The metabolic profiles of HIV-infected and non-infected women in Mangaung, South Africa

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Abstract

Objective: To determine the biochemical nutritional status of HIV-infected women in Mangaung.

Design: Cross-sectional.

Setting: The community of Mangaung, Free State, South Africa.

Subjects: A representative group of 500 black women (25–44 years) was selected randomly to participate.

Outcome measures: Biochemical analyses were performed for total lymphocytes, serum protein, serum albumin, plasma fibrinogen, serum insulin, serum glucose, serum triglycerides and serum cholesterol using standard methodology. Values were compared to standard references, and between HIV-infected and HIV-uninfected women.

Results: After screening for eligibility, 488 women qualified. Sixty-one per cent of the younger women (25–34 years) and 38% of the older women (35–44 years) were HIV-infected. HIV-infected women had significantly lower median blood values for total lymphocytes ($p = 0.0001$ and $p = 0.02$ for younger and older group respectively) and serum albumin ($p = 0.0001$ for both age groups), but significantly higher median concentrations of serum protein ($p = 0.0001$ for both age groups) than uninfected women. Plasma fibrinogen and serum insulin concentrations were significantly lower in HIV-infected younger women than in their uninfected counterparts ($p = 0.002$ for both parameters). Older HIV-infected women had significantly lower total serum cholesterol values ($p = 0.01$) than older HIV-uninfected women. Serum glucose and serum triglycerides did not differ significantly between HIV-infected and HIV-uninfected women.

Conclusions: The results indicate a possible impact of HIV infection on serum protein and serum albumin, which may adversely affect biochemical nutritional status and the course of HIV progression. Future research into the causes and possible treatment of metabolic changes in women in this community should be prioritised.

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Introduction

Human Immunodeficiency Virus (HIV) infection has reached epidemic proportions in South Africa, where increasing numbers of people now die because of Acquired Immune Deficiency Syndrome (AIDS).[1] Malnutrition remains a significant but intriguing consequence of HIV infection.[2] Besides factors such as decreased food intake and malabsorption, HIV infection is typically associated with adverse metabolic events.[3] Abnormalities in protein, glucose and lipid metabolism have been evident in HIV infected patients since recognition of the AIDS epidemic (reviewed by Salas-Salvadó and Garcia-Lorda).[4] Although there is consensus that major nutritional changes are rare in clinically stable HIV-infected populations,[5] alterations in the biochemical nutritional status of asymptomatic HIV-infected black people have been documented.[6] Factors such as HIV, opportunistic infections and the host's immune response to the disease can affect metabolic changes directly or indirectly. However, questions regarding metabolism in HIV infection remain a puzzle, and the causes thereof should be determined.[4]

Until the end of 2003, when the South African government initiated its long-awaited "Operational plan for Comprehensive HIV and AIDS Care, Management and Treatment for South Africa", antiretroviral therapy (ART) could only be afforded by a few privileged South Africans living with this disease. With the approval of this plan, the South African government committed itself to provide free ART, which is, however, currently restricted to AIDS patients with CD4+ cell counts ≤ 200 mm^3.[7] Current studies conducted on individuals with HIV infection and AIDS mainly focus on the effect of ART on the metabolic profile of patients using this medication. In South Africa, literature on the metabolic effect of HIV infection in ART-naive black people is limited.

In this article, the authors provide information that could lead to a better understanding of the effect of HIV infection on metabolic profiles in human subjects, with special emphasis on black females not on any current treatment for HIV infection.

