Research Paper

Assessment of Parathyroid Hormone, Vitamin D, Calcium, and Renin-angiotensin-aldosterone System in Nigerians With Hypertension

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ABSTRACT

Background and Purpose: Hypertension is a major medical condition that can cause many complications and sudden death when not appropriately controlled. This study determined serum calcium, parathyroid hormone, vitamin D, renin, angiotensin II, angiotensin I converting enzyme, and aldosterone in hypertensive individuals, as these compounds play key roles in regulating human blood pressure.

Materials and Methods: This case-control study was conducted on 549 (324 hypertensive cases and 225 controls) individuals between October 2018 and September 2020. Fasting blood samples were collected into plain vacutainer bottles to determine serum calcium, parathyroid hormone, vitamin D, and renin-angiotensin components using ion selective electrode and ELISA methods. Continuous and categorical variables were subjected to appropriate statistical analyses using the STATA version 16 (StataCorp LLC).

Results: The demographic comparison showed that the mean age did not differ between the case and control groups, but the body mass index was higher (P<0.05) among the case group. The mean calcium value was elevated in the case group (2.41±0.26 mmol/L) vs the control group (2.20±0.54 mmol/L) (P<0.001). Comparing between case and control groups, the median values of parathyroid hormone (PTH) (47.26 pg/mL, interquartile range [IQR]=25.05-71.70 vs 26.43 pg/mL, IQR=17.67-45.70) (P<0.001), renin (339.77 pg/mL, IQR=227.61-566.89 vs pg/mL 269.295, IQR=159.30-420.13) (P<0.001), angiotensin II (402.74 pg/mL, IQR=253.79-594.77 vs 328.19 pg/mL, IQR=264.24-383.51) (P<0.001), angiotensin I converting enzyme (3.13 ng/mL, IQR=1.77-7.35 vs 1.82 ng/mL, IQR=1.25-3.58) (P<0.001), and aldosterone (307.18 pg/mL, IQR=204.05-502.32 vs 187.85 pg/mL, IQR=163.89-306.13) (P<0.001) were higher in the hypertensive group. However, Vitamin D (42.91 nmol/L, IQR=24.32-55.48 vs 55.33 nmol/L, IQR=42.67-99.73) was reduced (P<0.001) among hypertensive individuals. Multivariate analysis showed that increase in calcium (odds ratio=5.012, P<0.001; 95% CI, 2.885%, 8.707%, PTH (odds ratio=1.0204; P<0.001; 95% CI, 1.0139%, 1.02699%) and aldosterone (odds ratio=1.0008; P=0.001; 95% CI, 1.00032%, 1.00129%) were related with higher odds of hypertension and its associated complications.

Conclusion: Abnormal parathyroid, vitamin D, aldosterone hormones, and calcium were associated with pathophysiology and prominence of hypertension.

Keywords: Hypertension, Parathyroid hormone, Vitamin D, Renin-angiotensin-aldosterone system (RAAS)

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Introduction

Hypertension is a major medical condition that results in many complications and sudden death when not properly managed [1]. High blood pressure doubles the long-term risk of cardiovascular diseases [2, 3].

Hypertension has been reported as a major health problem in Nigeria, as recent studies have suggested a significant surge in its prevalence among some major cities in Nigeria [4, 5].

Abnormality in parathyroid hormone (PTH) and vitamin D may be associated with or aggravate hypertension [6]; however, there is no consensus on this issue so far. Studies suggest associations between vitamin D, PTH deficiencies, and hypertension [7, 8]. The previous studies also indicate that abnormal levels of these two hormones may exacerbate the already known or confirmed hypertensive disorder [7, 9, 10]. Kota et al. [7] demonstrated that individuals who had vitamin D inadequacy experienced blood pressure increase. They spoke out that the vitamin D deficiency could be related to renin-angiotensin-aldosterone system (RAAS) regulation. A reverse relationship appears between cholecalciferol level and blood pressure [11]. Low cholecalciferol is an independent risk factor for hypertension and cardiovascular mortality [12]. A prospective study and meta-analysis report that a deficiency of cholecalciferol was associated with an increased danger of hypertension [13]. At the same time, vitamin D supplementation was observed to impact blood pressure positively [14].

Cholecalciferol deficiency has also been correlated with a higher risk of some chronic diseases [15-17]. Likewise, an inverse relationship between 25-hydroxycholecalciferol levels and incident hypertension has been reported in a previous study [18]. However, few studies showed no association between these factors [11, 10]. Hence, it is important to investigate if there is any association between 25-hydroxycholecalciferol levels and hypertension among Nigerian population.

