An association between vasoactive agents and etiology of hypertension and obesity in HIV patients in Mthatha, South Africa

S Zono, E Umapathy, K Awotedu

Department of Human biology,

Faculty of Health Sciences,

Walter Sisulu University, Mthatha, South Africa

Presentation layout

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- Aim and objectives
- Materials and methods
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Introduction .

* The regulation of vascular tone: Endothelium releases: vasodilators like: Nitric Oxide (NO), Prostacyclin, Endothelium derived hyperpolarizing factor (EDHF) or

  Vasoconstrictors Endothelin-1 (ET-1) or Thromoxane.

* NO maintains basal vasodilator tone of blood vessel. Three forms exist: nNOS (neuronal) which regulates synaptic NT release: iNOS (inducible NOS) like in inflammation from macrophages and : eNOS (endothelial) from the endothelium.

* Endothelin is a vasoconstrictor: Three forms: ET-1, ET-2, ET-3. Endothelial cells only release ET-1. ET-1: increases interleukins & TNF- and decreases NO & Prostacycline

* Three ET-1 receptors: ETA & ETB2 in smooth muscle cells & ETB1 in endothelial cells.

* Activation of ET-B1 receptors in endothelium: vasoconstriction and in Endothelial dysfunction (ED):

* ET-B1 receptors on smooth muscle cells are upregulated: Vasoconstriction. (Sandoo et al., 2010).

* NO & ED are counterparts in vascular function and an imbalance between these two mediators lead to endothelial dysfunction and play a role in vascular disease. (Bourque et al 2011)

- NO tonically inhibits ET-1 function, and if NO is diminished, the uncontrolled action of ET-1 results in vasoconstriction and lead to vascular remodelling and dysfunction.

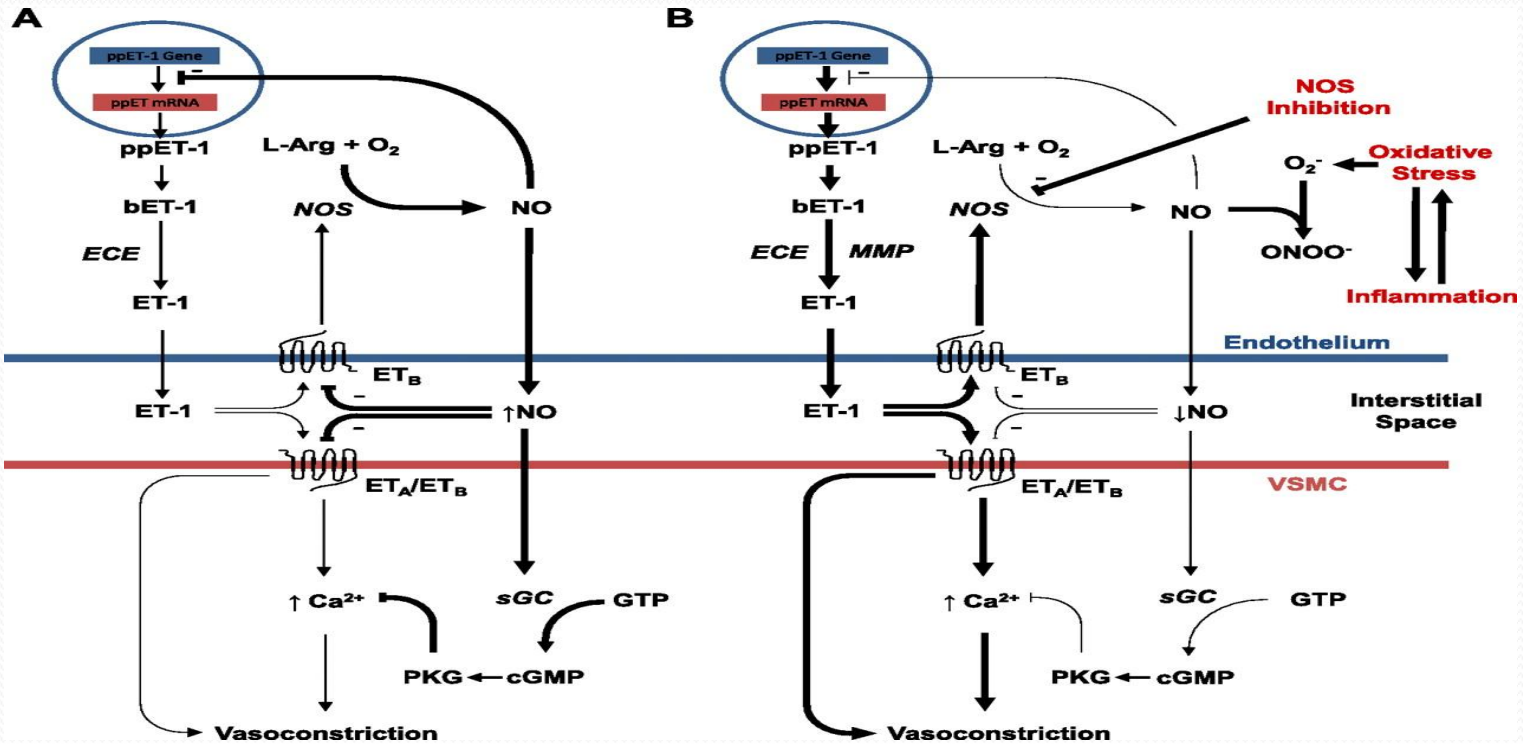
Introduction & Literature review.

