

The Possible Role of Vasoactive Agents in the Etiology of Hypertension in HIV Patients in Mthatha, South Africa

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Endothelial dysfunction is a sensitive marker and an early event in atherosclerosis. Dysfunction of the vascular endothelium is an early finding in the development of cardiovascular disease and is closely related to clinical events in patients with atherosclerosis and hypertension [1]. It is known that an impaired ability to vasodilate and/or an enhanced sensitivity to vasoconstrictor agonists underlie vascular dysfunction [2]. The endothelium releases vasoactive agents such as nitric oxide (NO), prostacyclin (PGI₂) and endothelium derived hyperpolarizing factor (EDHF) which are vasodilatory. It also releases vasoconstrictors such as thromboxane (TXA₂) and endothelin-1 (ET-1) [3]. Nitric oxide (NO) and endothelin-1 (ET-1) are natural counterparts in vascular function and it is becoming increasingly clear that an imbalance between these two mediators is a characteristic of endothelial dysfunction and is important in the progression of vascular disease [4,5]. Enhanced ET-1 mediated vasoconstriction is also associated with overweight and obesity which contributes to endothelial vasodilator dysfunction and may play a role in the increased prevalence of hypertension with increased adiposity [6].

HIV treatment is based on Protease inhibitors (PI), Nucleoside reverse transcription inhibitor (NRTI) and Azidothymidine (AZT). PI promote endothelial dysfunction indirectly by elevating circulating lipids, NRTI has direct effects on the vascular endothelium while AZT may induce direct vascular effects. However, the benefits of the PIs should be balanced against the long term risk of CV diseases. A direct impairment of mitochondrial function and an induction of oxidative stress is one of the proposed mechanisms for anti-retroviral induced endothelial dysfunction [7].

HAART (Highly Active Anti-Retroviral Therapy) may induce dyslipidemia, insulin resistance, body fat distribution- similar to metabolic syndrome. HAART may also induce hypertension [8]. 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 [8].

In a recent study, Ekambaram Umapathy, et al. (2015), [9] have shown a significant trend between age and weight, age and waist circumference, age and waist/hip ratio, and also age and diastolic pressure in HIV patients on treatment. All these variables increase steadily as age increases from middle age to older age group, so this clearly stipulate high risk of cardiovascular diseases in older participants. However, there was no significance trend to the rest of variables. This therefore means, HIV itself may have an impact on the weight of HIV positive participants. HIV positives on treatment and HIV positive not on treatment had levels of BMI, whole fat, SMF, resting metabolism, similar to those of HIV negatives, the levels indicate overweight of the participants. This suggests that all the groups are in risk of pre exposure to type II diabetes, hypertension, urinary stress, sleep apnea because of elicited BMI. A high BMI is a risk factor for mortality from overall cardiovascular disease. In our study, in all groups of participants small number (n=54) were presented with arterial hypertension. However, the other variable did not vary significantly across these three groups.

Another significant finding in our study is that both endothelin and nitric oxide showed significant correlation among HIV groups. In HIV positive patients on treatment,

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the levels of endothelin were significantly increased. This clearly demonstrates that treatment also has a role in progression of hypertension. Elevated ET-1 may predispose participants to vascular remodeling (change in the vessel structure), vascular hypertrophy, cardiac hypertrophy and endothelial dysfunction. The cellular signaling pathway of endothelin and NO have been well illustrated by Khimji & Rockey, 2010 [10].

Early work on the impact of ET-1 in blood pressure regulation has demonstrated that the vasoconstrictor effects were mediated via the ETA receptor located on the vascular smooth muscle cells but simultaneously addresses the ETB receptor subtype expressed on the endothelial cells, where it leads to vasodilatation by inducing the release of NO and PGI₂ [11]. Thus, ET-1 effects were found to be different, if blood vessels were denuded or if examined in the presence of hemoglobin, which scavenges NO. In addition, *in vivo* studies have shown that an increased vasoconstriction results from inhibiting NO synthesis [12]. However, more investigations have shown that the interaction is even more complex. Binding of ET-1 induces increased NO synthesis by the endothelial NOS (NOS-3) and also increases NOS-3 expression, but in addition, ET-1-mediated signaling leads to an increased production of the endogenous NOS inhibitor asymmetric dimethyl arginine (ADMA), which will potentially lower the bioavailability of NO. Synthesis of both ET and NO are shown to be increased in several inflammatory diseases, such as asthma, arthritis, inflammatory bowel disease and sepsis [12].

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. Further studies on macrovascular assessment and arterial stiffness in HIV + on treatment with HAART may shed more light on the etiology of hypertension in this group of patients

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