Also, it has been observed that blood pressure is significantly linked with PTH (positively) than with 25-hydroxycholecalciferol (negatively) [19]. This issue could imply that cholecalciferol's impact on blood pressure might be influenced by its effects on parathyroid hormone.

Furthermore, the RAAS has been known as a key regulator of blood pressure [20]. Thus, an abnormality in RAAS promotes the enhancement of hypertension and cardiovascular complications [21, 22]. Therefore, this study assessed serum PTH hormone, cholecalciferol, calcium, and renin-angiotensin-aldosterone in Nigerians with hypertension, as all these biochemical variables are related to the pathophysiology and pathogenesis of hypertension.

Materials and Methods

Study population and design

A case-control study was conducted with 549 participants. Out of the total, 324 volunteers were referred to the Cardiology Unit of Lagos State University Teaching Hospital (LASUTH) in Ikeja, and the Medical Outpatient Departments of General Hospital Ijede and General Hospital Mushin, where the study was conducted. On account of the detection of elevation in blood pressure (after a repeated check) during routine checks, elevated blood pressure was confirmed on all the referred subjects. Among these registered (consenting) volunteers, 8 mL of venous blood sample was collected from a well-disinfected surface of the antecubital vein within the cubital fossa. A fasting blood sample was taken from all consenting hypertensive volunteers (case) and consenting normotensive volunteers (control).

The sample size was determined using a previously validated formula based on the recently documented occurrence of high blood pressure among the Nigerian population [23] at a 20%-25% prevalence rate based on publication by Ogah et al. [24].

Inclusion and exclusion criteria

The inclusion criteria for the case group were as follows: Ambulatory newly diagnosed and long-standing hypertensive (primary) volunteers aged 18 and above without any other known disease or complication(s). A simple random sampling technique was adopted for this study.

The inclusion criteria for the control group were as follows: Healthy normotensive adults aged 18 years and above. All volunteers were recruited using simple random sampling techniques.

The exclusion criteria for the case group were children below the age of 18 years, hypertensive volunteers with other known comorbidities, and female hypertensive volunteers who were pregnant.

The exclusion criteria for the control group were adult participants who were presented with any form of ailment or disease in the absence of hypertension.

Study methods

Before sample collection, intending participants were given questionnaires to fill out after an explanation of the purpose of the research. A well-designed structured questionnaire consisting of sections for all anthropometric data, educational background, family history of hypertension, lifestyle, history of medications, and any possible comorbidity during this study was adapted from the Centers for Disease Control and Prevention of Blood Pressure [25]. The participants were then requested to take anthropometric height and weight measurements using standard graduated meters and scale equipment. Blood pressure measurements of all volunteers were taken from the left upper arm using an accosson sphygmomanometer and Omron IT series 10 sphygmomanometers. In contrast, body temperature was taken using a clinical thermometer.

Sample collection

A total of 8 mL of fasting blood sample was taken from all consenting hypertensive volunteers (case) and normotensive volunteers (control). Fasting blood was obtained from the cubital fossa of the subjects after an overnight fast of between 10 and 16 h in a sitting position in a plain and lithium heparinized vacutainer bottle. Blood samples were centrifuged, separated, and preserved at -20 °C pending analysis.

Biochemical analysis

Vitamin D hormone was estimated using 25-hydroxyl vitamin D. Angiotensin 1 converting enzyme (ACE), renin, angiotensin II, aldosterone, vitamin D hormone, and PTH were estimated using Elabscience ELISA commercial kits following the manufacturer's instruction. On the other hand, calcium was determined using an SFRI 4000 ion selective electrode.

Aldosterone (catalog No: E-EL-0070), human angiotensin II (catalog number: E-EL-H0326), 25-hydroxyl vitamin D (catalog No: E-EL-0015), intact PTH (catalog number: E-EL-0015), ACE (catalog number: E-EL-H0281), and human REN (renin) (Catalog No: E-EL-H0119) are all enzyme-linked immunosorbent assay based on either competitive or non-competitive immunoassay reactions.

Statistical analysis

The Kolmogorov-Smirnov test was conducted to assess the normality of the continuous data. Variables normally distributed were analyzed using a parametric test, while the skewed variables were analyzed using a non-parametric test. Variables were presented as Mean±SD and analyzed using the independent t-test. The skewed variables were presented as median and interquartile range (IQR) and were analyzed using the Mann-Whitney U test. The associations between these variables were analyzed using the Pearson and Spearman rank correlation for normally distributed and skewed variables. A multivariate logistics regression analysis was conducted to assess or predict the risks of developing hypertension among the healthy control group using all the continuous biochemical independent covariates. All data were analyzed using statistics and data science (STATA software, version 16 (StataCorp) and SPSS software, version 23. The significant level of probability was set at $P<0.05$.

