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Use of Hormonal Profile and Lipid Profile as an Index of Atherosclerosis in Menopausal and Perimenopausal Women at Lokoja International Market, Lokoja, Kogi State, Nigeria

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Abstract

This was a cross – sectional study designed to evaluate hormonal and lipid profiles as indicators of menopause. 552 participants {138 (group A), 138 (group B), perimenopausal and menopausal {138 (menopausal woman designated group A), 138 (perimenopausal designated group B) (as test participants) and 276 (women of reproductive age designated as group C which served as control group} aged 18 and 64 years that were randomly recruited. One point sample collection was taken from each participant for determination of FSH, LH, PRL, TSH, Inh, Amh, E2, Prog, calcitonin, T.chol, Trig, HDL-C and LDL-C. FSH, LH, TSH were significantly high while PRL, Inh, Amh, E2, Prog and calcitonin were significantly lower in test participants when compared with control $P< 0.05$ respectively. T.chol, Trig, LDL-C were significantly higher while HDL-C was significantly lower in test participants when compared with control $P< 0.05$ respectively. The hormonal profile showed good correlations with lipid profile. The high sensitivities and positive predictive values of both hormonal and lipid profiles in groups A and B showed their predictive priorities in the diagnosis of menopause.

Keywords: Menopause • Perimenopause • Hormonal profile • Lipid profile • Atherosclerosis

Introduction

Menopause is defined as the time in a woman's life when menstrual cycle ends due to the natural depletion of ovarian oocytes from aging and the deficiency of estrogen. It marks the end of fertility and it usually begins between ages 51 and 52, but can develop before or after this age [1]. Menopause is diagnosed after 12 months of absence of menstruation. Hormonal changes and clinical symptoms occur over a period of time and it is immediately followed by menopause, this period is frequently termed perimenopause or menopausal transition [2]. Menopause occurs due to the following factors; age, premature ovarian failure, hysterectomy, chemotherapy and radiation therapy, oophorectomy. The stages of menopause include; perimenopausal stage (between 40 to 47years), early menopausal stage (between 50 to 55 years), menopausal phase (55 to 60 years) and post-menopausal stage (60 years and above) [1]. In advanced setting, the tests done to diagnose menopause are; hormonal assay, transvaginal ultrasound, hysteroscopy, computed tomography or magnetic resonance imaging. During menopausal transition, physiological changes occurs and it causes a range of symptoms which includes; insomnia, vaginal dryness, mood changes, weight gain and bloating, depression, increased urination, painful or stiff joints, osteoporosis, hot flashes and reduced bone mass [3].

In woman of advanced age, cessation of menses is commonly used to diagnose menopause in resource-limited settings. This has been found to have its setbacks or limitation. Therefore, identifying and evaluating biochemical markers that will aid in the proper diagnosis of menopause will help in the management of menopausal symptoms. These biochemical parameters will help to rule-out pseudomenopause in which women of reproductive age stops ovulating or menstruating due to hormonal interruption [4]. Also, little is known about the health effects of this natural biological occurrence in our resource –limited settings. Menopausal symptoms vary in their severity from person due to the effects of confounding factors such as lifestyles, social status, body composition and psychological status [2]. Menopausal symptoms, especially the vasomotor and sexual symptoms, are associated with impaired quality of life in women [5]. Quality of Life is "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns [5].

Menopause is estimated to be about 50 million cases worldwide. Menopausal women are projected to increase to 1.2 billion worldwide by the year 2030. In Nigeria, menopausal women are estimated to be about 20 million occurring between the ages of 45 to 52 years of age. In rare cases in Nigeria, menopause can occur between the ages of 36 to 40years and this can be referred to as early menopausal stage. In Nigeria, about 100,000 women enter menopause annually (UNAIDS, 2014). However, there is paucity of data related to menopause in Kogi State perhaps due to lack of interest in this field of research. The complications of menopause are: cardiovascular diseases, osteoporosis, urinary incontinence, sexual dysfunction, weight gain. These complications usually occur if the diagnosis are not made early for proper management. Management of menopause involves hormonal replacement therapy, vaginal estrogen, low-dose antidepressants, gabapentin, and medications to prevent osteoporosis, exercise, practice relaxation technique, and dietary measures [6].

