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Full length Research Article

Assessing the Interplay between Dyslipidemia and Bone-Related Markers in Postmenopausal Women.

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Summary: Dyslipidemia, marked by abnormal lipid levels, contributes to cardiovascular disease risk and affects bone health, particularly in postmenopausal women. Hormonal changes during menopause disrupt lipid and bone metabolism, increasing the likelihood of cardiovascular and bone-related disorders. This study explores the relationship between dyslipidemia and bone-related markers in postmenopausal women to understand its implications for bone and cardiovascular health. A cross-sectional study was conducted on 100 women: 60 postmenopausal (PMP), 20 premenopausal (PRM), and 20 reproductive-age (RWA) women. Fasting blood samples were collected and analyzed for lipid profile, alkaline phosphatase (ALP), inorganic phosphate, calcium, and vitamin D using standard laboratory techniques. Statistical analysis was performed using ANOVA and posthoc tests. Postmenopausal women showed significantly elevated levels of total cholesterol, LDL-C, and triglycerides, along with higher ALP and inorganic phosphate levels compared to premenopausal and reproductive-age women ($p<0.05$). Calcium and vitamin D levels were lower in the PMP group. Dyslipidemia in postmenopausal women is associated with disrupted bone metabolism, indicating an increased risk of cardiovascular and bone-related disorders. Comprehensive health assessments are recommended for early intervention.

Keywords*: menopause, dyslipidemia, vitamin D, osteoporosis, cardiovascular risk*

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INTRODUCTION

Menopause, defined as the cessation of menstruation for 12 consecutive months due to estrogen deficiency, marks a significant physiological transition in women's lives. It typically occurs between the ages of 48 and 52, primarily influenced by genetic factors rather than socio-economic status or previous ovulation history (Araujo *et al.*, 2023; Pardhe *et al*., 2017; Soares, 2019). Beyond its reproductive implications, menopause impacts various bodily systems, including urogenital, psychogenic, and cardiovascular functions. The transition encompasses perimenopause, menopause, and postmenopause, each characterized by hormonal shifts and physiological changes (Soares, 2019; Achie *et al*., 2021).

During menopause, ovarian follicles decline in number, accompanied by a reduction in granulosa cell activity, the primary producers of estrogen and inhibin. Decreased estrogen and inhibin levels lead to elevated follicle-stimulating hormone (FSH) and luteinizing hormone (LH) production, disrupting the hypothalamic-pituitary-ovarian axis and causing irregular menstrual cycles until cessation (Faulds *et al*., 2012). Additionally, menopause triggers significant changes in vaginal tissue, marked by mucosal atrophy due to decreased estrogen levels, resulting in dryness and fragility (Sarmento *et al*., 2021). Surgical procedures, such as hysterectomy with bilateral oophorectomy, or medical treatments for conditions like endometriosis or breast cancer, can induce menopause prematurely (Sarmento *et al*., 2021).

Dyslipidemia, characterized by an imbalance in cholesterol and lipid levels, poses a risk factor for cardiovascular diseases. In Nigeria, dyslipidemia has become an increasingly prevalent health issue, reflecting the global rise in non-communicable diseases. Urbanization, changes in dietary habits, and sedentary lifestyles have contributed to the growing incidence of lipid disorders. Recent studies have shown that dyslipidemia affects approximately 20-40% of adults in Nigeria, with a higher prevalence in urban areas compared to rural settings (Ayogu *et al*., 2021; Ekpenyong *et al*., 2012). Factors contributing to dyslipidemia include diet, tobacco use, genetics, and hormonal changes, such as those occurring during menopause (Kopin & Lowenstein, 2017). Additionally, menopause has been identified as a significant factor contributing to dyslipidemia in Nigerian women, exacerbating their risk of cardiovascular diseases (Igweh *et al*., 2005; Nie *et al*., 2022). The increasing prevalence of dyslipidemia highlights the need for targeted public health interventions and lifestyle modifications to mitigate the risk of cardiovascular complications. Contrary to the perception of bones as static structures, they function dynamically as organs, playing crucial roles in mobility, organ protection,

and hematopoiesis. Bone remodeling, a continuous process influenced by hormonal regulation, involves the resorption and formation of bone tissue. Bone markers, detectable in blood and urine, serve as indicators of bone turnover and can aid in diagnosing bone disorders like osteoporosis and Paget's disease (Song *et al*., 2023; Schini *et al*., 2023). Postmenopausal women face heightened risks of bone disorders and low serum calcium levels, with dyslipidemia potentially exacerbating these risks.