Methodology

A representative sample of 500 women from two formal settlements (Phahameng and Botchabela) and two informal settlements (Joe Slovo and Namibia) from the existing 13 sites in Mangaung, the black residential township of Bloemfontein, was randomly selected to participate, using township maps. The four sites were considered to be representative of the Mangaung area. The residential plots in the four selected areas were counted and numbered. Namibia had 2 995 plots, Pahameng 1 711, Joe Slovo 1 359 and Botchabela 2 308. Non-pregnant, pre-menopausal, but post-pubertal women between the age of 25 and 44 years were targeted to participate. The sampling strategy was designed specifically to compare (as part of the larger study) the two age categories to render the study results comparable with those of another study in the same geographical area.[8] A proportionate number of respondents (180 from Namibia, 100 from Pahameng, 80 from Joe Slovo and 140 from Botchabela) was randomly selected from these settlements. Twenty subjects were recruited per week over a 25-week period (March 2000 – November 2000). A randomly selected residential plot was approached by a community health care worker who received prior training in obtaining informed consent and explaining the purpose and procedures of the study to possible participants. One woman per selected residential plot was screened for eligibility (not pregnant and within the age group). If no one was at home, the residential plot to the right was targeted and if still unsuccessful, the residential plot to the left of the original address was approached. If these attempts failed, another residential plot was randomly selected. The assigned community health workers explained the purpose of the study to possible participants. The women took part voluntarily, after giving written informed consent. The study was approved by the Ethics Committee of the Faculty of Health Sciences, University of the Free State (ETOVS no. 02/00). All participants were originally unaware of their HIV-status, and therefore not receiving any antiretroviral medication. Subjects could indicate whether they would like to receive their HIV test results or not. Those preferring to be informed of their HIV status (< 30% of total sample) were confidentially seen by a medical practitioner, who referred HIV-infected patients for counselling and further follow-up. The research team was kept blinded to the outcome of the individual HIV tests.

Laboratory determinations were done for HIV status, total lymphocytes, total serum protein, serum albumin, plasma fibrinogen, serum insulin, serum glucose, serum triglycerides and total serum cholesterol at the Fibrinogen Unit, Central University of Technology, Free State. Respondents fasted overnight, abstained from exercise and avoided consuming alcohol and caffeine for 24 hours prior to the collection of the blood samples. All blood samples were taken in the morning. Not all samples could be evaluated due to clotting or haemolysis. The number of samples that could not be used was very low and did not result in bias. Respondents were not requested to return for repeat samples. See Box 1 for the methods and equipment used.

Statistical analysis

Data was processed using the SAS software program.[10] All datasets were categorised into two age groups (25–34 years, and 35–44 years), and two HIV status groups (HIV-uninfected and HIV-infected).

Box 1: Methods and equipment used

Parameter	Methods and equipment
HIV tests	Human Immunodeficiency Viruses (HIV 1/HIV-2: Recombinant antigens and synthetic peptides) reagent pack (Abbott, Germany, catalogue no 3D41-20)
Total lymphocyte counts	Via a full blood count on ethyldimethylacetic acid (EDTA) blood using a Coulter Microdiff 18 Cell Counter
Total serum protein	Colorimetric method using Boehringer Mannheim-Roche Diagnostics, Mannheim, Germany (catalogue no 1553836)
Total serum albumin	Colorimetric method using Roche Diagnostics GmbH, Mannheim, Germany (catalogue no 1970569)
Plasma fibrinogen concentration	The method of Clauss[9] for a quantitative determination
Serum glucose	Enzymatic colorimetric method using Roche Diagnostics GmbH, Mannheim, Germany (catalogue no 1448668)
Serum insulin	DRG insulin ELISA
Fasting triglycerides	GPO-PAP method using Roche Diagnostics GmbH, Mannheim, Germany (catalogue no. 148872) based on an enzymatic colorimetric principle
Total serum cholesterol	CHOD-PAP method using Roche Diagnostics GmbH, Mannheim, Germany (catalogue no 1489232) based on an enzymatic colorimetric principle

For each group, continuous variables were described by medians, and categorical variables were described by frequencies and percentages. The significance of the median difference between laboratory blood values of younger and older HIV-uninfected and HIV-infected women was determined by 95% non-parametric confidence intervals (CI) and the Mann-Whitney test. P values ≤ 0.05 were considered statistically significant.

Results

Of the original sample of 500, 488 subjects met the inclusion criteria. Of these subjects, 273 were 25 to 34 years and 215 were 35 to 44 years old. In the respondents that were 25 to 34 years old, 167 of the 273 (61%), and in the age group 35 to 44 years, 82 of the 215 (38%) were HIV infected. Twelve respondents were excluded from the study: four were found to be pregnant during the medical examination, and eight did not meet the age requirement.

