Hypertension and the effect of dietary salt on inflammation: An interventional study

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Research note

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Abstract

Objective

Hypertension and dietary salt are associated with inflammation in murine models. Studies in humans are scare and yet critical for the prevention and treatment of hypertension. This was an interventional study of 85 participants. Participants were instructed to follow a one week of low (4 g/day)- and high (9 g/day)-salt diet. BioLegend's LEGENDplex™ bead-based immunoassay (USA) was used to quantify cytokine levels in plasma. Mann-Whitney, logistic regression and the Wilcoxon matched-pairs signed-rank test were used to compare inflammation markers on low- and high-salt diets. The goal of this study was to determine the association between hypertension and inflammation and the effect of high dietary salt intake on pro- and anti-inflammatory cytokines in HIV positive and HIV negative individuals.

Results

43 participants among the 85 were hypertensive with equal sex distribution. Hypertensives had higher plasma levels of IL-6, IL-17A, tumor necrosis factor-alpha, monocyte count and fasting blood glucose. High salt intake was associated with higher IL-2 in hypertensive persons with HIV and lower IL-21 plasma levels in the HIV-negative. These findings suggest that there is an association between hypertension, salt and inflammation. Hypertension is associated with inflammation, and dietary salt intake may play a role in modulating inflammation.

Registration

Pan African Clinical Trial Registry (www.pactr.org) PACTR202007493610166. Retrospectively registered.

Introduction

Hypertension has gained clinical and public health interest as the prevalence has increased over the years in many countries [1]. Owing to the adverse events associated with hypertension such as stroke [2], heart attack [3], kidney disease [4] and cardiovascular disease [5], studies to understand its pathogenesis and risk factors are critical for prevention and management. It is now evident that an inflammatory milieu is present in and contributes to the development of hypertension [6]. Hypertension is very common in sub-Saharan Africa (SSA) compared to other parts of Africa [5]. Dietary salt-intake is positively correlated with development of hypertension and has been associated with inflammation in mice models and some human studies [7, 8]. Population level data consistently show high salt consumption in SSA [9]. In Zambia for example, respondents in a survey always added salt to their food before eating and salt consumption was estimated to be twice higher than that recommended by the World Health Organization (WHO), even among hypertensive patients [10, 11]. A reduction in dietary salt from the current intake of 10 grams per day to the recommended level of less than 5 grams per day, could have major benefits for cardiovascular health with significant healthcare cost savings for both patients and the general population [5, 12, 13]. With these data in view, the relationship between hypertension, dietary salt intake

and inflammation is not well established especially in African countries where the prevalence of hypertension is high. The aim of this study was to determine the relationship between hypertension and inflammation and to test the hypothesis that high dietary salt intake increases plasma inflammatory cytokines.

Methods

Reporting of study adheres to CONSORT guidelines (additional file 1.)

Study design and setting

We conducted a crossover interventional study where participants were instructed to be consuming low salt (4 grams) with their food for one week and high salt (9 grams) for the following week. This study was conducted at Livingstone Central Hospital which is situated in the southern province of Zambia.

Eligibility criteria

This study included persons with and without hypertension that were coming for routine check-ups at the hospital. Persons without hypertension served as a control group and where matched for age and sex. We excluded persons with diabetes, tuberculosis, kidney disease and existing cardiovascular disease. The diagnosis of hypertension was based on the use of antihypertensive medication. All participants with hypertension were taken off medication during the intervention to avoid confounding or bias from the effects of antihypertensives.

Study procedure intervention

All the participants were instructed not to consume any added salt or processed food in the first week. In the second week, participants were instructed to consume low sodium (1, 560 mg) per day, and in the third week, high salt (3, 510 mg). The dietary salt used were sodium chloride tablets (from the research consolidated midland corporation division, New York, USA) which participants crashed and put in their food and/or ingested. Each tablet weighed one (1) gram and contained 394 mg of sodium and 606 mg of chloride. Salt sensitivity was defined as a mean arterial pressure (MAP) difference between low- and high-salt diet of ≥ 8 mmHg and salt resistance as a MAP of ≤ 5 mmHg [14]. Ambulatory blood pressure monitor model ABPM50 (Contec, USA) was used to measure 24-hour BP at the end of each salt diet. 24-hour sodium, potassium and chloride levels in urine were assayed using Ion-selective electrode technology (humalyte plus 3, Human diagnostics) to ensure compliance with salt intake at the end of each phase [15].