Imbalances in bone resorption and formation, detectable through bone markers, are associated with various diseases. Postmenopausal women represent a group that is especially susceptible to bone-related disorders as a result of hormonal changes (Faulds *et al*., 2012; Adewole *et al*., 2021). Despite previous research on bone markers and metabolic bone diseases, gaps persist in understanding the relationship between post-menopause, bone markers, and dyslipidemia. Existing literature has explored the utility of bone-associated biomarkers in diagnosing and monitoring bone disorders. However, gaps remain regarding the interplay between bone markers, dyslipidemia, and postmenopausal status. Given the increased risk of bone disorders and dyslipidemia in postmenopausal women, elucidating these correlations is crucial for preventive and therapeutic interventions. Therefore, this study aims to explore the relationship between dyslipidemia and bone-related markers in postmenopausal women to better understand the implications for bone and cardiovascular health.

MATERIALS AND METHODS

Experimental Design: A cross-sectional study was undertaken involving 100 women aged 50 years and above, selected randomly from the Owo metropolis, Ondo State, Nigeria. The research spanned from January to August 2022. Among the participants, 60 were PMP aged between 50 and 60 years, while 40 were tagged controls, comprising 20 PRM and 20 RWA. Data collection involved obtaining medical histories and personal information through a comprehensive questionnaire, following approval from the hospital's ethical committee. All participants provided informed consent prior to inclusion in the study.

Consent and Ethical Clearance: All participants in this study received detailed explanations of the research protocols at the clinic, followed by the requirement to sign written consent forms. Ethical clearance, bearing reference number FMC/OW/380/VOL.CL/200, was obtained from the Ethical Review Committee of the Federal Medical Center, Owo, and ensuring adherence to ethical standards throughout the study.

Inclusion and Exclusion Criteria: The study included women aged 50 years and above categorized as postmenopausal women, while women aged 30 to 50 years were considered either premenopausal or within the reproductive age range. Participation required informed consent from the participants. Participants with known comorbidities including hypertension, HIV, hepatitis, cancer, or those undergoing oral anticoagulant treatment, with bleeding tendencies, and breastfeeding mothers were excluded from the study. Additionally, individuals who did not provide consent were also excluded.

Samples Collection and Storage: Blood samples were collected from each participant following standard procedures. 5 milliliters (5ml) of fasting blood samples were collected into sterile lithium heparin bottles. After gentle mixing, samples were centrifuged at 4000 revolutions per minute (rpm) for 5 minutes to obtain serum. Serum was stored at -20°C until analysis for vitamin D, calcium, uric acid, lipid profile, inorganic phosphate, and alkaline phosphatase (ALP).

Analytical Methods: Using reagents provided by Randox Laboratories Ltd. (UK), standard enzymatic methods were used to determine serum levels of total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C), as well as fasting plasma glucose, ALP, phosphorus, uric acid, calcium (Ca2+). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedwald equation (Friedwald *et al*., 1972). Additionally, ELISA kit from Melsin Medical Company, USA, was used to assess the serum levels of vitamin D. Every participant had their height and weight measured, and their body mass index (BMI) was calculated using the guidelines provided by Atere *et al*. (2020).

Statistical Analysis: The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25.0 0 (SPSS Inc., Chicago, IL, USA). One-way analysis of variance (ANOVA) was employed to compare variables within the groups, while correlation analysis was used to assess associations between variables. Quantitative values were presented as mean ± standard deviation (mean ± SD). The level of significance was set at a 95% confidence interval, with p-values ≤ 0.05 considered statistically significant.