Results

The anthropometric data of the case and control participants showed that female volunteers were higher in both groups, constituting 65.34% and 60.89%, respectively. Both groups were age-matched, but the weight, body mass index, systolic and diastolic blood pressure, mean arterial blood pressure, and pulse pressure were higher ($P<0.05$) among the case group [26].

Figure 1 shows the various categories of hypertensive volunteers based on the body mass index. Out of the 323 hypertensive volunteers studied, 7(2.17%) were underweight (BMI<18.5 kg/m^2), 121(37.46%) had regular weight (BMI=18.5-24.5 kg/m^2), whereas 105 (32.51%) were overweight (BMI>25-29 kg/m^2). On the other hand, a total of 90 (27.86%) hypertensive participants were obese (BMI of >30 kg/m^2).

Table 1 presents the median values of neurohormones and other hormones that play some roles in blood pressure regulation. The median parathyroid and vitamin D values for hypertensive and control groups were 47.26 pg/mL (25.05-71.70) vs 26.45 pg/mL (17.67-45.70) ($P<0.001$) and 42.91 nmol/L (24.32-55.48) vs 55.325 nmol/L (42.67-99.73) ($P<0.001$), respectively. Renin and angiotensin II values were 339.77 pg/mL (227.61-566.89) vs 269.295 pg/mL (159.70-420.15) ($P<0.001$); 402.74 pg/mL (253.79-594.77) vs 328.19 pg/mL (264.24-383.51) ($P<0.001$) for hypertensive and control group, respectively. The median human angiotensin I converting enzyme in the case and control groups were 3.13 ng/mL (1.77-7.35) vs 1.82 ng/mL (1.25-3.58) ($P<0.001$), respectively. While the median aldosterone levels for the case and control groups were 307.18 pg/mL (204.05-502.32) vs 187.85 pg/mL (163.89-306.13) ($P<0.001$), respectively.

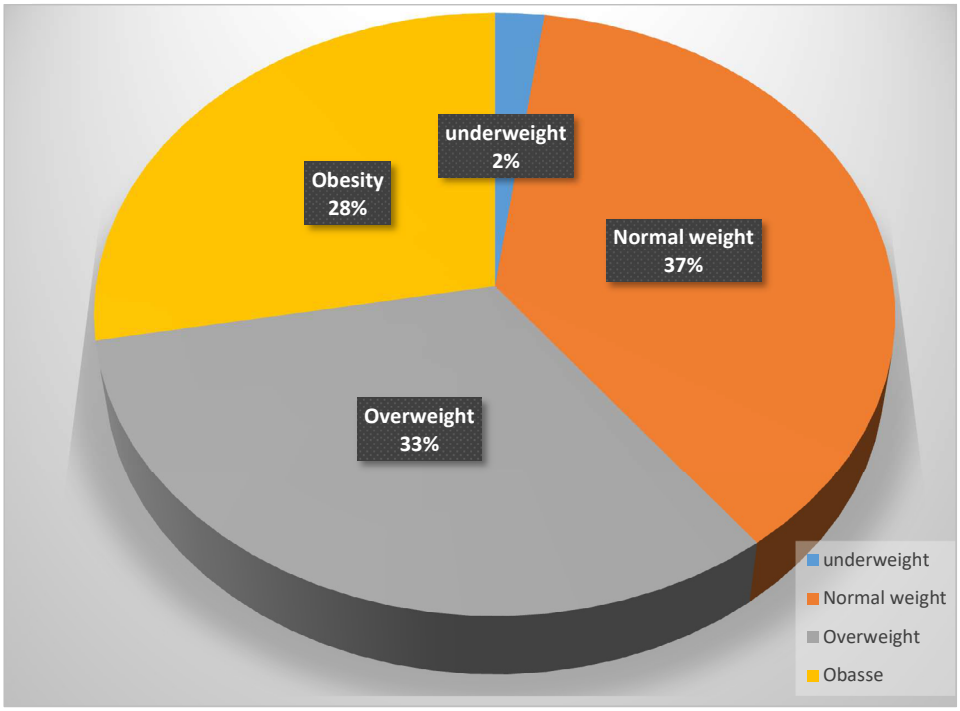

Figure 1. Body mass index categories among hypertensive study group

Table 2 presents the Spearman rank correlation of the skewed continuous variables. Among hypertensive participants, there was a positive relationship between aldosterone and ACE (rs=0.112, P=0.0091). Also, a positive but insignificant association was found between PTH and ACE (rs=0.0605, P=0.1601). On the other hand, there was a negative association between renin and aldosterone (rs=-0.1078, P=0.0122). Vitamin D, aldosterone, and ACE correlated negatively, but these associations were non-significant. Other variables did not produce any significant association.