- An increase in ET-1 indicate damage or injury to endothelial cells and elevated levels of ET-1 have been implicated in atherosclerosis and other vasculopathies
- ET-1 acts upon vascular smooth muscle through the G-protein coupled receptor subtype ETA leading to vasoconstriction in resistance vessels (Webb, 1997)
- NO is a labile-free radical with multifaceted action, wide tissue distribution and ubiquitous presence (Moncada & Higgs, 1993)
- NO is synthesised from L-arginine through the actions of NO synthase type 3 or endothelial NO synthase (eNOS) (Michel & Feron, 1997).
- Inactivation of eNOS may be mediated by oxidized lipoproteins, a major chemical component in initial proatherogenic milieu (Chin et al., 1992).
- ET-1 is quickly removed from the circulation by a receptor mediated pathway in the lungs
- Statins might influence vascular tone by modulating the expression of endothelial vasoactive factors (Hernandez-Perera et al., 1998)

Introduction Contd

- Endothelial dysfunction is a sensitive marker and an early event in atherosclerosis.
- Protease inhibitors (PI) promote endothelial dysfunction indirectly by elevating circulating lipids.
- PIs are associated with an increased risk of cardiovascular diseases: lead to elevated cholesterol, TGs, increased carotid intima thickness or atherosclerotic lesions & implicated to have atherogenic properties However, the benefits of the PIs should be balanced against the long term risk of CV diseases. (Rhew et al., 2003).
- Nucleoside reverse transcription inhibitor (NRTI) has direct effects on the vascular endothelium. Azidothymidine (AZT) may induce direct vascular effects.
- A direct impairment of mitochondrial function and an induction of oxidative stress: proposed mechanism for anti-retroviral induced endothelial dysfunction. (Jiang et al., 2006).
- HAART (Highly Active Anti Retroviral Therapy) may induce dyslipdemia, insulin resistance, body fat distribution- similar to metabolic syndrome. HAART may also induce hypertension (Bergersen et al., 2003).
- Prevalence of hypertension was higher in patients on HAART (21%)almost similar to HIV- controls. BMI was similar in both HAART and without HAART, but elevated in controls (HIV-).
- Considering the marked drop in mortality due to HAART in HIV + the side effects on hypertension is a minor problem (Bergersen et al., 2003).
- The present study was therefore initiated to study the interaction between vaso-active factors and the etiology of hypertension in HIV+ on HAART.

- **Schematic of proposed interaction between endothelin-1 (ET-1) and nitric oxide (NO) within the vasculature.**



Stephane L. Bourque et al. Am J Physiol Regul Integr Comp Physiol 2011;300:R1288-R1295