RESULTS

Figure 1 depicts the demographics of the subjects investigated. The results showed that the mean age (years) of RWA was 33.9±2.0, PRM was 44.4±2.2, and PMP was 57.8±7.4. The subjects' age, BMI, and SBP showed significant differences ($p<0.05$). Table 1 compares atherogenic indices and bone-related biomarkers in premenopausal and postmenopausal women with reproductive age. PMP and PRM individuals had significantly higher mean TC, HDL-C, and LDL-C levels than the RWA group ($p<0.05$). PMP and PRM participants had considerably greater mean values of ALP, inorganic phosphate, and uric acid compared to the RWA group. However, FBS, calcium (Ca^{2+}), and vitamin D were significantly lower ($p<0.05$). The PMP group had significantly greater mean levels of ALP, inorganic phosphate, and uric acid compared to the PRM group ($p<0.05$). However, Ca^{2+}, FBS, and vitamin D levels were lower. Additionally, bone-associated markers (ALP, inorganic phosphate, Ca2+, and Vitamin D) linked with atherogenic indices (TC, TG, and LDL-C) in postmenopausal women. Inorganic phosphate had a statistically significant positive correlation with TC, TG, and LDL-C, however vitamin D had a negative link with TC. Finally, TG showed significant positive correlation with inorganic phosphate only among premenopausal women (Figure 3).

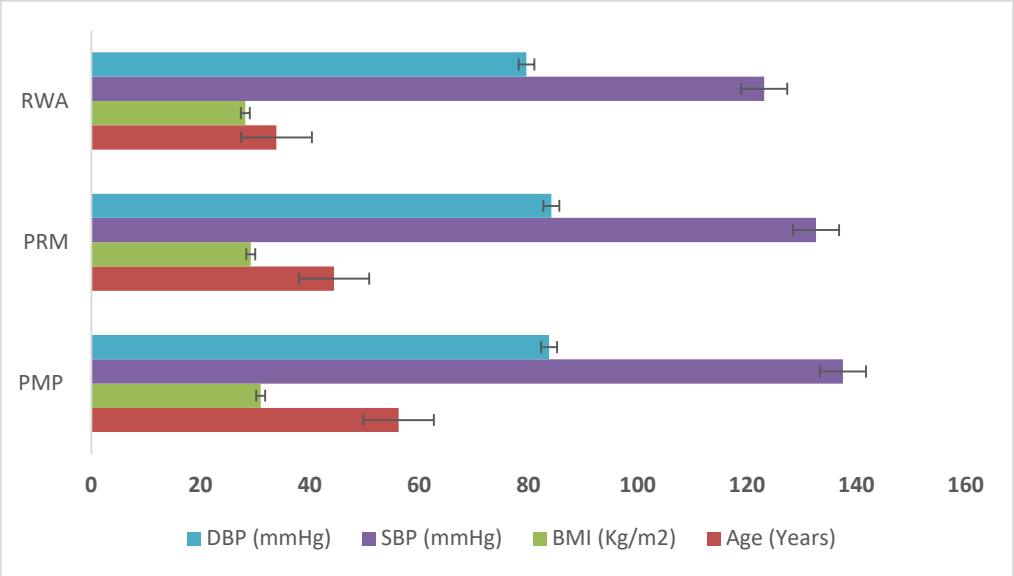

Figure 1:
Demographic Characteristics of the Participants
Key: RWA= Reproductive women age, PRM = Premenopausal, PMP= Postmenopausal, DBP= diastolic blood pressure, SBP= systolic blood pressure, BMI= body mass index

Table 1:
Comparison of atherogenic indices and bone related markers in postmenopausal women, premenopausal women and reproductive women age

Parameters	RWA (n=20)	PRM (n=20)	PMP (n=60)	p-value
HDL-C (mg/dl)	40.10±10.10[a]	50.12±11.10[b]	50.49±10.59[c]	0.000*
LDL-C (mg/dl)	100.25±30.30[a]	110.15±34.15[b]	157.93±19.47[c]	0.000*
TG (mg/dl)	60.14±20.31[a]	45.56±14.92[b]	83.99±19.53[c]	0.000*
TC (mg/dl)	170.22±40.44[a]	180.36±35.40[b]	208.22±21.25[c]	0.001*
FBG (mg/dl)	77.24±7.13[a]	87.24±20.30[b]	102.49±18.73[c]	0.001*
ALP (U/L)	330.47 ± 68.45[c]	187.37 ± 49.80[b]	138.90 ± 36.74[a]	0.000*
Inorganic phosphate (mmol/L)	4.41 ± 0.84[b]	3.65 ± 0.54[a]	3.31 ± 0.63[a]	0.000*
Uric Acid (mg/dl)	5.07 ± 1.08[c]	3.51 ± 0.99[b]	2.77 ± 0.36[c]	0.000*
Calcium (mg/dl)	6.75 ± 0.88[a]	7.88 ± 0.76[b]	10.33 ± 1.29[c]	0.000*
Vitamin D (ng/mL)	13. 96 ± 3.18[a]	22.34 ± 4.18[b]	30.40 ± 10.03[c]	0.000*