Materials and Methods

Before the commencement of the prospective cross-sectional study, ethical approvals were obtained from Kogi State Ministry of Health Ethical Review Committee. A total of 552 participants (aged 18 and 65 years) were randomly studied, among these were 138 menopausal participants(group A), 138 perimenopausal participants (group B) and 276 participants of women of reproductive age that served as control (group C). Informed consent was obtained from all participants before the commencement of the study. Participants aged between 16 and 65 years without any known infertility challenges in their life were recruited for this study while women aged between 16 and 64years with previously known fertility challenges were excluded from this study.

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Study area: The study was carried out at International Market, Lokoja, Kogi State. The Lokoja International market is located at opposite Ibro Park, Felele express road, Lokoja. International market was established in the year 18th March, 2010 by Governor Ibrahim Idris Administration. It is a market placed at the bypass section of the Lokoja township. It is a standard market with both buyers and sellers from far and nearby state like Niger, Edo, Benue, Enugu, Ondo, Ekiti, Kano, Gombe and Abuja. Food items are also relatively cheap compare to other market within Kogi State. Lokoja is situated at 7.8oNorth Latitude, 6.74°C East longitude and 55meters elevation above the sea level. Lokoja is a town in Nigeria, the capital of Kogi State, having about 60,579 inhabitants.

Study population: The study population consist of 552 women aged between 16 and 64 years that were randomly recruited for the study. They were grouped as follows:

Group A: 138 women of menopausal age group that served as test participants.

Group B: 138 women of perimenopausal stage that served as test participants.

Group C: 276 women of reproductive age that served as control.

Specimen collection and analysis: Eight milliliters of venous blood was collected from each participant at the point of joining research. Each sample taken was dispensed into a 10ml plain bottle. The sample was allowed to clot, dislodged and was centrifuged immediately at 3000 rpm for 5 minutes, serum obtained was aliquoted into two cryovial bottles and were stored at -20°C until analysis. All the samples for hormones and lipid profile were analyzed at Federal Medical Centre, Lokoja, Kogi State, Nigeria.

Methods

All the hormones were measured using enzyme linked immunosorbent assay.

Serum Calcitonin was measured according to Moretti G, et al. [7]

Serum total cholesterol was measured according to Allain CC, et al. [8]

Serum triglyceride was measured according to Bucolo G and D Harold [9].

High density lipoprotein cholesterol was measured according to Bucolo G and David H [9].

Low density lipoprotein cholesterol was calculated according to Friedewald equation.

Statistical Analysis

Values obtained were expressed as mean plus or minus standard deviation (SD) using SPSS Version 20.0. All numerical results were analyzed with one way ANOVA with post hoc multiple comparisons tests, while spearmen correlation analysis between parameters was done amongst menopausal participants. The diagnostic performance of the parameters in groups A and B were assessed using sensitivity, specificity, positive predictive value and negative predictive values. P value below 0.05 was considered statistically significant.

Results

Table 1 showed the characteristics of the study population (mean age and residential status). Table 2 showed the hormonal levels amongst the participants (groups A, B and C). The hormonal levels in menopausal and perimenopausal participants (groups A and B) were significantly different from hormonal levels of participants of women of reproductive age (group C) (P≤0.05). (Table 3) showed the lipid profile levels amongst the participants (groups A, B and C). The lipid profile levels in menopausal and perimenopausal participants were significantly different from the lipid profile levels in women of reproductive age (P≤0.05). (Table 4) showed correlation analysis between hormonal profile and lipid profile levels in group A participants (menopausal women). There were significant associations between hormonal profile and lipid profile, all were found significant (P≤0.05). (Table 5) showed the high sensitivities, specificities and positive predictive values of both hormonal profile and lipid profile in groups A and B (P≤0.05).

Table 1. Characteristics of the study population and residential status of rural and semi urban.