Table I illustrates the descriptive biochemical parameters of HIV-infected and HIV-uninfected women (25–34 years and 35–44 years). On average all parameters were within the normal reference ranges, except for serum total protein, which was elevated in the HIV-infected group (both age groups). The median serum total protein was statistically significantly higher in HIV-infected women than in uninfected women ($p = 0.0001$ for both age groups). In contrast, the median serum albumin was statistically significantly lower in HIV-infected women than in uninfected women ($p = 0.0001$ for both age groups).

Table I: Descriptive biochemical parameters of HIV-infected and HIV-uninfected women (25–34 years and 35–44 years)

Age group	25–34 years old				35–44 years old			
	Median		Mann-Whitney p-value	Median difference (uninfected-infected); [CI]	Median		Mann-Whitney p-value	Median difference (uninfected-infected); [CI]
Biochemical parameters	HIV-uninfected	HIV-infected			HIV-uninfected	HIV-infected		
Total lymphocytes (x 10^9/L)	2.4	2.1	*0.0001	0.4; [0.2; 0.5]	2.2	2.0	*0.02	0.2; [0.0; 0.4]
N	104	158			130	80		
Serum total protein (g/L)	82	91	*0.0001	-7; [-10; -5]	82	91.5	*0.0001	-9; [-11; -6]
N	106	167			132	82		
Serum albumin (g/L)	42.9	40.2	*0.0001	2.6; [1.5; 3.7]	42.2	39.6	*0.0001	2.7 [1.7; 3.7]
N	106	167			131	82		
Plasma fibrinogen (g/L)	3.6	3.2	*0.002	0.33; [0.13; 0.56]	3.4	3.2	0.18	-0.17; [-0.44; 0.08]
N	100	157			127	76		
Serum glucose (mmol/L)	4.4	4.3	0.26	-0.11; [-0.30; 0.08]	4.4	4.3	1.0	0 [-0.21; 0.22]
N	105	167			133	82		
Serum insulin (µU/ml)	9.1	5.8	*0.002	2.4; [1.0; 4.0]	5.8	6.3	0.17	-61.85; [-171.03; 34.52]
N	106	166			133	82		
Triglycerides (mmol/L)	0.90	1.0	0.69	0.02; [-0.08; 0.12]	1.10	1.21	0.42	0.05; [-0.08; 0.19]
N	106	167			132	82		
Total cholesterol (mmol/L)	4.3	4.1	0.30	-0.01; [-0.04; 0.1]	4.7	4.3	*0.01	0.4; [0.1; 0.7]
N	106	167			132	82		

* Significant difference

Apart from serum insulin, all other parameters had on average a similar pattern in the two age groups when comparing HIV-infected and uninfected women. Total lymphocytes, serum albumin, plasma fibrinogen, serum glucose and total cholesterol decreased in the HIV-infected group, whereas serum triglycerides and serum total protein increased in the infected group. The difference was significant for total lymphocytes ($p = 0.0001$ and 0.02 in young and older group respectively) and plasma fibrinogen in the younger group ($p = 0.002$) and for total cholesterol in the older group ($p = 0.01$). The pattern in median serum insulin differed between the two age groups comparing infected and uninfected women. In the younger group the serum insulin was significantly lower ($p = 0.002$) in the infected group, whereas it was elevated in the older infected group (although not significantly so) (Table I).

Although most parameters were within the normal reference ranges, it is evident that many women in both age groups and HIV status groups had laboratory values outside these ranges (Tables II and III). As also reflected by the average parameter values, a similar pattern in the two age groups (when comparing HIV-infected and uninfected women) was seen for all parameters, except for serum insulin.