* Significant at p≤0.05
a = postmenopausal women; b = premenopausal women; c = reproductive age women
**Values were represented with Mean± SD. Mean values were compared using one-way ANOVA with level of significance set at p<0.05. Values in the same column with the same superscript are not statistically different at p<0.05 using the Post-Hoc test.*
Key: n=sample size, HDL-C= High density lipoprotein Cholesterol, LDL-C= Low density lipoprotein, TG= Triglycerides, TC= Total Cholesterol, FBG- Fasting blood glucose, RWA= Reproductive women age, PRM = Premenopausal, PMP= Postmenopausal

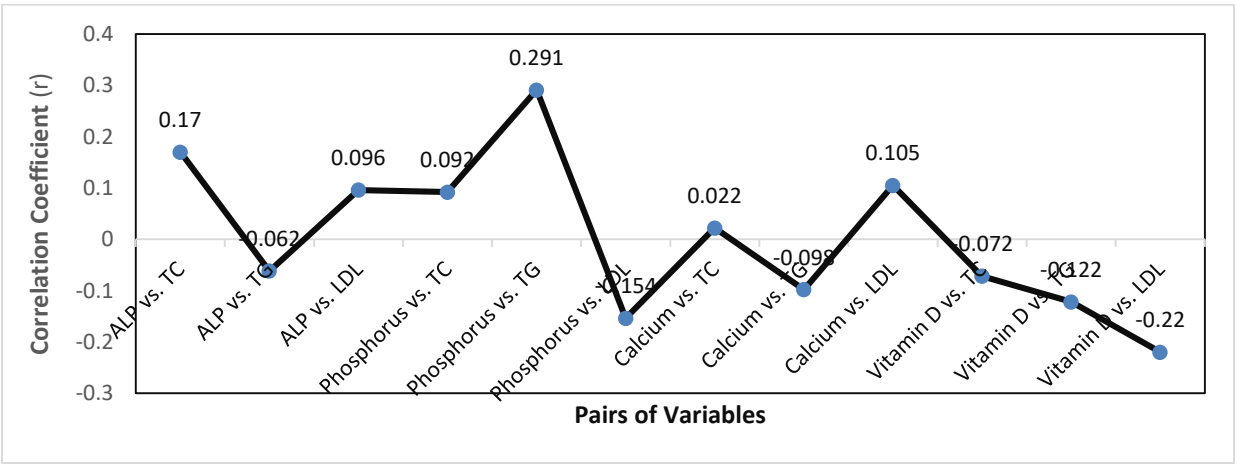

Figure 2:
Correlation of mean Bone associated-markers (ALP, Inorganic phosphate, Ca^{2+}, Vitamin D) with atherogenic indices (TC, TG and LDL-C) in Postmenopausal Subjects

