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Research Article

Assessment of the levels of serum parathyroid hormone in rural postmenopausal women in Zuturung district, Zangon Kataf Local Government Area, Kaduna State, Nigeria.

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ABSTRACT

The physiological role of parathyroid hormone (PTH) in calcium homeostasis and the maintenance of bone mass in humans has been elucidated by several authors. The main objective of the present study was to evaluate basal PTH levels in premenopausal, perimenopausal and postmenopausal women in Zuturung district, Kaduna state, Nigeria. One hundred and thirty-five subjects comprising of 38 premenopausal, 22 perimenopausal and 75 postmenopausal women were assessed. The subjects were selected based on some inclusion and exclusion criteria. After administering a questionnaire, anthropometrical parameters were determined using standard methods while five milliliters of blood were collected via venipuncture. The blood was transferred to plain bottles, centrifuged and serum PTH levels were determined using ELISA method at the Department of Chemical Pathology, Ahmadu Bello University Teaching Hospital, Shika. Results were presented as mean ± SD and data were analyzed using ANOVA with $p<0.05$ being considered as statistically significant. The study revealed that postmenopausal and perimenopausal women were more likely to be overweight (mean BMI 26.07±5.99 kg/m^2, 26.42±7.27kg/m^2 respectively) as compared with their premenopausal counterparts (25.18±3.48kg/m^2); $p<0.001$. The postmenopausal and perimenopausal women also had a higher waist circumference (89.63±10.66cm, 92.19±11.91cm) as compared with the premenopausal women (83.73±8.00cm) $p<0.001$. Mean serum parathyroid hormone levels were slightly decreased among the postmenopausal subjects (2.25±1.88pg/ml) and perimenopausal (2.91±1.44pg/ml) as compared to the premenopausal subjects (3.38±3.48pg/ml) although not significant ($p>0.05$). These findings suggest a higher cardiovascular risk and lower mean serum parathyroid hormone in the postmenopausal women as compared with their premenopausal subjects.

We recommend further studies in a larger sample, comparing with women in urban regions and determining serum cadmium levels in the subjects to identify if its toxicity is responsible for the pattern of serum parathyroid hormone levels observed.

INTRODUCTION

With the aging of the population a study has reported that age-induced increased parathyroid hormone plasma levels occur and is associated with cognitive decline and dementia (Lourida *et al*., 2015). Levels of serum intact PTH also increase progressively with age in women and correlate significantly with increases in bone turnover values. Bone turnover increases to high levels in women soon after menopause (Sowers *et al*., 2013). This is also believed to be due principally to a diminution of a direct action of estrogen on bone cells. In addition, estrogen deficiency may induce calcium loss by indirect effects on extra skeletal calcium homeostasis. These indirect effects include decreased intestinal calcium absorption and decreased renal calcium conservation after the onset of estrogen deficiency (Heshmati *et al*., 1998; Dick and Prince, 1997)

There are classical actions of parathyroid hormone, but its effect on other target tissues, such as the cardiovascular system, are less appreciated. Recent