Table II: Frequency and percentage of HIV-infected and HIV-uninfected younger women (25–34 years) with reduced, normal and elevated biochemical parameters

Parameter	HIV-uninfected						HIV-infected						
	Reduced		Normal		Increased		Reduced		Normal		Increased		
	n	%	n	%	N	%	n	%	n	%	n	%	Normal value
Total lymphocytes	0	0	94	90.4	10	9.6	0	0	145	91.8	13	8.2	0.8–3.3 x 10^9/L
Serum total protein	0	0	54	50.9	52	49.1	0	0	34	20.4	133	79.6	60–82 g/L
Serum albumin	0	0	90	84.9	16	15.1	14	8.4	134	80.2	19	11.4	34 < 48 g/L
Plasma fibrinogen	0	0	73	73.0	27	27.0	3	1.9	126	80.6	28	17.8	1.5–4 g/L
Serum glucose	7	6.7	84	80.0	14	13.3	8	4.8	144	86.2	15	9.0	3.05–6.38 mmol/L
Serum insulin	5	4.7	82	77.4	19	17.9	33	19.9	120	72.3	13	7.8	2–25 (µU/ml)
Serum triglycerides	0	0	100	94.3	6	5.7	0	0	157	94.0	10	6.0	< 2 mmol/L
Total serum cholesterol	0	0	83	78.3	23	21.7	0	0	135	80.8	32	19.2	> 0.9 < 5.2 mmol/L

Table III: Frequency and percentage of HIV-infected and HIV-uninfected older women (35–44 years) with reduced, normal and elevated biochemical parameters

Parameter	HIV-uninfected						HIV-infected						
	Reduced		Normal		Increased		Reduced		Normal		Increased		
	n	%	n	%	n	%	n	%	n	%	n	%	Normal value
Total lymphocytes	0	0	121	93.1	9	6.9	2	2.5	75	93.8	3	3.8	0.8–3.3 x 10^9/L
Serum total protein	0	0	67	50.8	65	49.2	0	0	21	25.6	61	74.4	60–82 g/L
Serum albumin	2	1.5	124	94.7	5	3.8	9	11.0	71	86.6	2	2.4	34 < 48 g/L
Plasma fibrinogen	2	1.6	90	70.9	35	27.6	0	0	61	80.3	15	19.7	1.5–4 g/L
Serum glucose	9	6.8	120	90.2	4	3.0	4	4.9	73	89.0	5	6.1	3.05–6.38 mmol/L
Serum insulin	27	20.3	97	72.9	9	6.8	13	15.9	55	67.1	14	17.1	2–25 (µU/ml)
Serum triglycerides	0	0	116	87.9	16	12.1	0	0	69	84.2	13	15.9	< 2 mmol/L
Total serum cholesterol	0	0	88	66.7	44	33.3	0	0	65	79.3	17	20.7	> 0.9 < 5.2 mmol/L

Although the median serum protein in HIV-uninfected women was within the normal reference range for both age groups, approximately 49% of uninfected women in both age groups had serum total protein values above the normal reference range. The percentage of HIV-infected women with elevated serum total protein values was 79.6% and 74.4% in the younger and older age groups respectively.

Of the HIV-infected younger women, only 11.4%, and of the HIV-infected older women, only 2.4% had elevated serum albumin levels. The percentage of women with normal serum lymphocyte counts was almost the same in HIV-infected and uninfected women in both age groups (90.4% and 91.8% respectively of younger HIV-uninfected and infected women; 93.1% and 93.8% respectively of older HIV-uninfected and infected women). Less than 10% of all women had elevated lymphocyte counts and only 2.5% of older HIV-infected women had decreased total lymphocyte levels (Tables II and III).

Discussion

In this cross-sectional study, the metabolic status of both HIV-infected and HIV-uninfected black women was determined, and the observed blood values were compared with normal values. Although the original study was designed to investigate the prevalence of diseases of lifestyle in urbanised black women in Mangaung, the unexpected high prevalence of HIV infection necessitated the determination of the relationship between HIV status and selected metabolic parameters.

Some researchers reported no significant changes in lymphocyte count in HIV asymptomatic subjects during a follow-up period of 15 months. However, patients with more advanced disease showed significantly reduced total lymphocyte counts over a period of five months.[11] When men and women during all stages of HIV infection were investigated, no significant differences in absolute lymphocyte counts were found between patients with stable weight and those who had lost weight.[12] In the younger group in the present study (with the higher prevalence of HIV infection) there was no evidence of lymphocyte depletion in the infected women. This might be due to a shorter duration of infection and an early stage of the disease. In the older group, the majority of infected women did not suffer from lymphocyte depletion, with a very small percentage of HIV-infected women demonstrating low lymphocyte counts. The extent of this reduction is not known and therefore no correlation between disease progression and the lymphocyte values can be speculated upon.