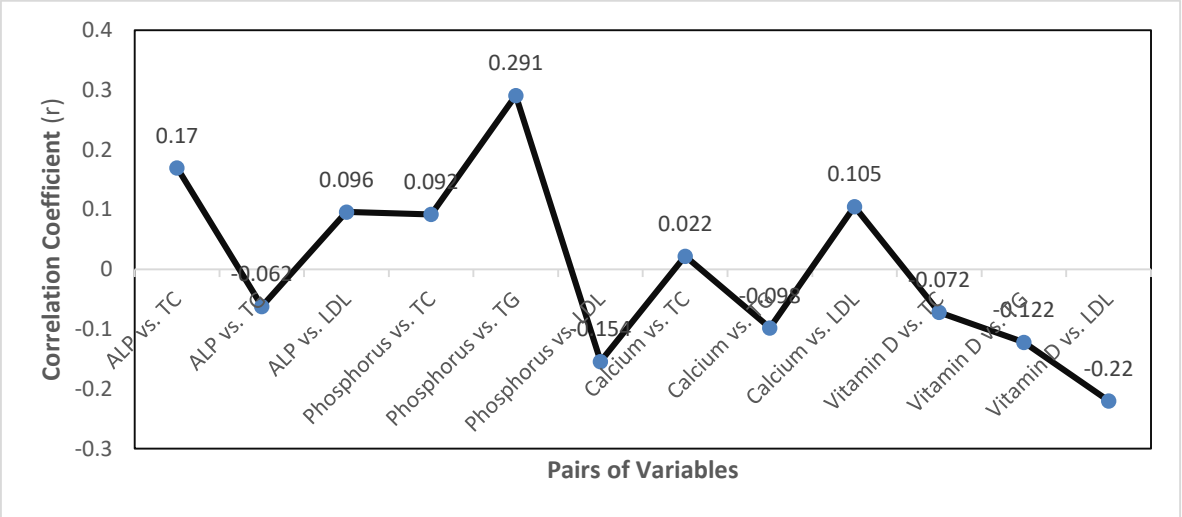

Figure 3:
Correlation of mean Bone associated-markers (ALP, Inorganic phosphate, Ca^{2+}, Vitamin D) with atherogenic indices (TC, TG and LDL-C) in Pre-menopausal Subjects

DISCUSSION

Menopause represents a significant physiological milestone in a woman's life, marked by profound hormonal changes and associated physiological alterations. The decline in estrogen levels during menopause plays a pivotal role in various metabolic and biochemical shifts, particularly affecting bone mineral metabolism (Faulds *et al*., 2012; Araujo *et al*., 2023). This study highlights the multifaceted impact of menopause on lipid metabolism, bone health, and associated biomarkers.

Consistent with existing literature, our findings demonstrate a transition towards a more atherogenic lipid profile during menopause, characterized by elevated plasma levels of TC, LDL-C, and TG, coupled with decreased levels of HDL-C (Fernandez & Murillo, 2016; Otsuki *et al*., 2017; Nandhini *et al*., 2022). The observed alterations in lipid parameters highlight the metabolic consequences of estrogen deficiency post-menopause, predisposing women to increased cardiovascular risk.

Moreover, our results shed light on the intricate relationship between menopause, bone-related biomarkers, and dyslipidemia. Postmenopausal women exhibited significantly higher levels of bone turnover markers, including ALP, inorganic phosphate, and uric acid, compared to their counterparts and reproductive-age women. Concurrently, lower levels of Ca2+, FBG, and vitamin D were observed among PMP women, indicating potential disruptions in bone homeostasis and metabolic regulation (Black & Rosen, 2016; Pardhe *et al*., 2017).

The correlation analysis further elucidates the interplay between bone-associated markers and atherogenic indices among postmenopausal women. Inorganic phosphate levels exhibited significant positive correlations with TC, TG, and LDL-C, underscoring the potential influence of bone metabolism on lipid homeostasis. Conversely, vitamin D levels displayed a negative correlation with total cholesterol, suggesting a possible protective role against dyslipidemia in postmenopausal women (Manninen *et al*., 1992; Kim *et al*., 2022; Romandini *et al*., 2023). Vitamin D may enhance lipid metabolism by promoting calcium absorption and regulating adipocyte function, thereby reducing total cholesterol levels. Its anti-inflammatory properties can also mitigate dyslipidemia, highlighting its potential protective role against cardiovascular risk in postmenopausal women through improved lipid profiles (Kim *et al*., 2022; Romandini *et al*., 2023).

These findings emphasize the importance of comprehensive metabolic evaluation in postmenopausal women, considering the complex interrelationships between bone health, lipid metabolism, and cardiovascular risk. Strategies aimed at mitigating dyslipidemia and preserving bone health post-menopause warrant further exploration, encompassing lifestyle modifications, pharmacological interventions, and targeted therapeutic approaches (Libby & Theroux, 2005; Suresh & Naidu, 2006; Bristow *et al*., 2019).