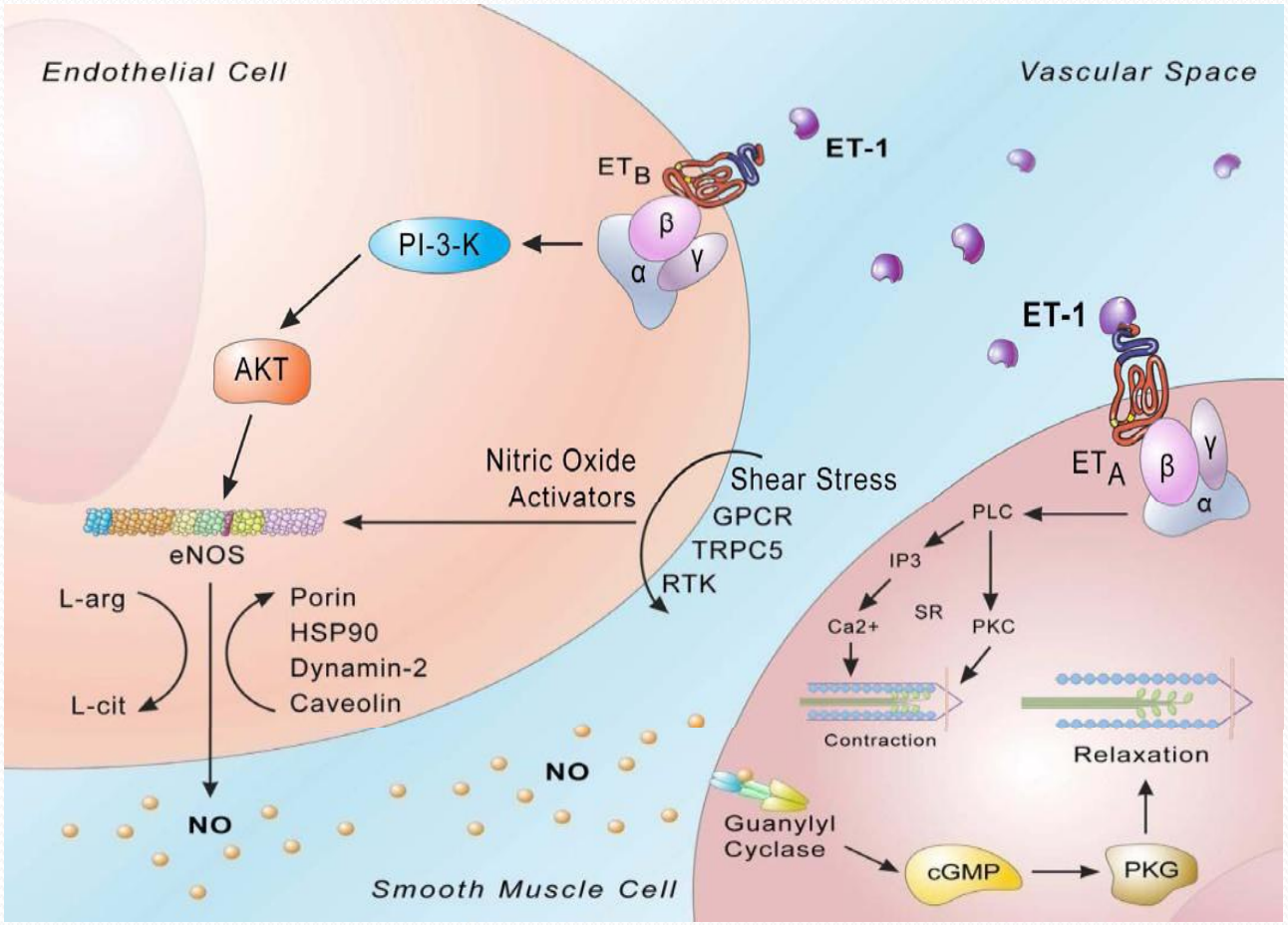


Figure 2: Cellular signalling pathway of endothelin and NO (Khimji & Rockey 2010).

AIM OF THE STUDY:

To determine the effects of HIV infection and antiretroviral treatment on blood pressure and BMI and correlate the changes to ET-1 and NO.

OBJECTIVES:

1) To determine the association between blood pressure, body composition with endothelin in each group;
2) To determine the association between blood pressure, body composition with nitric oxide in each group.
3) To measure the variations of blood pressures across the groups of HIV status and BMI in each group

Materials and methods

- This was a descriptive and comparative study.
- A Quota sample method was used
- Participants were recruited from Clinics (Gateway and Infectious disease clinic), Nelson Mandela Academic Hospital (NMAH) in KSD Municipality, Eastern Cape Province, South Africa.
- This study was conducted in a random manner, planned to convenience population according to inclusion and exclusion criteria and the expected sample size was 150 participants of different sex groups

Materials and methods cont...

Sample size

- 154 participants took part in the study and were categorized into the following groups: 57 HIV positive participants (A), 40 HIV positive on HAART participants (B) and 57 HIV negative participants (C) (controls). Questionnaires and consent forms were issued to the participants.