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clinical and molecular research has shown that direct and indirect actions of PTH also affect the heart and vasculature through downstream actions of G protein-coupled receptors in the myocardium and endothelial cells. Patients with disorders of the parathyroid gland have been shown to have higher incidences of hypertension, arrhythmias, left ventricular hypertrophy, heart failure, and calcific disease which translate into increased cardiac morbidity and mortality (Fujii, 2018; Brown *et al*., 2017). The PTH acts on an L-type calcium channels located on cardiomyocytes. The L-type calcium channel is strongly associated with the contraction of cardiomyocytes and the cardiac electrical conduction system (Palmeri and Walker 2019; Fujii, 2018; Tastan *et al*., 2009). As the detailed mechanisms, PTH increases the entry of calcium ions into the cell and promotes apoptosis of cardiomyocytes. These findings indicated that PTH induces oxidative stress and necrotic cell death by promoting mitochondrial Ca2+ excess, which in the long-term causes or exacerbates myocardial fibrosis (Deska *et al*., 2017; Schluter *et al*., 1998). As shown by experimental studies, the correlation between PTH and cardiac hypertrophy is well known. There are clinical studies regarding this issue (Assaad *et al*., 2017; Fujii, 2018; Saleh *et al*., 2003). There is a report on plasma PTH levels predicting cardiovascular mortality in a community, even in individuals with PTH within the normal range. Further studies are warranted to evaluate the clinical implications of measuring PTH in cardiovascular risk prediction and to elucidate whether PTH is a modifiable risk factor (Goettsch *et al*., 2014; Hagstrom *et al*., 2009). As a possible mechanism, it is thought that parathyroid hormone is associated with the renin-angiotensin-aldosterone system and has direct effects on the cardiovascular system. The PTH is associated with heart failure, however, also reported to directly dilate the coronary artery and promotes myocardial microcirculation, thereby improving the myocardial oxygen supply and cardiac pump function (Osto *et al*., 2012). Furthermore, PTH is said to promote the release of vascular endothelial growth factor and angiogenesis. Hence, may be applicable as a therapeutic agent for acute myocardial infarction alongside PTHrP (Zhang *et al*., 2019; Deska *et al*., 2017; Isowa *et al*., 2010).

Parathyroid hormone (PTH) is of interest in relation to cognitive function and dementia as it crosses the blood brain barrier. PTH receptors are found throughout the human brain (Dobolyi *et al*., 2012; Harvey and Hayer, 1993). Elevated PTH levels are associated with reduced regional cerebral blood flow. PTH also promotes the conversion of vitamin D to its active form (1,25-dihydroxyvitamin D) which an emerging body of evidence suggests may be neuroprotective (Banerjee *et al*., 2015). Patients with primary hyperparathyroidism (high PTH and calcium levels), often report cognitive complaints and observational studies have described poorer cognitive function in those patients compared to control groups (Lourida *et al*., 2015). Even though recent findings suggest that elevated PTH levels may be associated with increased risk of cognitive decline and incident dementia, there is some indication that hypoparathyroidism (low serum PTH and calcium levels) may also be associated with poorer cognitive function too (Banerjee *et al*., 2015; Cermik *et al*., 2007).

Data published over the last two decades indicate that PTH may act as an immunomodulator. Parathyroid hormone (PTH) functions as an immunologic mediator with evidence indicating PTH receptors were found on most immunologic cells; neutrophils, B and T cells (Geara *et al*., 2010). The mechanism by which PTH influences leukocytes though unclear involves an increase in intracellular calcium level. Potentially, this might lead to an increase in cellular adenylate cyclase activity. Studies examining the effect of PTH on T lymphocytes showed that PTH produces an inhibitory effect on various parameters of the immune system while other studies demonstrated that PTH had a stimulatory function under certain laboratory conditions (Geara *et al*., 2010). A study was suggestive of an indirect effect of PTH on B lymphocytes via T-lymphocytes dysfunction, even though the discovery of PTH receptors on B lymphocytes has favored a more direct effect of PTH. PTH was found to affect several aspects of the B-cell function (inhibition of proliferation, antibodies production, and metabolism), (Pacifici, 2014; Geara *et al*., 2010).

There is significant evidence that PTH and PTHrP influence the proliferation and differentiation of hair follicle cells. The PTH/PTHrP receptor signalling plays an important role in the hair follicle cycle and may induce premature catagen-telogen transition. Transgenic mice with an overexpression or blockade (PTH/PTHrP receptor knockout mice) of PTHrP activity revealed impaired or increased hair growth, respectively. Some findings also suggest that PTHrP may additionally influence the hair cycle by inhibiting angiogenesis. Antagonists of the PTH/PTHrP receptor have been shown to stimulate proliferation of hair follicle cells and hair growth (Skrok *et al*., 2015; Jankovic and Jankovic, 1998; Holick *et al*., 1994). Indicating that the PTH/PTHrP receptor may serve as a potential target for new (topical) hair growth-

stimulating drugs, especially for chemotherapy-induced alopecia.