Studies reviewed by Gramlich and Mascioli[13] indicated elevated total protein and normal or reduced serum albumin levels in asymptomatic HIV-infected and AIDS patients. Significantly higher total serum protein levels between asymptomatic HIV-infected and uninfected black South Africans have also been reported.[6] Notwithstanding significantly lower albumin concentrations in the HIV-infected subjects in that study, albumin levels were still high. Furthermore, anthropometric indices and nutrient intake between HIV-infected and uninfected subjects did not differ significantly. The authors therefore suggested a possible decrease in nutritional status. Asymptomatic HIV-infected subjects who followed a diet rich in animal foods also reflected smaller decreases in serum albumin and lipid variables.[6] It has been suggested that factors such as infection, changes in vascular permeability and hydration status can affect circulating proteins,[13] including total protein. During infection, the acute-phase response is rapidly harnessed to eliminate microbes, control further damage, clear infectious debris, and initiate repair processes.[14] These factors could possibly have contributed to elevated serum protein levels in the present study, where median values of total serum protein of both groups of HIV infected women were significantly higher than the levels in their uninfected counterparts (Table I). The elevated total protein levels in 49.1% of the younger HIV- uninfected women and in 49.2% of the older HIV-uninfected women may be attributed to other infections that need further investigation. However, it is also known that black people have significantly higher immuno-globulin G levels than white people,[15] and this could be a contributing factor to the elevated levels in the HIV-uninfected group. The differences between the infected and uninfected groups (both age groups) were significant and HIV infection is probably the main reason.

While some proteins increase as a reaction to the acute-phase response, others, such as albumin, decrease in concentration,[14] and have been associated with shorter survival in women with HIV infection.[16] Most women (infected or not) in both age groups had normal serum albumin levels. The 8.4% and 11% of infected women (younger and older group respectively) with reduced levels of albumin possibly reflect the reaction of the acute-phase response to the infection.[17] Luder et al[12] reported no significant differences in albumin levels between HIV-infected or AIDS patients with stable weight and those who had lost weight. However, Van Staden et al[17] found significantly lower serum albumin levels between patients with CD4 cell counts < 200/mm^3 and those with CD4 cell counts of 200 to 499/mm^3. In the uninfected older women, 1.5% had reduced levels of albumin. The possibility of other infections at play should be investigated.

Fibrinogen is an acute-phase protein involved in blood clotting. The acute-phase response is the primary mechanism used by the body to restore homeostasis following infection, and is characterised by increased concentrations of circulating fibrinogen.[18] In the present study, in both age groups, median plasma fibrinogen concentrations were lower in HIV-infected women than in HIV-uninfected women (to a significant degree in the younger group). This is not due to fibrinogen levels in the sub-normal range in HIV-infected women, but rather to the larger percentage of uninfected women with elevated fibrinogen levels, possibly resulting from a complex interplay of factors such as alcohol consumption, smoking, following a less prudent diet and physical inactivity.[19] In the Transition and Health during Urbanisation of South Africans (THUSA) study, fibrinogen concentrations between HIV-infected and uninfected subjects did not differ significantly, possibly indicating the absence of the acute-phase response in the HIV-infected subjects.[6] In the HIV-infected group in the present study, 17.8% and 19.7% and in the HIV-uninfected group 27% and 27.6% of the younger and older groups (respectively) had elevated plasma fibrinogen levels. Increased plasma fibrinogen levels are associated with cardiovascular disease[20] and purely based on these levels, 17.8 % to 27.6% of the women have increased risk of this disease.