Selection criteria

- HIV patients were considered eligible for inclusion in the study if at the time of data collection they were aged 18 to 60 years and signed the consent form.
- Questionnaire were also Issued to acquire participant background.

Exclusion criteria

- Excluded from participation were individuals who were under treatment for hypertension, had used anti-diabetic agents, steroids, growth hormone, oral contraceptives pills, or any anabolic agent, substance abuse, appetite suppressor, pregnant, or had breast-fed in the past year, who have or who had an acute infection within 3 months of the study

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Material and methods cont....

Body composition

- Body composition indices were measured using anthropometry and Omron BF 500 Body Composition monitor (Omron, Tokyo, Japan).
- Height was taken to the nearest 1 mm with the aid of Harpenden's stadiometer with participant wearing light clothes without shoes.
- Blood pressure was measured using sphygmomanometer (Automatic blood pressure monitor)

Materials and methods cont....

- 20 millilitres of venous blood was drawn between 08:00 and 09:30 am before breakfast after 10-12 hours overnight fast.
- Enzyme immunoassay kit was used for the quantitative determination of ET-1 and
- Nitrate/nitrite colorimetric assay kit was used for the determination of NO.

- Data was analysed by using the Statistical Package for the Social Sciences (SPSS) Version 19.0 for Windows (SPSS, Chicago, U.S.A.).
- Multiway analysis of variance (MANOVA) and covariance (ANCOVA) were used to explore the association between blood pressure groups, body composition, gender and HIV status groups.
- Descriptive statistics and Comparison study was used to calculate mean ± SD of all variables. Correlation analysis was done to analyse a degree of correlation between ET-1, NO levels, body composition and arterial blood pressure. A p-value of <0.05 was considered statistically significant.
- The Ethical approval was obtained from the Ethics Committee, Faculty of Health Science, Walter Sisulu University for ethical and bio-safety clearance, protocol number: 023/2012
- WSU Research Directorate funded the study.

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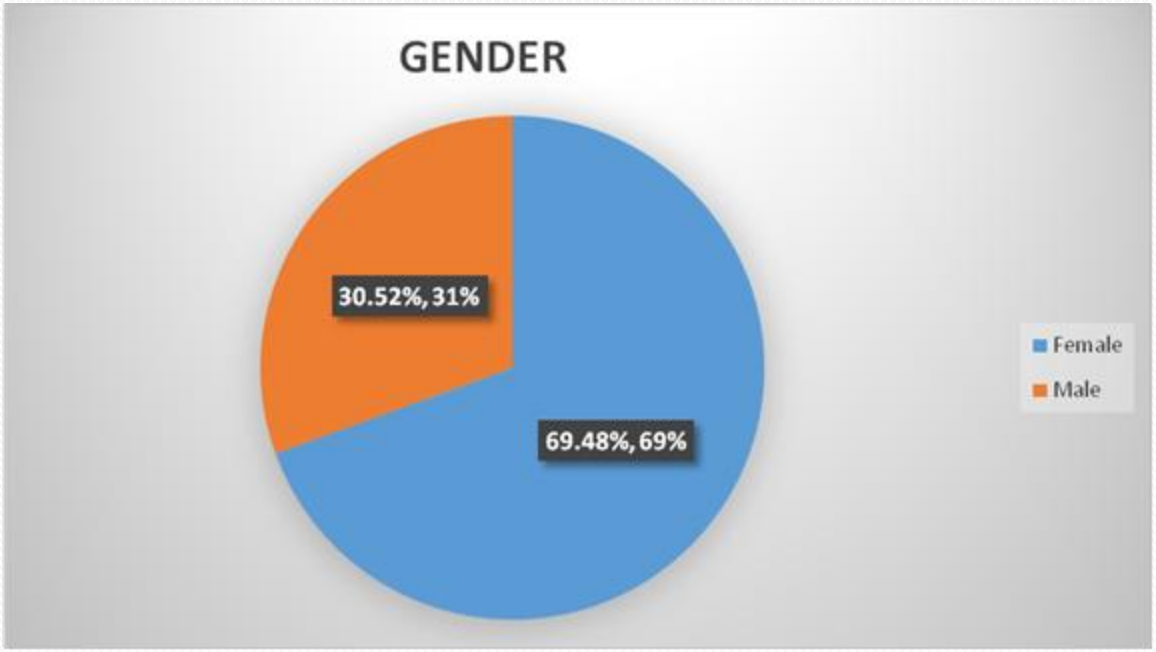
Results

Figure 1: Distribution of study population according to gender.