In conclusion, this study highlights the significant interplay between dyslipidemia and bone-related markers in postmenopausal women. The observed alterations in lipid profiles, characterized by elevated total cholesterol and LDL-C levels, alongside disrupted bone metabolism, emphasize the increased risk of cardiovascular and bone disorders. These findings highlight the need for comprehensive health assessments and targeted interventions to mitigate dyslipidemia and enhance bone health in postmenopausal women. Future research should focus on developing specific therapeutic strategies to address the unique metabolic challenges faced by this population.

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Authors' contributions: *The ADA conceived of the research and drafted the first manuscript. OMO, KYA and RMO conceptualized and evaluated the intellectual content of the final manuscript. Each author made a contribution to the final draft of the manuscript and bears the responsibility for ensuring the integrity and precision of this review*

REFERENCES

Achie, L. N., Olorunshola, K. V, Igashi, J., & Toryila, J. E. (2021). Assessment of the levels of serum parathyroid hormone in rural postmenopausal women in Zuturung

district , Zangon Kataf Local Government Area , Kaduna State , Nigeria . 9(December), 130–137.

Adewole, O. A., Idowu, S. O., Shoga, M. O., Kayode, M. O., & Adelowo, O. O. (2021). Frequency of Osteoporosis in Black Nigerian Women Aged 50 and above with Degenerative Musculoskeletal Diseases and Fractures. *West African Journal of Medicine*, 38(4), 342–346.

Araujo, L. C. C., Cruz, A. G., Camargo, F. N., Sucupira, F. G., Moreira, G. V, Matos, S. L., Amaral, A. G., Murata, G. M., Carvalho, C. R. O., & Camporez, J. P. (2023). Estradiol Protects Female ApoE KO Mice against Western-Diet-Induced Non-Alcoholic Steatohepatitis. *International Journal of Molecular Sciences*, 24(12). https://doi.org/10.3390/ijms24129845

Atere, A. D., Okpoli, H. C., Uwumarogie, K. A., & Moronkeji, A. I. (2020). Correlation between Anemia and Malaria Infection Severity in Patients with Type 2 Diabetes Mellitus in Nigeria. *Althea Medical Journal*, 7(4), 170–175. https://doi.org/10.15850/amj.v7n4.2085

Ayogu, R. N. B., Ezeh, M. G., & Okafor, A. M. (2021). Prevalence and predictors of different patterns of hypertension among adults aged 20-60 years in rural communities of Southeast Nigeria: a cross-sectional study. *Archives of Public Health = Archives Belges de Sante Publique*, 79(1), 210. https://doi.org/10.1186/s13690-021-00724-y

Black, D. M., & Rosen, C. J. (2016). Clinical Practice. Postmenopausal Osteoporosis. *The New England Journal of Medicine*, 374(3), 254–262. https://doi.org/10.1056/NEJMcp1513724

Bristow, S. M., Horne, A. M., Gamble, G. D., Mihov, B., Stewart, A., & Reid, I. R. (2019). Dietary Calcium Intake and Bone Loss Over 6 Years in Osteopenic Postmenopausal Women. *The Journal of Clinical Endocrinology & Metabolism*, 104(8), 3576–3584. https://doi.org/10.1210/jc.2019-00111

Ekpenyong, C. E., Akpan, U. P., Ibu, J. O., & Nyebuk, D. E. (2012). Gender And Age Specific Prevalence And Associated Risk Factors Of Type 2 Diabetes Mellitus In Uyo Metropolis, South Eastern Nigeria. https://api.semanticscholar.org/CorpusID:489126

Faulds, M. H., Zhao, C., Dahlman-Wright, K., & Gustafsson, J.-Å. (2012). The diversity of sex steroid action: regulation of metabolism by estrogen signaling. *The Journal of Endocrinology*, 212(1), 3–12.

Fernandez, M. L., & Murillo, A. G. (2016). Postmenopausal women have higher HDL and decreased incidence of low HDL than premenopausal women with metabolic syndrome. Healthcare (Switzerland), 4(1). https://doi.org/10.3390/healthcare4010020

Igweh, J. C., Nwagha, I. U., & Okaro, J. M. (2005). The effects of menopause on the serum lipid profile of normal females of South East Nigeria. *Nigerian Journal of Physiological Sciences*. 20 (1–2), 48–53.