There are reports of a predilection to develop primary hyperparathyroidism with age and after the menopause in women. There is paucity of studies on serum parathyroid hormone levels in rural Nigerian women. The aim of our study was to assess the mean serum levels of parathyroid hormone amongst rural postmenopausal women in Zuturung district, Kaduna state, Nigeria.

METHODS

Study Subjects and Site

This cross-sectional community-based study was conducted in one hundred and thirty-five (135) women comprising of 38 premenopausal women, 22 perimenopausal women and 75 postmenopausal women in Zuturung district, Kaduna state, Nigeria. The following settlements Zuturung Tintaa, Zuturung Mago, Fadia and Zuturung Pama formed part of the district. Postmenopausal women aged - 40 – 70 years who were diabetics, hypertensive, who smoked cigarette, amenorrhoeic due to hysterectomy or cessation of periods other than by a natural cause, having a history of hormone replacement therapy, hysterectomy and fractures were excluded. The premenopausal subjects (aged 15 – 45 years) included regularly menstruating, non-pregnant, non-lactating women with no history of use of hormonal contraception for at least 1 year. Postmenopausal women selected were at least 1-year amenorrhoeic due to a natural cause. While the perimenopausal women (aged 35 – 45 years) had menses within the last 12 months but not predictable in the last 3 months (NAMS, 2010).

The study was undertaken after obtaining consent from the participants and approval from the Ethical Committee on Human Research of the Ministry of Health and Human Services of Kaduna State, Nigeria.

Anthropometric Parameters Determination

Height (cm) and weight (kg) of each woman were determined utilizing a stadiometer and the body mass index was calculated (BMI). Underweight was defined as a BMI<18.5 kg/m^2, normal BMI as >18.5-24.9 kg/m^2, overweight as BMI between 25-29.9 kg/m^2, obese as BMI>30-39.9 kg/m^2 and BMI≥35 kg/m^2 was considered as morbid obesity. The waist circumference was measured for the subjects using a flexible metric tape (Estrella-Castillo and Gómez-de-Regil, 2019; Visscher *et al*., 2001)

Sample Collection and Analysis

Five milliliter of venous blood was drawn from each subject, transferred into plain bottles, and centrifuged at 3,000 rpm for 10 minutes after which serum was separated. The serum was stored at -18° C until used for the different analysis.

i. Serum calcium from the fasted subjects was measured. The specimens were mixed with the reagent, incubated for 5 minutes at room temperature and the results read at the specified absorbance. The principle was based on metallochromogen Arsenazo III which combines with calcium ions to form a colored chromophore that was measured at the absorbance of 630nm as described by the instruction manual (Recton Diagnostics P. LTD, India). All specimens with hemolysis were excluded

ii. Serum phosphorus was measured based on the method using Ammonium Molybdate. The specimen (0.01ml) was mixed with the reagent (1ml), incubated at room temperature for 5 minutes and the color change was measured. The principle of the test is inorganic phosphorus reacts with Ammonium molybdate in the presence of sulphuric acid to form unreduced phosphomolybdate complex which was measured at absorbance of 340nm.

iii. Serum albumin was determined by mixing the sample (10µL) with the reagent (1mL), incubated for 10 minutes at room temperature and the product measured as specified by the instruction manual. The principle is described as: using an acidic medium, albumin binds with bromocresol green causing a shift in the absorption spectra of the yellow BCG dye. The blue green color formed is directly proportional to the albumin present and was measured at the absorbance of 630nm.

Hormone Assay

Serum parathyroid hormone was determined using commercial kits (Microwell enzyme linked assay kits) and with methods described by the manufacturer (Monobind Inc., USA) in the Department of Chemical Pathology, Ahmadu Bello University Teaching Hospital, Shika. The samples were thawed, 50µl transferred using a micro pipette to the individual microwell plates. Some standards were used alongside the test wells. The reagents were then added to the wells, incubated, washed and eventually the color change read using a microplate readser. The principle of the test was a sandwich assay in an antibody- coated plate. Sensitivity of the kits was 0.49pg/ml.