Sample size

The principle investigator selected 43 hypertensive and 42 normotensives using systematic random sampling without blinding from an existing study cohort protocol [15]. The sample size assumptions are elucidated in the full published protocol [15]. Participants were grouped into four namely, HIV-positive hypertensive, HIV-positive normotensive, HIV-negative hypertensive and HIV-negative normotensive.

Outcome measure

The primary and secondary outcomes were plasma levels of inflammatory markers and blood pressure between the last day of low- and high-salt diets.

Data analysis

We used descriptive statistics (medians, frequencies) and non-parametric tests when describing our data and testing for associations. We used Wilcoxon matched-pairs signed-rank test to compare median BPs for repeated measures between low- and high-salt diets. To compare medians of continuous variables such as body mass index (BMI), fasting blood glucose (FBG), cholesterol, low density lipoprotein, high density lipoprotein, triglycerides, monocytes, neutrophils, platelets, lymphocytes, between the hypertensive and the normotensive, a Mann-Whitney test was used. We used the Chi-square to test for associations between hypertension status and the independent categorical variables such as sex and HIV status. Multivariable logistic regression was used to determine the factors associated with hypertension. Wilcoxon matched-pairs test was used to test the effect of high salt on cytokines. P-value < 0.05 was used to determine a significant finding.

Results

Participant enrolment flow diagram is shown in the additional file 2.

Table 1
Relationship between hypertension and demographic and clinical characteristics of the study population

	Hypertensive n, 43 median (IQR)	**Normotensive n, 42 median (IQR)**	**p-value**
Age (years)	40 (38, 42)	40 (38, 41)	0.389
Sex, *n(%)*			
Male	20 (46.5)	18 (42.9)	0.735
Female	23 (53.5)	24 (57.1)	
HIV Status, *n(%)*			
Positive	22 (51.2)	21 (50.0)	0.915
Negative	21 (48.8)	21 (50.0)	
Body mass index, kg/m^2	25.6 (23.1, 30.0)	17.6 (16.9, 19.6)	**< 0.001**
Fasting blood glucose, *mmol/l*	5.4 (5.0, 6.2)	4.9 (4.5, 5.6)	**0.038**
Cholesterol, *mmol/l*	4.1 (3.1, 4.6)	3.6 92.0, 4.2)	0.626
High density lipoprotein, *mmol/l*	1.2 (1.1, 1.8)	1.4 (1.0, 1.5)	0.633
Low density lipoprotein, *mmol/l*	2.0 (1.4, 2.9)	1.5 (1.2, 2.1)	0.789
Triglycerides, *mmol/l*	1.0 (1.0, 2.0)	1.0 (1.0, 1.5)	0.680
Platelets, x 10^9/L	232 (193, 327)	261 (195, 290)	0.562
Neutrophils, *$x10^9$cell/L*	2.7 (2.1, 3.5)	2.0 (1.6, 3.7)	0.060
Lymphocytes, *$x10^9$cell/L*	2.1 (1.5, 2.5)	1.9 (1.4, 2.2)	0.343
Monocytes, *$x10^9$cell/L*	0.56 (0.39, 0.72)	0.34 (0.25, 0.45)	**0.001**
IQR, interquartile range			

The study consisted of 45% (n, 38) males and 55% (n, 47) females. 43 of the study population were hypertensive and HIV positive. The youngest was 29 and the oldest was 49 years old with the median age of 38 years. There was no significant difference in age, sex, HIV status and lipid profile distribution between hypertensives and normotensives in the study population. While platelet, neutrophil and lymphocyte count were similar in both, hypertensives had elevated FBG, BMI and monocyte count when compared with normotensives (Table 1).

In multivariate logistic regression (Table 2), age, sex, BMI, HIV status, FBG, IL-6, tumor necrosis factor-alpha (TNF-α) remained significantly associated with hypertension, $p < 0.05$. The HIV positive had a 3% reduced risk of developing hypertension compared to the normotensive individuals (0.02, 0.50, 95% CI, $p = 0.014$).

Serum levels of pro- and anti-inflammatory cytokines were also compared between hypertensives and normotensives and it was found that IL-6, TNF-α and IL-17A were elevated among hypertensives, $p < 0.01$ (Fig. 1; see also Additional file 2).