Kim, K., Ginsberg, H. N., & Choi, S. H. (2022). New, Novel Lipid-Lowering Agents for Reducing Cardiovascular Risk: Beyond Statins. *Diabetes & Metabolism Journal*, 46(4), 517–532. https://doi.org/10.4093/dmj.2022.0198

Libby, P., & Theroux, P. (2005). Pathophysiology of coronary artery disease. *Circulation*, 111(25), 3481–3488. https://doi.org/10.1161/CIRCULATIONAHA.105.537878

Manninen, V., Tenkanen, L., Koskinen, P., Huttunen, J. K., Mänttäri, M., Heinonen, O. P., & Frick, M. H. (1992). Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. *Circulatio*n, 85(1), 37–45. https://doi.org/10.1161/01.cir.85.1.37

Nandhini, R., Nath, B., Gaikwad, H. S., Sharma, M., & Meena, S. (2022). Metabolic Syndrome and Its Components: A Cross-Sectional Analysis of Its Distribution among Pre- and Post-Menopausal Women from Northern India. *Journal of Mid-Life Health*, 13(4), 310–316. https://doi.org/10.4103/jmh.jmh_38_22

Nie, G., Yang, X., Wang, Y., Liang, W., Li, X., Luo, Q., Yang, H., Liu, J., Wang, J., Guo, Q., Yu, Q., & Liang, X. (2022). The Effects of Menopause Hormone Therapy on Lipid Profile in Postmenopausal women: A Systematic Review and Meta-Analysis. *In Frontiers in pharmacology* (Vol. 13, p. 850815). https://doi.org/10.3389/fphar.2022.850815

Otsuki, M., Kasayama, S., Morita, S., Asanuma, N., Saito, H., Mukai, M., & Koga, M. (2007). Menopause, but not age, is an independent risk factor for fasting plasma glucose levels in nondiabetic women. *Menopause* (New York, N.Y.), 14(3 Pt 1), 404–407. https://doi.org/10.1097/01.gme.0000247014.56254.12

Pardhe, B. D., Pathak, S., Bhetwal, A., Ghimire, S., Shakya, S., Khanal, P. R., & Marahatta, S. B. (2017). Effect of age and estrogen on biochemical markers of bone turnover in postmenopausal women: a population-based study from Nepal. *International Journal of Women's Health*, 9, 781–788. https://doi.org/10.2147/IJWH.S145191

Romandini, A., Baldassarre, D., Genovese, S., Capri, S., Pompilio, G., Scatigna, M., & Werba, J. P. (2023). Atherogenic Dyslipidemias: Unmet Needs and the Therapeutic Potential of Emerging and Novel Approaches and Drugs. *Pharmaceuticals (Basel, Switzerland)*, 16(2). https://doi.org/10.3390/ph16020176

Sarmento, A. C. A., Costa, A. P. F., Vieira-Baptista, P., Giraldo, P. C., Eleutério, J. J., & Gonçalves, A. K. (2021). Genitourinary Syndrome of Menopause: Epidemiology, Physiopathology, Clinical Manifestation and Diagnostic. *Frontiers in Reproductive Health*, 3, 779398. https://doi.org/10.3389/frph.2021.779398

Schini, M., Vilaca, T., Gossiel, F., Salam, S., & Eastell, R. (2023). Bone Turnover Markers: Basic Biology to Clinical Applications. *Endocrine Reviews*, 44(3), 417–473. https://doi.org/10.1210/endrev/bnac031

Soares, C. N. (2019). Depression and Menopause: An Update on Current Knowledge and Clinical Management for this Critical Window. *Medical Clinics of North America*, 103(4), 651–667. https://doi.org/10.1016/j.mcna.2019.03.001

Song, M.-K., Park, S. I., & Cho, S. W. (2023). Circulating biomarkers for diagnosis and therapeutic monitoring in bone metastasis. *Journal of Bone and Mineral Metabolism*, 41(3), 337–344. https://doi.org/10.1007/s00774-022-01396-6

Suresh, M., & Naidu, D. M. (2006). Influence of years since menopause on bone mineral metabolism in South Indian women. *Indian Journal of Medical Sciences*, 60(5), 190–198.