More females than males



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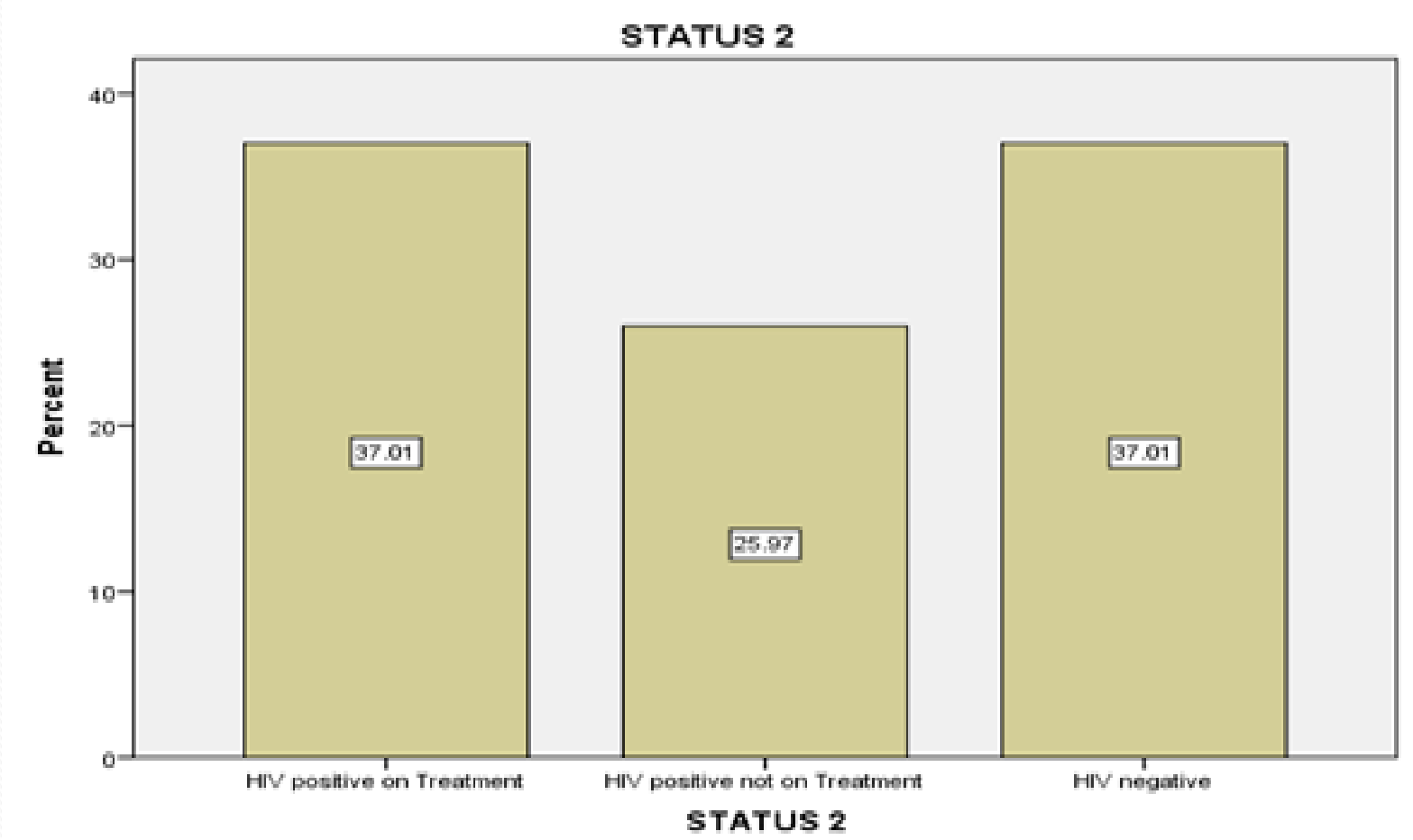
Results

Figure 2: Percentage of patients in different study groups.