Figure 1. **Pro- and anti-inflammatory cytokine plasma levels in hypertensive and normotensive individuals**. IL-6, tumor necrosis factor alpha and IL-17A were elevated in hypertension. HTN, Hypertensive; NT, normotensive. ***$p < 0.001$, **$p < 0.01$

Pro- and anti-inflammatory cytokines were compared between the last day of low- and high-salt diets to compare the effect of high dietary salt on inflammatory markers (Additional file 2). IL-2 was higher ($p = 0.013$) while IL-10 was lower ($p = 0.042$) in the normotensive group compared to the hypertensive group (high salt minus low salt cytokine concentration). IL-21 was lower in the hypertensive group compared with the normotensive in the high salt.

Table 2
Association between hypertension and clinical characteristics in logistic regression

Variable	Unadjusted Odds Ratio OR (95%CI)	p-value	Adjusted Odds Ratio AOR (95%CI)	p-value
Age (years)	1.1 (0.9, 1.2)	0.364	1.3 (1.0, 1.7)	**0.043**
Sex, *n(%)*				
Female	1		1	
Male	1.2 (0.5, 2.7)	0.735	7.6 (1.3, 46.0)	**0.026**
HIV Status, *n(%)*				
Negative	1		1	
Positive	1.0 (0.4, 2.4)	0.915	0.03 (0.02, 0.50)	**0.014**
Body mass index, kg/m^2	1.3 (1.1, 1.5)	**< 0.001**	1.3 (1.0, 1.6)	**0.016**
Fasting blood glucose, *mmol/l*	1.7 (1.0, 2.8)	**0.037**	10.7 (2.0, 58.3)	**0.006**
Monocytes, $x10^9 cell/L$	38.7 (3.5, 69.3)	**0.003**	13 (0.27, 69.0)	0.193
IL-6, *pg/ml*	2.3 (1.5, 3.5)	**< 0.001**	4.3 (1.8, 10.0)	**0.001**
Tumor necrosis factor-alpha, *pg/ml*	1.4 (1.1, 1.8)	**0.006**	1.9 (1.2, 3.0)	**0.007**
IL-17A, *pg/ml*	1.9 (1.2, 2.9)	**0.004**	2.1 (0.9, 4.7)	0.065
P-value less than 0.05 are in bold				

Discussion

This was a study to determine if an association exists between hypertension and inflammation and to determine the effect of dietary salt on inflammatory cytokines. Median age, sex distribution and HIV status were similar and comparable between the hypertensive and normotensive. However, hypertensives had a higher body mass index and an elevated fasting blood sugar and monocyte count compared with normotensives, $p < 0.05$.

Similar to our study findings, several studies [16–18] have reported that fasting blood sugar is a predictor for future incidence of hypertension and is elevated in hypertensive patients. A higher monocyte count is a surrogate for inflammatory processes and a predictor of future hypertension as reported in one study [19]. Elevated monocyte count was associated with hypertension in our study and this has previously been reported elsewhere [20] in the HIV negative population. However, it is plausible that HIV infection

could have contributed significantly to the elevated levels of monocytes as half of the participants in the current study where HIV-infected.

Hypertension and inflammation

To test the hypothesis that hypertension is associated with inflammation, 13 cytokines were measured and compared between normotensive and hypertensive patients (Fig. 1). Hypertensive patients had elevated levels of IL-6, TNF-α and IL-17A which are markers of inflammation, $p < 0.05$. This is consistent with reports elsewhere [21]. After adjusting for age, sex, HIV status and body mass index in logistic regression (Table 2), IL-17A was not significantly associated with hypertension but IL-6 and TNF-α remained significantly associated with hypertension. IL-6, IL-17 and TNF-α correlates positively with blood pressure in several studies [22]. Though the mechanism is elusive, it is thought that IL-6, IL-17 and TNF-α are released in response to activated cells of the innate and adaptive immune system following a hypertensive stimuli such as viral infection, high dietary salt intake, activation of the renin angiotensin aldosterone system (RAAS) et cetera. Moreover we have previously shown that hypertensive patients infected with HIV had higher levels of inflammatory cytokines, including TNF-α receptor 1, IL-6, IL-17, IL-5, intercellular adhesion molecule 1 and macrophage inflammatory protein-1α [23]. It is well established in both mice models and human studies that hypertension is associated with elevated levels of IL-6 suggesting the clinical and diagnostic value of IL-6 in hypertension pathogenesis.