Variables	All subjects N=552	Group A:Menopausal Women n=138	Group B:Premenopausal women	Group C:Reproductive women	P values
Mean age in years (±SD)	39.91 (±13.30)	58.41 (±8.11)	49.11 (±7.30)	33.4 (± 7.40)	0.03
Semi Urban	282 (51.09%)	48 (34.78%)	71 (51.45%)	150 (54.35%)	0.05
Rural	270 (48.91%)	90 (65.22%)	67 (48.55%)	126 (45.65%)	0.05

Table 2. Mean (+SD) values of hormonal levels amongst the participants.

Group	N	FSH (mIu/ml)	LH (ml/u/ml)	PRL (ng/ml)	TSH (µIu/ml)	Inh (pg/ml)	AMH (ng/ml)	E2 (pg/dl)	PROG (ng/ml)	Calc. (pg/ml)
A	138	95.00	51.00	2.00	11.00	3.00	0.70	20.00	0.06	4.00
B	138	61.00	30.00	3.50	9.00	8.00	1.20	25.00	0.07	6.00
C	276	5.00	4.80	17.0	3.6	34.00	4.10	175.00	1.70	10.00
F-Value		21.03	20.00	31.05	40.05	41.03	41.06	21.03	45.31	38.51
P-Value		0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.02
A *vs.* B		0.005	0.025	0.112	0.05	0.02	0.25	0.06	.19	0.025
A *vs.* C		0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.05
B *vs.* C		0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.05

Table 3. Mean (+SD) values of Lipid profile amongst the participants.

Group	N	T.chol	Trig	HDL-C	LDC-C
		(mg/dl)	(mg/dl)	(mg/dl)	(mg/dl)
A	138	280	210	29	170
B	138	265	192	33	163
C	276	195	130	37	110
F-Value		100.01	82.03	21	62
P-Value		0.02	0.02	0.02	0.01
Post Hoc:		-	-	-	-
A *vs.* B		0.06	0.06	0.07	0.08
A *vs.* C		0.001	0.001	0.001	0.001
B *vs.* C		0.001	0.001	0.001	0.001

Table 4. Correlation analysis between hormonal profile and lipid profile amongst menopausal participants.

Parameters	N	R	P	S	Significant
FSH *vs.* Tchol	138	.581	0.03	S	P<0.05
FSH *vs.* Trig	138	.603	.002	S	P<0.05
FSH *vs.* HDL-C	138	-. 706	.001	S	P<0.05
FSH *vs.* LDL-C	138	.703	.001	S	P<0.05
LH *vs.* Tchol	138	.513	.008	S	P<0.05
LH *vs.* Trig	138	.671	.005	S	P<0.05
LH *vs.* HDL-C	138	-.803	.001	S	P<0.05
LH *vs.* LDL-C	138	.677	.003	S	P<0.05
PRL *vs.* Tchol	138	.654	.009	S	P<0.05
PRL *vs.* Trig	138	-.406	.05	S	P<0.05
PRL *vs.* HDL-C	138	.905	.001	S	P<0.05
PRL *vs.* LDL-C	138	-.609	.001	S	P<0.05
TSH *vs.* Tchol	138	.704	.001	S	P<0.05
TSH *vs.* Trig	138	.801	.001	S	P<0.05
TSH *vs.* HDL-C	138	.741	.001	S	P<0.05
TSH *vs.* LDL-C	138	.801	.001	S	P<0.05
Inh *vs.* T.chol	138	-.593	.002	S	P<0.05
Inh *vs.* Trig	138	-.767	.001	S	P<0.05
Inh *vs.* HDL-C	138	.908	.001	S	P<0.05
Inh *vs.* LDL-C	138	-.606	.009	S	P<0.05
Amh *vs.* Tchol	138	-.592	.05	S	P<0.05
Amh *vs.* Trig	138	-.581	.05	S	P<0.05
Amh *vs.* HDL-C	138	.705	.002	S	P<0.05
Amh *vs.* LDL-C	138	-.678	.002	S	P<0.05
E2 *vs.* Tchol	138	-.908	.001	S	P<0.05
E2 *vs.* Trig	138	-.906	.001	S	P<0.05
E2 *vs.* HDL-C	138	.901	.001	S	P<0.05
E2 *vs.* LDL-C	138	-.916	.001	S	P<0.05
Prog *vs.* Tchol	138	-.875	.001	S	P<0.05
Prog *vs.* Trig	138	-.809	.001	S	P<0.05
Prog *vs.* HDL-C	138	+.795	.001	S	P<0.05
Prog *vs.* LDL-C	138	-.801	.001	S	P<0.05

