess intake of energy needed to be addressed while improving undernutrition in the form of micronutrient deficiencies such as iron.

Author's contributions – Dr Chara Biggs planned and implemented the study, processed and interpreted the data and authored the manuscript.

Dr Beth Spooner was the study clinician and assisted with writing the clinical aspects of the paper.

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