HIV + on treatment: 37% HIV+ not on treatment 25% HIV – 37%



Results: Table 1: Mean levels of variables by gender in all

Variables of Interest	Males n=47 mean±SD	Females n=107 mean±SD	ANOVA P-value
Age (years)	37.8±12.7	36.9±11.4	0.672
Weight (kg)	64.2±12.2	71.3±16.5	0.009
Height (m)	1.691±0.08	1.581±0.07	<0.0001
Waist circ (cm)	82.31±9.8	91.6±12.9	<0.0001
Hip circ (cm)	93.5±10.2	107.4±12.9	<0.0001
W/H ratio	0.883±0.075	0.856±0.094	0.078
SMF (%)	37.7±6.7	25±4.3	<0.0001
Whole fat (%)	19.8±10.4	41.3±9.1	<0.0001
BMI (Kg/m^2)	22.5±4	28.4±6.1	<0.0001
RM (Kcal)	1503.8±168.8	1383.4±162.9	<0.0001
SBP (mmHg)	131.8±28.3	128.1±22.4	0.385
DSP (mmHg)	84.9±13.1	84.9±13.4	0.994
PP (mmHg)	83.7±22.3	84.1±15.1	0.906
Endothelin (pg/ml)	8.1±3.5	8.6±3.4	0.325
Nitric oxide (nmol)	15.5 ±5.4	17.9±5.5	0.048

Table 2: Influence of aging on the mean levels of variables in all

Variables of	<30 years mean±SD	30-39 years mean±SD	≥40 years mean±SD	ANOVA P-value
Weight (kg)	63.9±15	70±16.9	72.5±14	0.021
Height (m)	1.626±0.09	1.615±0.09	1.610±0.09	0.525
Waist circ (cm)	84±13.3	87.6±12.6	93.8±10.8	<0.0001
Hip circ (cm)	100±12.5	100.4±14.1	105.4±14	0.143
W/H ratio	0.840±0.076	0.853±0.108	0.894±0.069	0.005
SMF (%)	29.2±8	29.8±8.1	27.8±7.3	0.388
Whole fat (%)	32.7±13.2	34.3±13.8	36.8±13.9	0.328
BMI (Kg/m²)	24.6±5.5	26.6±6	28.3±6.5	0.009
RM (Kcal)	1374.6±166.1	1430.1±182	1447.6±165.9	0.096
SBP (mmHg)	127.5±26.4	124.5±20.4	135.2±25.2	0.060
DBP (mmHg)	80.4±8.7	82.8±12	90.7±15.5	<0.0001
PP (mmHg)	80.4±19.7	88.1±12.9	82.9±19.6	0.087
Endo (pg/ml)	9.5±4.6	8±2.8	8±2.6	0.051
NO (nmol)	15.6±4.7	18±6.1	17.6±5.5	0.082

Table 3: Levels of continuous variables in all and by HIV status groups

Variables Of Interest	all mean±SD	HIV+ on ART mean±SD	HIV+ not on ART mean±SD	HIV (-) mean±SD	ANOVA P-value
Age (years)	37.2±11.8	37.4±10.6	34.1±10.4	39.1±13.4	0.111
Weight (kg)	69.1±15.6	66.4±15.8	65.7±11.8	74.3±16.7	0.007
Height (m)	1.615±0.089	1.623±0.084	1.601±0.088	1.617±0.098	0.483
WC (cm)	88.8±12.8	86.1±12.4	88.8±11.4	91.4±13.6	0.079
HC (cm)	103.1±13.7	100.2±13.4	100.4±11.8	108.1±14	0.002
WHR	0.864±0.089	0.862±0.080	0.900±0.108	0.848±0.081	0.080
BMI (kg/m²)	26.7±6.1	25.1±5.2	25.9±5	28.8±7.1	0.003
SMF (%)	28.9±7.8	30.7±8.1	28.7±6.7	27.1±7.8	0.048
Whole fat (%)	34.7±13.7	31.5±14	34.1±12.1	38.4±13.8	0.023
RM (Kcal)	1420.1±173.3	1396.1±162.5	1383.1±144.2	1470.1±192.6	0.021
SBP (mmHg)	127.1±20.5	121.5±21	129.1±18.6	131.3±20.3	0.029
DSP (mmHg)	84.7±13.4	81.4±14	85.6±15	87.5±10.8	0.044
PP (mmHg)	86.9±12.8	87.1±12.8	89.5±12.8	84.7±12.7	0.189
Endo (pg/ml)	8.2±3.9	9.7±3.8	6.9±2.5	7.6±4.2	<0.0001
NO (nmol)	18.1±5.8	19.6±7.5	19.6±4.5	15.6±3.6	<0.0001

Results cont…

Table 4:Variations of mean levels on endothelin, across the groups of interaction of HIV status and BMI in all . Endothelin pg/ml.