Table 5. Diagnostic performance of FSH, LH, PRL, TSH, HDL-C, LDL-C and trig in group A and B using E2 as gold standard.

Parameters	Groups	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
FSH (mIu/ml)	A	97	85	95	28%
	B	95	90	95	25%
LH (mIu/ml)	A	96	90	93	47%
	B	92	89	96	45%
PRL (ns/ml)	A	82	80	89	39%
	B	85	79	86	38%
TSH (uiu/ml)	A	79	80	90	30%
	B	76	81	91	38%
HDL-C	A	92	46	93	67%
	B	95	89	94	72%
LDL-C	A	96	80	90	71%
	B	93	84	93	70%
Trig (mg/dl)	A	72	49	91	68%
	B	79	63	93	61%

Discussion

The present study focused on some indices that could be used to diagnose menopause and monitoring the management of menopause related symptoms. The indices used were hormonal and biochemical markers. The hormonal profile are follicle stimulating hormone, luteinizing hormone, prolactin, thyroid stimulating hormone, inhibin, antimullerian hormone, estradiol, progesterone and calcitonin while the lipid profile are, total cholesterol, triglyceride, high density lipoprotein cholesterol and low density lipoprotein cholesterol. In this study, gonadotropin hormones (follicle stimulating hormone, FSH and luteinizing hormone, LH) Concentration in menopausal and perimenopausal subjects were dramatically high when compared to that of women of reproductive age. The follicle stimulating hormone (FSH) levels was higher than luteinizing hormone (LH) levels and both FSH and LH rise to even higher values than those seen in the surge during normal menstrual cycles. The observed elevated FSH and LH levels could be due to decline or declining ovarian function as a result of exhaustion of the pool of primary ovarian follicles and decreased steroidogenesis. This affects the pituitary – hypothalamic feedback mechanisms causing an increase in pituitary gonadotropins. This finding is supported by the work of Sherman BM, et al. [10] that loss of oocytes and follicles ultimately results in a series of endocrine changes in the hypothalamic – pituitary – gonadal axis and gradual diminution of estrogen

and inhibin occurs [10]. Research findings further revealed that decreased levels of inhibin result in raised levels of follicle-stimulating-hormone which is the first laboratory indication of the perimenopause and that the increased FSH induces rapid follicular development with consequent shortening of cycles. This change in menstrual cycle is due to a shortening of the follicular, but not luteal phase and may be the first clinical sign of the perimenopause. This showed that FSH and LH could be used as potential markers of menopause.

In this study, the serum prolactin levels in menopausal and perimenopausal subjects were significantly lower when compared with prolactin level of women within reproductive age. This suggests that prolactin concentration drops at menopausal stage of life and could be used as a potential marker for the diagnosis of menopause. This finding concur with the study done by Eleni A, et al. [11] that dopamine restrains the production of prolactin while estrogen increases it; that estradiol send message to the pituitary gland primarily indicating whether to begin the production of prolactin. In addition, Estradiol do not only promote prolactin synthesis but also decreases the production of luteinizing hormone and follicle stimulating hormone from the pituitary gland. This finding is also supported from another study that in pregnancy and just after parturition, estrogen and progesterone stimulate prolactin production but at menopause, there is a significant decrease in estradiol and progesterone and so there is no stimulation of prolactin secretion. Similarly, this study concurs with the study done by Buckler HM, et al. [12] that prolactin levels decrease significantly during menopause.