Data Analysis

Results were presented as mean ± SD and data were analyzed using one way analysis of variance (ANOVA), while $p< 0.05$ was selected as the level of significance. Which was followed by Tukey post-hoc

test. A p-value of <0.05 was considered statistically significant while associations between variables were determined by Pearsons' correlation using SPSS version 23.

RESULT S

A total of 135 subjects participated in the study. They comprised of 38 premenopausal women, 22 perimenopausal women and 75 postmenopausal women. The mean age for the premenopausal, perimenopausal and postmenopausal women was 33.60±4.59 years, 46.00±5.80years and 57.67±9.19years respectively. While the mean and median age at menopause for the postmenopausal women were 44.23±2.74years and 44years respectively.

Table 1: The anthropometric parameters, Family history and social history of the Premenopausal, Perimenopausal and Postmenopausal Women in Zuturung district.

Parameters	Premenopausal (n=38)	Perimenopausal (n=22)	Postmenopausal (n=75)
BMI (kg/m^2)	25.18±3.48	26.42±7.27	26.07±5.99
Waist circ. (cm)	83.73±8.00	92.19±11.91*	89.63±10.66*
Hip circ. (cm)	98.97±8.38	102.19±12.97	100±9.8
Waist-Hip ratio	0.85±0.04	0.90±0.05*	0.89±0.07*
Family history of fracture (%)	29.58%	31.82	27.03%
Drink alcohol (%)	18.31%	22.72%	36.99%

P< 0.05* BMI-Body mass index, Waist circ-Waist circumference, Hip circ-Hip circumference. All values are indicated as mean ± SD.

There was a statistically significant increase in waist circumference (p=0.000) and waist hip ratio in the perimenopausal and postmenopausal women as compared to the premenopausal group. However, their BMI (p=0.120) and hip circumference (p=0.08) was not significantly different from that of the premenopausal group. No subject reported a history of smoking while all the 3 groups reported a history of consumption of alcohol along with a family history of fracture.

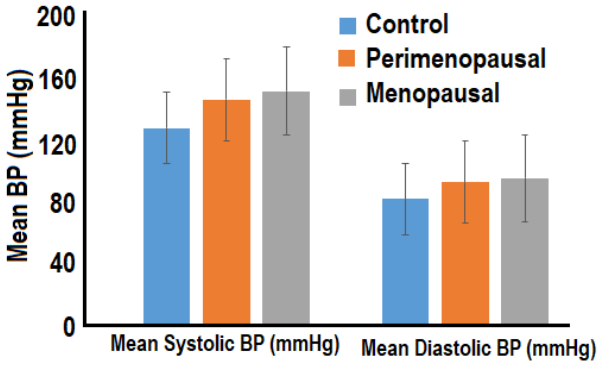

Fig. 1. Blood Pressure measurements of the premenopausal, perimenopausal and postmenopausal women in Zuturung district.

There was a significant increase in the systolic blood pressure (p <0.001) and the diastolic blood pressure (p<0.001) of the perimenopausal and postmenopausal women as compared to that of the premenopausal group. There was no significant difference in the mean blood pressures (systolic and diastolic) of the perimenopausal women as compared with the postmenopausal women (p>0.05).

Table 2: Biochemical analyses for the premenopausal, perimenopausal and postmenopausal women in Zuturung district

Biochemical Analytes	Premenopausal (n=38)	Perimenopausal (n=22)	Postmenopausal (n=75)
ALB (g/dl)	39.00±4.49	41.07±3.71	38.48±7.05
CA (mg/dl)	2.37±0.15	2.36±0.13	2.30±0.35
PHOS (mg/dl)	1.09±0.14	1.10±0.12	1.09±0.19

ALB-albumin CA-calcium PHOS-phophorus p<0.05=* All values are indicated as mean ± SD

There was a slight decrease in mean serum calcium in the perimenopausal and postmenopausal women as compared to the premenopausal which was not statistically significant. There was no significant difference in the mean serum albumin and phosphorus for both the perimenopausal and menopausal women as compared to their premenopausal subjects (p>0.05).