Table 1. Hormones and neurohormones modulators of blood pressure in participants

Variables	Median (IQR)/Mean±SD		P
	Hypertensive (n=324)	Control (n=225)	
PTH (pg/mL) Interquartile range (IQR)	47.26 (25.05-71.70)	26.45 (17.67-45.70)	<0.001*
Vitamin D hormone (nmol/L) Interquartile range (IQR)	42.91 (24.32-55.48)	55.325 (42.67-99.73)	<0.001*
Renin (pg/mL) Interquartile range (IQR)	339.77 (227.61- 566.89)	269.295 (159.70-420.15)	<0.001*
Angiotensin II (pg/mL) Interquartile range (IQR)	402.74 (253.79- 594.77)	328.19 (264.24-383.51)	<0.001*
Human angiotensin I converting enzyme (ng/mL) Interquartile range (IQR)	3.13 (1.77-7.35)	1.82 (1.25-3.58)	<0.001*
Aldosterone (pg/mL) Interquartile range (IQR)	307.18 (204.05- 502.32)	187.85 (163.89-306.13)	<0.001*
Calcium (mmol/L)	2.41±0.26	2.20±0.54	<0.001*

*Significant P.

Table 2. The Spearman rank correlation between the variables for the skewed data

Variables	Spearman Correlation Coefficient (r_s)	P
Aldosterone and ACE	0.112	0.0091*
Renin and ACE	-0.0124	0.7731
Renin and aldosterone	-0.1078	0.0122*
Vitamin D and ACE	-0.0267	0.5360
Vitamin D and aldosterone	-0.0536	0.2134
Vitamin D and renin	-0.0499	0.2471
PTH and ACE	0.0605	0.1601
PTH and aldosterone	0.0508	0.2383

*Significant P.

Table 3 presents the multivariate logistics regression analysis used to forecast the risk of hypertension among the healthy control group. The odds of hypertension among the healthy control group increased significantly (Odds ratio [OR]: 5.012; 95% CI, 2.885%, 8.707%) with an increase in plasma calcium concentration, ACE ([OR]: 1.013; 95% CI, 0.9979%, 1.02877%), renin ([OR]: 1.0088; 95% CI, 1.0034%, 1.00142%), angiotensin II (OR: 1.001; 95% CI, 1.000%, 1.00095%), aldosterone ([OR]: 1.008; 95% CI, 1.00032%, 1.001298%), PTH ([OR] 1.0204; 95% CI, 1.01392%, 1.026994%), whereas an increase in vitamin D was associated with decreased odds (risk) of hypertension and its associated complication ([OR]: 0.9747; 95% CI, 0.9688%, 0.9807%).

Discussion

In this study, the largest percentage of volunteers were within healthy weight, but some hypertensive patients were overweight and obese. The underweight hypertensive participants were the least, representing only 2.17% of the total hypertensive participants (Figure 1). The causal association between BMI and hypertension was significant.

In addition, the calcium value in the case group was elevated. This finding agrees with previous observations by Sabanayagam and Shankar [27] and Chou et al. [28]. It has been documented that this electrolyte plays a vital role in developing primary hypertension [29, 30] because of its significance for vascular smooth muscle cell function [30]. A previous study has observed that a normotensive individual from a familial hypertensive disposition exhibits elevated intracellular calcium compared to others without hypertension lineage [31]. This study supported this finding through the multivariate logistics regression analysis study, where an increase in extracellular calcium demonstrated a strong odds of

Table 3. Multivariate logistics regression analysis predicting the odds (risk) of hypertension among apparently healthy participants

Variables	Odds Ratio	Std Error	P	95% Confidence Interval
Calcium	5.012	1.410	<0.001*	2.885-8.707
Angiotensin-converting enzyme	1.013	0.0078	0.091	0.9979-1.02877
Renin	1.009	0.00027	0.001*	1.0034-1.00142
Angiotensin II	1.001	0.0002	0.029*	1.000-1.00095
Aldosterone	1.0008	0.00027	0.001*	1.00032-1.001298
Parathyroid hormone	1.0204	0.0333	<0.001*	1.01392-1.026994
Vitamin D	0.9747	0.0030	<0.001*	0.9688-0.9807

hypertension, suggesting a possible link between calcium and the pathogenesis of hypertension. Thus, high serum calcium has been seen in hyperparathyroidism and vice vasa [32]. In this study, hypertensive volunteers demonstrated a significant increase in extracellular calcium and PTH levels. The impact of calcium on blood pressure is initiated by its interaction with sodium, potassium, and magnesium [33].