The study observed an increase in thyroid stimulating hormone amongst perimenopausal and menopausal participants when compared to thyroid stimulating hormone (TSH) of women within the reproductive age. This suggests that TSH concentration increases at menopause and could be used to indicate laboratory symptoms of perimenopause or menopause. It is important to say from this study that elevated TSH level was associated with increased triglycerides, total cholesterol, low-density lipoprotein cholesterol with significant decrease in high-density lipoprotein cholesterol (HDL-C). The findings of the present study could suggest that TSH levels could be used as an independent predictive marker of atherosclerosis in menopausal and perimenopausal participants.

The elevated TSH levels observed in this study which is associated with high triglycerides, low density lipoprotein cholesterol (LDL-C), total cholesterol and decreased HDL-C is supported by the work done by Elsabagh E, et al. [13] that menopause is a natural aging process causing estradiol deficiency. That in reproductive period, women have a significantly lower risk for cardiovascular disease compared to perimenopausal, menopausal and postmenopausal women. This is because at perimenopause and menopausal stage, a decline in serum estrogen accelerates atherogenic process presenting dyslipidemia, endothelial dysfunction, arterial stiffness, and increase risk for cardiovascular disease (CVD) which threaten women health [14]. This disparity between prevalence of CVD in perimenopausal, menopausal and women of reproductive age has been elucidated to the actions of estrogens on cardiovascular systems, particularly on vascular endothelium. Previous studies have reported that both endogenous and exogenous estrogens have cardio-protective effects in women; therefore, starting estrogen therapy after menopause is imperative. Meanwhile initiating estrogen therapy many years after menopause may have hazardous effects on cardiovascular system [15]. Like this actions of estrogen depends on the time of initiation of estrogen therapy in postmenopausal women, and it may be due to endothelial injury, changes in vascular estrogen receptor expression, intracellular signaling which could alter the cardiovascular effects of this steroid hormone [16].

This study also observed the significant decrease in the levels of progesterone, estradiol, inhibin and antimullerian hormone in perimenopausal and menopausal subjects when compared to levels of progesterone, estradiol, inhibin and antimullerian hormone of women of reproductive age. This finding could indicate decline or complete cessation of ovarian function at menopause due to exhaustion of the pool of primary ovarian follicles. Inhibin, unlike gonadotropin surge inhibiting factor, selectively suppresses pituitary release of FSH. Inhibin is a non-steroidal inhibitor present in follicular fluid and its peptides moiety is synthesized by the granulosa cells and secreted into the follicular fluid. The decrease in inhibin secretion by the ovarian follicles begins early at around 35 years of age but accelerates after the age of 40 [12]. Similarly, low levels of estrogen and progesterone is the primary basis for the progressive decrease and complete cessation of the cyclic function of the female reproductive organs, this deficiencies in estrogen and progesterone appears to lie in the ovary itself [17]. There is continuing loss of the primordial follicles during intrauterine life and throughout the reproductive years until menopause. After about 35 years, the human ovary begins to decrease in weight and size, and contains much fewer oocytes and follicular structures and more atretic and degenerating follicles [18]. It is important to realize that the feedback mechanisms may cause readjustments between the pituitary and ovary as long as there are follicles remaining in the ovary to respond. Also over a period of 1 or 2 years, reversal f laboratory findings as well as clinical signs and symptoms may occur [19-22].

In the menopausal ovary, although ovarian estradiol, antimullerian hormone and progesterone secretions are sharply reduced, the ovary is nevertheless capable of substantial steroidogensis. The ovarian stroma cells as well as the adrenal cells have a steroidogenic capacity for producing androstenedione which is converted by the skin and appendages to oestrone [12]. The primary steroidogenic element of the menopausal and postmenopausal ovary is the stroma, which frequently contains islands of thecal cells and may have the appearance of a generalized bilateral thecal hyperplasia. The steroids secreted by the menopausal and postmenopausal ovary in response to the stimulus from high concentrations of LH are primarily androgens (androstenedione, testosterone), but some estradiol may also be produced in insignificant concentrations. Hence, the ovarian stroma continues to be stimulated by LH to produce androstenedione and testosterone, with oestrone accounting most of the circulatory estrogen in the postmenopausal women [11]. From this study, it is therefore important to say that menopausal women have an estrogen milieu that is lower than necessary for reproductive function. It is also important to say that Antimullerian hormone (Amh) levels is one of the important markers of ovarian reserve and it is highly associated with ovarian follicular development.