In contrast to our previous study [23], HIV positive individuals in this current study had reduced odds for developing hypertension when compared with the HIV negative (0.03, AOR; 0.02–0.50 95%CI, $p = 0.014$). The difference could be attributed to heterogeneity in the age, sex and HIV-related characteristics. In addition, the small sample size could have accounted for the difference and a larger sample size is therefore recommended to validate our findings.

Dietary salt on inflammatory cytokine production

High salt intake causes high blood pressure in some people by its role in activating the RAAS resulting in fluid overload hence high blood pressure [24]. However, salt can also raise blood pressure by eliciting an inflammatory condition that results in direct vessel damage and constriction from activated macrophages, T cells and the effect of inflammatory cytokines [25–27]. Vasoconstrictors secreted in the process such as endothelin and a reduction in endothelial nitric oxide may contribute to high blood pressure [25–27]. Dendritic cells and T cells of hypertensive mice fed with high salt produced inflammatory cytokines IL-17, IL-6, interferon-gamma and other cytokines [25–28]. As most studies are conducted in murine models with dearth of literature of human studies employing salt and its effect on inflammation, we tested the hypothesis that high dietary salt is associated with elevated inflammatory markers by measuring levels of cytokines in the plasma of hypertensive and normotensive individuals at the end of low- and high-salt diet (Additional file 2). Surprisingly, the normotensive group recorded higher IL-2 ($p = 0.013$) and lower IL-10 ($p = 0.042$) on a high salt diet while in the hypertensive group IL-21 was lowered ($p = 0.017$). To control for the effect of HIV-infection, we then separated the groups by HIV status (Additional file 2). IL-2 was raised in the HIV-infected hypertensive group and not in the HIV negative while IL-21 was lowered in the HIV negative in contrast to the HIV-infected group. IL-10 did not remain significantly lowered in either groups suggesting that it was being modulated by HIV status. Though IL-2

is not a specific cytokine, IL-2 was shown to be increased with increased levels of CD4 + T cell immune activation correlating positively with cycling expression during acute infection and this was associated with less decline of CD4 + T cell after 2 years of infection [29]. IL-2 is a γ chain cytokine produced by activated T cells and plays a critical protective role in the maintenance of immune tolerance by controlling the survival and proliferation of T-regulatory cells [30]. IL-2 is known to prevent apoptosis of HIV-infected cells [30]. The role that IL-2 plays in hypertension remains unknown, however, IL-2 production is increased in hypertension compared to normotensive individuals [31] suggesting a protective anti-inflammatory role. IL-21 was lowered on a high salt diet in HIV-negative individuals from our study. We do not currently know, based on our knowledge, the implication and role of this finding in hypertension. A lager sample size may be required before we can generate any hypothesis. Taken altogether, these data suggest that short term high dietary salt may not be associated with inflammation, however further study is warrantable in this area. We think that long term follow-up periods are necessary to establish if an association exists between high dietary salt intake and inflammation.

Conclusion

Hypertensive patients have elevated levels of inflammatory cytokines and higher fasting blood sugar levels regardless of HIV status. While high dietary salt intake is associated with high inflammation markers in murine models, our study did not find this association.

Limitations

To understand the role of dietary salt on inflammatory cytokines, we need longer follow-up studies to validate our findings. Our study followed hypertensive and normotensive patients for a consecutive one week on low and high salt diets which may be too short to elicit an inflammatory milieu. Compliance to dietary salt intake could not be assured and the wideness of the confidence intervals warrants a follow up randomized crossover longitudinal study with a larger sample size to validate these findings.

Abbreviations

ABPM, ambulatory blood pressure monitor; AOR, adjusted odds ratio; ART, antiretroviral therapy; BMI, body mass index; BP, blood pressure; HIV, human immunodeficiency virus; IQR, interquartile range; MAP, mean arterial pressure; OR, odds ratio; RAAS, renin angiotensin aldosterone system; WHO, World health organisation

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the University of Zambia Health Sciences Research Ethics Committee (Assurance No. FWA00026270 IRB00011000) on the 27th of November 2018. Permission to conduct the study was granted by the Livingstone Central Hospital Administration. All participants were asked to consent by signing a consent form before being included in the study. All data collected were de-identified and used for research purposes only.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article. For other data, these may be requested through the corresponding author.

Competing interests

The authors declare that they have no competing interests

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Author’s contributions

SKM, SMM and AK conceived the study. SKM, AK, BMH, SN, GK, DCH, WM, JRK, LP and SMM contributed to the writing of the manuscript. SKM is the principal investigator and guarantor. All authors read, provided feedback and approved the final manuscript.