Furthermore, an evaluation of PTH and vitamin D showed that the hypertensive group had significantly higher parathyroid and lower vitamin D values. This observation agrees with previous literature. Zhao et al. [34] and Ulu et al. [35] demonstrated elevated PTH levels in hypertensive individuals with a positive association with hypertensive severity. Also, it was observed that PTH correlated positively with the RAAS components measured, whereas an opposite effect was observed between extracellular calcium and the components of RAAS studied. This association agrees with some previous studies [36, 37]. Thus, an increase in PTH could contribute to increased aldosterone and, by extension, increased sodium and water retention—all these contribute to hypertension. Also, an increase in the components of RAAS may elicit a decrease in serum calcium. This condition may accentuate hypertension [36, 37]. Thus, an elevation in serum PTH levels makes an individual prone to developing incident hypertension or accentuating existing hypertension [38, 39]. However, other studies did not observe any relationship between parathyroid and blood pressure [38, 39]. Li et al. [40] and Alpsoy et al. [41] could not establish any relationship between PTH levels and BP and reported similar P for PTH levels in systolic hypertension and normotensive individuals. This observation could be linked to genetic diversity and environmental variation as different research populations were involved in this study and their study. An increase in PTH was allied with increased odds of hypertension. Concerning the significantly lower vitamin D demonstrated by the test group, previous research has shown a reverse correlation between vitamin D and the risk of high blood pressure [42]. This condition could be related to the negative influence of vitamin D on RAAS and the association with endothelial vasodilator dysfunction [36, 37, 43-45]. This observation could result in a higher risk of atherosclerosis, left ventricular hypertrophy, and hypertension [43-45]. Additionally, vitamin D might affect lipid metabolism circuitously via its impact on insulin secretion and sensitivity [46, 47]. However, relatively higher serum 25(OH)D levels have been reported to lower average blood pressure, thus reducing hypertension prevalence [42, 48]. Few studies, however, did not show any alliance between low vitamin D values and hypertension [38, 44, 49-52].

The RAAS has been described as one of the most important hormonal mechanism systems responsible for controlling hemodynamic stability [53, 54]. In this study, renin, angiotensin II, and aldosterone were higher in the case group than in the control participants. Also, angiotensin I converting enzyme activity was significantly higher among the hypertensive group. Preceding experiments have shown that vitamin D deficiency leads to RAAS activation [42, 45]; this might have been possible among the hypertensive group studied. Hypertension results when there is hyperactivation of the sympathetic nervous system and RAAS [54]. The findings regarding the RAAS components of this study suggest the activation of this system in some Nigerians who are hypertensive. This condition is possibly accentuated by this study's significantly low vitamin D level. A multivariate logistics regression analysis showed that all RAAS components studied (except ACE) showed higher odds (risk) of hypertension and its associated complications with increased serum values of the RAAS component studied. Activation of RAAS is associated with a higher risk of hypertension [54, 22]. Thus, the results of this study concerning RAAS components agree with studies by Drummond et al. [54].

Conclusion

The case group demonstrated much higher serum values of PTH, RAAS components, and calcium, whereas vitamin D was vividly lower among the case group. Thus, it appears that abnormal blood concentration of these variables may play a part in the pathogenesis and accentuation of hypertension among the Nigerian population.

Study limitations

This study only had a snapshot encounter with all volunteers. Hence, there was no follow-up study on this group of volunteers where we would have been able to evaluate possible influences of medications, lifestyles, and diet on the biochemical variables studied.

Ethical Considerations

Compliance with ethical guidelines

Approval was sought and obtained from the Health Research and Ethics Committee of the Lagos State University Teaching Hospital (Lasuth) (Code: LREC

06/10/1074). Also, permission was obtained from the Lagos State Health Service Commission (HSC) to use some of the general hospitals in addition to Lasuth for sample collection. A detailed explanation of the purpose of the study was provided to all intended volunteers.

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Authors contributions

All authors equally contribute to preparing all parts of the research.

Conflict of interest

The authors declared no conflict of interest.

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