Abnormalities in glucose metabolism have been reported before treatment with highly active antiretroviral therapy (HAART) became the standard of care for HIV patients. Studies reviewed by Salas-Salvadó and Garcia-Lorda[4] showed that glucose levels may be normal or lower than normal, insulin levels may be normal or increased, while insulin sensitivity is increased in patients not receiving HAART. In the present study, the majority of HIV-infected women (both age groups) had normal serum glucose levels and no significant differences were detected between HIV infected and uninfected groups. These results are similar to those reported for black South Africans[6] and support the notions that HIV-infected ART-naive individuals may maintain normal serum glucose levels (studies reviewed by Salas-Salvadó and Garcia-Lorda).[4]

In the present study, most women had normal serum insulin levels, ranging from 67.1% in the older HIV-infected group to 77.4% in the younger HIV-uninfected group. In the younger group, median serum insulin concentrations were significantly lower in the HIV-infected than in the HIV-uninfected women (Table I). This is probably due to the 19.9% of the infected younger women with reduced levels of serum insulin and 17.9% of uninfected younger women with increased levels. In the older group there was no significant difference between the infected and uninfected groups. As the status of disease progression in the infected group is unknown, it is difficult to come to a conclusion or logical explanation for the differences. Some researchers found no differences between insulin levels and endogenous glucose production, but significantly lower plasma glucose levels in HIV infected men versus controls. The authors concluded that HIV-infected men have increased rates of insulin clearance and increased sensitivity of peripheral tissues to insulin.[21] In the present study, however, the serum glucose levels in both age groups and HIV groups did not differ significantly.

Studies reviewed by Salas-Salvadó[4] and Garcia-Lorda and Gramlich and Mascioli[13] showed that the metabolism of lipids may change during HIV infection and AIDS. Total cholesterol levels may be normal or reduced, while triglyceride levels may increase. This atypical pattern of lipid metabolism has been associated with immune impairment and may be a marker of disease progression.[22,23] Decreased cholesterol levels have been previously reported in antiretroviral (ARV)-naive HIV infected patients.[6,24] Although the median total cholesterol in older women was significantly lower in the HIV-infected group compared to the HIV-uninfected group (Table I), this is most probably due to the fact that 33.3% of the uninfected women had elevated levels (compared to the 20.7% of the infected group). Nobody in both age groups had decreased cholesterol levels. It has been reported that disease stage has a lowering effect on cholesterol levels,[25] which can occur despite stable or increased dietary intakes of saturated fat and cholesterol.[22] This was not evident in the current study, as subjects were possibly in an early stage of HIV infection.

Increased serum triglyceride levels during asymptomatic HIV infection have been reported in some studies,[23,26] while others do not support this notion.[22,24] Significantly lower triglyceride levels in asymptomatic HIV-infected black men and women than in uninfected groups have been documented.[6] No significant differences between median serum triglyceride levels of HIV uninfected and infected women from the two age groups were seen in the present study (Table I). Of the older women, 12.1% and 15.9% (HIV-uninfected and infected, respectively) fell in the increased risk category of elevated serum triglycerides. Smaller percentages were at risk in the younger age group. During HIV infection, decreased activity of the enzyme lipoprotein lipase can lead to reduced blood clearance of triglycerides.[27] Increased triglyceride concentrations have been reported, even in patients with CD4 cell counts > 400 X 10^6/l.[23] However, uninfected women in the present study also had elevations and other mechanisms are probably at play.

Some changes expected in HIV-infected people were seen in the uninfected group (indicating other factors at play). Significant differences were observed due to larger percentages of uninfected women with values outside the normal reference range than infected women. It is therefore not possible to ascribe most of these differences to HIV infection based on the data gathered during this study.

The results from the present study reinforce the fact that it is of paramount importance for the health of all people in South Africa to

be aware of their HIV status. This will enable health care workers to make informed and responsible decisions regarding interventions, and help governmental institutions to better plan for the health and treatment of these people.

Conclusion and recommendations

The results from the study indicate a possible impact of HIV infection on serum total protein and serum albumin in ARV-naive persons. For all other parameters no evidence could be found to indicate a major impact of HIV infection. More information is necessary to correlate changes in nutritional parameters to disease status. Future research into the causes and possible treatment of metabolic changes in both HIV-uninfected and HIV-infected black women in this community should be prioritised.

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