DISCUSSION

The waist circumference and waist hip ratio in the perimenopausal and postmenopausal women was significantly higher than that of the premenopausal group (Table 1). This finding is due to the overall increased adiposity and fat redistribution towards central-type obesity observed in menopause. Their BMI (p=0.120) and hip circumference (p=0.08) was higher than that of the premenopausal subjects which was not

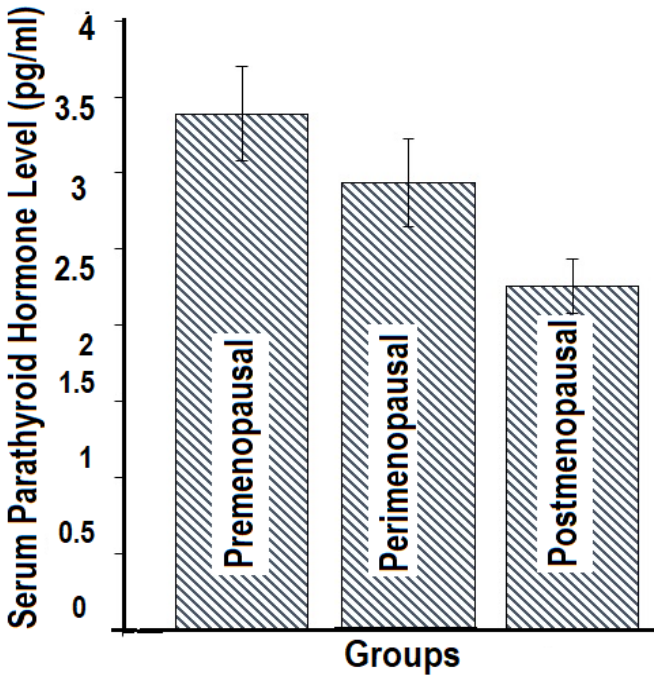

Fig. 2. Mean Serum Parathyroid Hormone levels for the premenopausal, perimenopausal and postmenopausal women in Zuturung district.

Mean serum parathyroid hormone levels showed a decrease in the perimenopausal and postmenopausal women as compared to the premenopausal subjects that was not significant ($p>0.05$).

significant (Table.1). Obesity as determined by BMI and waist circumference measurement is associated with diseases like hypertension, atherosclerosis, diabetes mellitus type II and metabolic syndrome. However, a beneficial effect of increased adiposity was reported by Mazocco and Chagas, (2017). Increase in body weight and by inference increase in BMI and waist circumference is reported to be contributed by a number of factors. A higher dietary intake of food, decreased energy expenditure in postmenopausal women, sex dimorphism in fat redistribution (favouring increase in visceral fat) in menopause occurs and is mediated by the declining oestrogen in menopause (Xu and Zhong, 2017; da Costa *et al*., 2014).

There was a significant increase in the systolic blood pressure ($p <0.001$) and the diastolic blood pressure ($p<0.001$) of the perimenopausal and postmenopausal women as compared to that of the premenopausal women (Figure 1). Reports by Zanchetti *et al* (2005), in a study of 18,326 women revealed similar findings even when the confounding effects of age, BMI and use of contraceptives were excluded.