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Figures

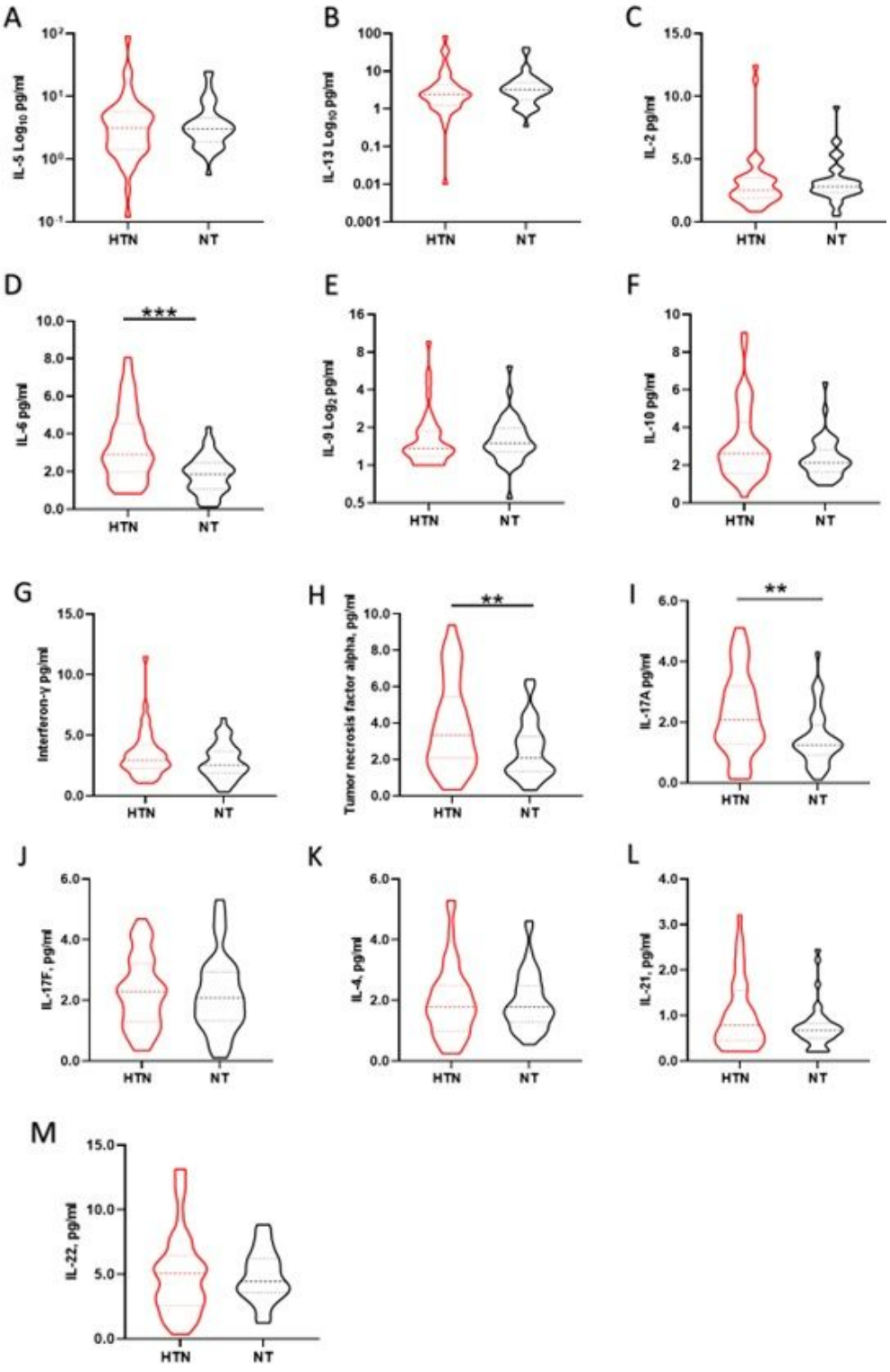

Figure 1

Pro- and anti-inflammatory cytokine plasma levels in hypertensive and normotensive individuals. IL-6, tumor necrosis factor alpha and IL-17A were elevated in hypertension. HTN, Hypertensive; NT, normotensive. ***p<0.001, **p<0.01

Supplementary Files

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- Additionalfile2.docx
- additionalfile1.CONSORT2010Checklist.doc