Also in this study, the levels of calcitonin and calcium were significantly lower while levels of phosphorus and alkaline phosphatase were significantly higher amongst premenopausal and menopausal participants when compared to calcitonin, calcium, phosphorus and alkaline phosphatase of women of reproductive age. A marked decrease in calcium and calcitonin with a marked increase in phosphorus and alkaline phosphatase amongst the menopausal women could be due to significant decrease in estradiol level. The decreased estradiol leads to release of a cytokine (receptor activator nuclear factor kappa B ligand; RANK L) which stimulate osteoclastic cascade leading to osteoporosis. Perhaps, the osteoporosis could be the cause of elevated alkaline phosphatase (ALP) and phosphorous with corresponding decrease in calcium and calcitonin. Since estradiol is an inhibitor of RANK L that prevent binding of RANK L to RANK. Hence the binding of Estradiol to RANK stimulate the secretion of calcitonin and calcitonin in turn stimulate osteoblast for born formation. This study is supported by the work done by Makara Studzinska MT, et al. [23] that long period of estrogen lack such as in menopause and postmenopause may be associated with a more pronounced calcitonin deficiency. This exaggerated deficiency of estradiol could be an important factor in the pathogenesis of postmenopausal bone loss due to bone resorption. This work was supported by another similar study by Li S, et al. [24] on the effects of estrogen treatment on circulating levels of calcitonin, parathyroid hormone and vitamin –D metabolites in postmenopausal women. The most striking change was a sharp rise in plasma calcitonin. Estrogen prevents postmenopausal bone loss, and it is suggested that this effect could be mediated, at least in part, through control of calcitonin secretion. Calcitonin may prove effective in the prevention of postmenopausal bone loss.

The study also observed that the total cholesterol, triglycerides and LDL-C levels of menopausal and premenopausal participants were significantly higher when compared to the total cholesterol, triglycerides and LDL-C of women of reproductive age. Meanwhile marked decrease in HDL-C levels was observed amongst menopausal and premenopausal participants with normal HDL-C levels amongst women of reproductive age. Also, noted in this study, simple person correlation showed association between lipid profile and estradiol; this could lead to atherosclerosis in menopausal and premenopausal participants. This finding is supported by the work done by Lobo RA, et al. [25] that increasing HDL-C seemed to have associations with a decrease in presence of atherosclerosis in simple logistic regression analysis amongst postmenopausal women [26-49].

Conclusion

The present study thus concludes that elevated levels of FSH, LH, TSH with decreased levels of E2, PRL, INH, AMH and progesterone were associated with perimenopause and menopause. This suggests that hormonal profiles are good markers for the diagnosis of menopause and per menopause. The study observed elevated levels of total cholesterol, triglycerides, LDL-C while decreased HDL-C levels were observed. From these findings, hormonal profile and lipid profile could be significant predictors of perimenopause and menopause. Also, screening and assessing risk for menopausal and perimenopausal women would be helpful

before the developments of certain clinical symptoms such as atherosclerosis and many other metabolic diseases. The decline in E2, AMH, Prog, Inh can also be used to identify women at risk of early menopause. Further studies should be carried out to establish alternative, appropriate, easy and simpler indices and methods suitable for assessing or diagnosing menopause in resource-limited settings.

Competing Interests

The authors declare that they have no competing interests.

Authors Contributions

This work was carried out in collaboration between all authors. Author EPI and ZU designed the study and performed the statistical analysis. Authors EPI, AAO and ZU conducted and managed the Laboratory analysis. All authors read and approved the final manuscript.

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