Mean serum PTH levels were lower in the postmenopausal (2.25±1.88pg/ml) and perimenopausal women (2.91±1.44pg/ml) as compared with the premenopausal women (3.38±3.48pg/ml). However, it was not significant (Figure 2); ($p>0.05$). PTH secreted by the parathyroid gland is responsible for the maintenance of serum calcium level. This hormone provides a powerful mechanism for controlling extracellular calcium and inorganic phosphate by regulating intestinal absorption, renal excretion and exchange between the extracellular fluid and bone of these ions. The study by Prince *et al* (1990), observed that estrogen deficiency at menopause was not associated with deficient parathyroid reserve. However, Haden *et al*., (2000) observed that serum PTH rises with age. The age dependent increase in PTH is suggested to be attributed to declining renal function, declining residual estrogen levels, declining calcium absorption, diminished response to vitamin D, and to aging itself (Need *et al*., 2004; Khosla *et al*., 1997). However, Oluboyo *et al*. (2018) reported an increase in mean serum PTH in Nigerian postmenopausal women which could be attributed to menopause. Aspray *et al*., (2005) also reported a similar increase in PTH in Gambian postmenopausal women which was higher than that of age matched Caucasian women from Cambridge, UK. Khosla *et al* (1997) suggests these increased PTH in menopause may be caused by estrogen decline indirectly. As evidenced by the elimination of the increased PTH levels in postmenopausal women receiving long term estrogen therapy. Esen *et al*., (2017) further elucidated that the increased PTH in menopause was caused by vitamin D deficiency and in some instances in the postmenopausal women was actually primary hyperparathyroidism. The elevated PTH levels is also reported to be associated with metabolic syndrome in females (Kim *et al*., 2018). Our subjects displayed a contrary finding of decline in mean serum PTH in both perimenopausal and postmenopausal women as compared to the premenopausal subjects, though it was not a statistically significant (Fig 2). Could this be due to unidentified confounders in the environment? Probably toxicity by cadmium which is apparently suggested to be higher in our subjects with increasing age as suggested by the lower serum PTH with advancing age (mean ages of the groups increased accordingly).

Cadmium occurs in the environment both naturally and as contamination from industries and agricultural fertilizers. These rural women are all farmers or involved in processing farm products and could have been exposed via agricultural fertilizers, or when in use in rice farming, which the community is extensively

involved in. That could have been responsible for the results showing a decreasing serum parathyroid hormone (synonymous to a lengthier duration of exposure) with increasing mean age of the subjects in the three groups (figure 2).

One of the major sources of Cadmium exposure in the general population is also diet; alcohol having contaminants ingested as a beverage in this case. Although women have lower energy intake and Cd intake than men, they usually have higher Cd concentrations in blood, urine and kidney, since iron deficiency, which is more common among women, is known to increase gastrointestinal absorption (Wallin *et al*., 2013). The pots utilized in preparing the local brew could serve as a source for heavy metal poisoning. However, determining exposure to cadmium, level of exposure and possible renal toxicity in the women was not carried out during our study. Hence, the reasons behind this trend of declining serum PTH are unclear.

Moderate alcohol consumption has been reported to alter calcitropic hormones, serum PTH included. We observed increase in the percentage of the intake of alcohol across the three groups to be premenopausal women < perimenopausal women < postmenopausal women. A reduction in PTH concentration caused by a lower bone remodeling (reduced bone resorption) has been reported to contribute to the decline in PTH levels with increasing alcohol ingestion (Rapuri *et al*., 2000). Similarly, hypoparathyroidism alongside a decrease in serum vitamin D is said to be caused by chronic alcoholism and reported to be a hallmark of acute alcohol intoxication too.

Exercise is associated with increase in some physiological parameters, amongst which is the increase in serum PTH. Increase in systemic PTH levels during exercise has been reported even when such exercise lasted just 30 minutes. In mice a two - fold increase in systemic PTH after exercise was also reported. The rural women are all farmers except a few in the postmenopausal women who exceed 60 years in age and though might not be active farmers in farms but are all involved in processing farm products. The younger premenopausal women serve as the active work force, which could explain why they presented with a higher serum PTH, which reduced across the other groups characterized by increasing mean age (table 1). However, other authors revealed an inverse relationship between physical exercise and the serum PTH concentration (Vaidya *et al*., 2016; Gardinier *et al*., 2015; Scott *et al*., 2014). We also observed a paucity in studies involving large sample sizes defining a definite reference range for serum PTH in healthy Nigerian postmenopausal women (Oluboyo et al., 2018).

CONCLUSION

We report a finding of reduction in the mean serum levels of parathyroid hormone in rural postmenopausal and perimenopausal women as compared to the premenopausal women in Zuturung district, Nigeria that was not significant. We recommend studies to determine the confounders in the community responsible for the observed changes in mean serum parathyroid hormone amongst the women.

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