Variables Of Interest	Underweight Mean±SD	Normal Mean±SD	Overweight Mean±SD	Obesity Mean±SD
HIV on HAART				
Endothelin	7.8±2.0	10±4.1	10.6±4.4	8.8±2.7
HIV not on HAART				
Endothelin	7.8±2.8	7.2±2.6	6.8±2.2	8.2±2.9
HIV negative				
Endothelin	5.9±2.8	6.3±2.2	6.3±1.8	6.8±2.0
P-value Anova	<0.0001	<0.0001	<0.0001	<0.0001

Table 5:Variations of mean levels on nitric oxide, across the groups of interaction of HIV status and BMI in all. Nitric oxide in nmol.

Variables Of Interest	Underweight Mean±SD	Normal Mean±SD	Overweight Mean±SD	Obesity Mean±SD
HIV on HAART				
Nitric oxide	5.1±1.0	18.1±6.6	18.5±7.7	21±7.0
HIV not on HAART				
Nitric oxide	18.1±3.3	19.4±4.2	18.7±4.8	20.5±3.4
HIV negative				
Nitric oxide	8.8±0.5	13.5±2.1	16.4±2.2	15±2.2
P-value Anova	<0.0001	<0.0001	<0.0001	<0.0001

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Table 6: Variations of mean levels SBP, DBP, PP, across the groups of the l interaction of HIV status and BMI in all

Groups of Interaction	SBP Mean±SD	DBP Mean±SD	PP Mean±SD
HIV(+) on ART			
Normal	116.8±15.0	79.1±9.5	87.4±14.1
HIV(+) not on ART			
Normal	122.6±11.3	80.3±9.7	86.4±10.7
HIV (-)			
Normal	125.2±9.8	83.4±8.9	61.9±25
ANOVA	0.018	<0.0001	<0.0001

Discussion and conclusion

- Females (69.48%) compared to males (30.52%) (sex ratio 2 females: 1 male). The most willing to participate in all kinds of research that can facilitate good health.
- Gender showed significant impact on weight, waist circumference and hip circumference. In our study, we included skeletal muscle fat and whole body fat, both are high in females compared to males. Excess weight: risk factor for high BP, high TG levels or blood fats & cholesterol (Dugdale, 2012).
- High visceral fat which around the waist is a specific risk : blood vessels inflammation?
- BMI high in females: bordering on obesity :risk factor for hypertension??
- Weight, waist circumference, waist/hip ratio and Diatolic pressure: all these increase steadily as age increases.
- HIV+ on treatment and not on treatment: no significant weight changes, but compared to HIV- the weight is decreased in HIV+
- In both HIV+ groups, BMI, whole fat, SMF, resting metabolism similar to those of HIV- All groups are in risk of pre exposure to type II diabetes, hypertension: BMI?

Discussion and conclusion.....

- Elevated endothelin--- pre dispose to vascular re modeling, vascular hypertrophy, cardiac hypertrophy ------ endothelial dysfunction.
- Decreased NO levels in HIV+ on HAART further confirms the view that the deleterious effects of unmitigated ET-1 actions result in vasoconstriction and result in vascular remodeling and dysfunction. (Bourque et al., 2011). Not shown in our studies.
- Prevalence of hypertension higher in HIV+ on HAART is confirmed from this study supporting the earlier study (Bergersen et al., 2003)
- The possible implications of the BMI and its role in arterial stiffness and NO bioavailability is the focus of our next study.
- Flow –mediated dilatation is a good surrogate marker of NO which is the focus of further studies. Using sphygmocor and Endopat: macro vascular assessment:
- Arterial stiffness will be analysed by determining pulse wave velocity and Augumentation Index.

Conclusions, Limitations and strengths

- Endothelin and nitric oxide therapy in case of deficiency states may assist in the future management of hypertension.
- Effects and safety of status (lowering-endothelin or lowering-nitric oxide drugs) should be taken in our hospitals.
- The present study might be limited to some degree by its design (case-control study) to demonstrate a causal association. Only longitudinal and prospective studies are able to do that.
- The study was limited by its small size and over representation of females.
- Associations using statistical analysis as well as from valid and standardized measurements of anthropometric/body composition, blood pressure, nitric oxide and endothelin.

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