

Coronary Artery Disease and Menopause: A Consequence of Adverse Lipid Changes

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Abstract: Changes in the level of hormones associated with menopause on the serum lipid profiles plays major role in most cardiac disorders. There are fewer chances of women developing cardio-vascular diseases (CVD) before menopause but its incidence after menopause is high and may be due to changes in plasma levels of lipids. Menopause is regarded as an independent risk factor for the development of CVD in our environment due to adverse lipid changes. The relationship between these adverse lipid profile changes and the development of coronary artery disease (CAD) is still a subject of controversy. This study aimed at evaluating the serum lipid profiles in postmenopausal and premenopausal women comparing the relative risk of developing CAD among them. The serum lipid profiles evaluated were TC, TG, HDL-C, LDL-C, VLDL-C as well as the atherogenic indices. Apparently healthy one hundred women were recruited for the study. These included sixty (60) postmenopausal and forty (40) premenopausal women. Data were obtained by direct clinical evaluation and laboratory investigation. TC, TG and HDL-C were all estimated using enzymatic methods while the LDL-C and VLDL-C was calculated using the established mathematical methods. Statistical analysis was carried out using the student's T-test and one-way analysis of variance. Results were expressed as mean \pm SEM. P-values $<$ 0.05 were considered to be statistically significant. A significant increase was observed in serum TC, TG, LDL-C, VLDL-C with significant decrease in the level of HDL-C (P-value $<$ 0.05). The atherogenic indices also significantly increased in the postmenopausal women (P-value $<$ 0.05). Thus increase in plasma levels of TC, TG, LDL-C, and VLDL-C as well as atherogenic indices in postmenopausal women are indication that CAD risk increases after menopause.

Keywords: Lipid profile, cardiovascular, postmenopausal, premenopausal and women.

I. Introduction

Menopause is the cessation of the menstrual period resulting from the eventual atresia of almost all the oocytes in the ovaries. It is usually heralded by various cyclic changes. Changes in mood usually seen in menopause can lead to an increase blood pressure with subsequent stroke and other cardiovascular diseases (CVD) (Butler and Santoro, 2011). Menopause results from loss of ovarian sensitivity to gonadotropin stimulation, which is directly related to follicular attrition (Samantha, 2008). The oocytes in the ovaries undergo atresia leading to a decline in both the quantity and the quality of follicles (Samantha, 2008). Thus, the variable menstrual cycle length during the menopausal transition (MT) is due more to a shrinking follicle cohort size than to follicle failure. A nonovulatory cycle and absence of cyclicality become common, with a highly variable pattern of gonadotropin and steroid hormone production, estrogen insensitivity, failure of the luteinizing hormone (LH) surge, the occurrence of the final menstrual period, and permanent amenorrhea (Butler and Santoro, 2011).

Hormonal fluctuation may not account for all irregular bleeding at this time (Ponjola, 2014). Uterine fibroids, uterine polyps, endometrial hyperplasia, or cancer become more prevalent at this age and must be ruled out. Towards the 5th decade of life, many women think that they are no longer fertile because they are so close to menopause. Although fertility declines, pregnancy can still occur as evidenced by a relatively high rate of unintended pregnancies in women aged 40-44 years. In fact, the number of unintended pregnancies in this age group has increased over the past decade (Henshaw, 1998). Since functional follicles, which are stimulated by follicle-stimulating hormone (FSH) during the first part of the menstrual cycle decline in number, less recruitment of oocytes occurs, and follicular phase shortens. Once ovulation occurs, the luteal phase remains fairly constant, at 14 days.

Over time, as aging follicles become more resistant to gonadotropin stimulation, circulating FSH and LH levels increase. Increased levels of FSH and LH levels lead to stromal stimulation of the ovary, leading to increase in estrone levels and a decrease in estradiol levels. Levels of inhibins also drop during this period due to negative feedback of elevated FSH levels (Lenton et al, 1991; Santoro and Randolph, 2011). With onset of menopause and loss of follicular function, there are significant changes in hormonal profile. These include:

- A dramatic decrease in circulating estradiol over a period of four years (starting 2 years before the final last menstrual period and stabilizing about 2 years after the final period).
- The level of estrone increases and becomes the major source of circulating estrogen in postmenopausal women.
- Total serum testosterone levels do not change during menopausal transition (MT). The dehydroepiandrosterone (DHEAS) levels do decline with age. A trend towards higher total cholesterol, low density lipoprotein (LDL) and apolipoprotein B levels in conjunction with loss of protective effect of high density lipoprotein (HDL) is characteristic in menopause (Smith and Judd, 1994).

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in postmenopausal women and few other cardiovascular diseases (CVD) are also predominant such as atherosclerosis. The effect of changes in the level of hormones associated with menopause on the serum lipid profiles plays major role in most cardiac disorders associated with menopause (Do et al, 2000). Studies have shown that the chances of women developing CAD before menopause is less compared to their male counterparts. This advantage is abolished after menopause (Rich-Edward et al, 1995).

The incidence of CVD after menopause may be caused by changes in plasma levels of lipids which usually occur at this period (Jan et al, 2007). Lipid profiles consist of a group of biochemical tests often used in the prediction, diagnosis and treatment of lipid related disorders including atherosclerosis. The lipid profiles assess the lipoprotein molecules which enable the transportation of lipids such as cholesterol, phospholipids and triglycerides within the ECF including the blood stream. There are five (5) major groups of lipoproteins namely:

- Chylomicrons
- Very Low Density Lipoproteins (VLDL)
- Intermediate Density Lipoproteins (IDL)
- Low Density Lipoproteins (LDL)
- High Density Lipoproteins (HDL).

LDL is informally referred to as “bad cholesterol” because it can transport its content of many fat molecules into arterial walls, attracts macrophages and so drives the development of atherosclerosis. HDL, on the other hand, can remove fat molecules from macrophages in the arterial walls. There is variation in the particle size and density of LDL. Campose et al (1992) have shown that a pattern with more small dense LDL particles (called pattern B) is associated with higher risk for coronary heart disease (CHD) than pattern with more of the larger and less dense LDL particles (pattern A). This is because the smaller particles are more easily able to penetrate the endothelium (Campose et al, 1992). There is a correspondence between higher triglyceride levels and higher levels of pattern B LDL particles and alternatively lower triglyceride levels and higher levels of pattern A LDL (Superko et al, 2002). Cardiovascular risk becomes higher with increasing level of triglycerides (Guerin et al, 2001).

The relationship between the concentrations of lipids and their associated blood transporting lipoproteins (HDL-C, LDL-C, VLDL-C) with the occurrence of atherosclerosis and CAD has been proven (Cummings, 2003). There is a strong association between the risk of CAD, increased level of LDL-C and reduced levels of HDL-C (Igweh et al, 2005). It has been shown that at postmenopausal period, women have less cardiovascular friendly lipid profiles than in premenopausal state (Dowling, 2001). Alterations in the lipid profile characterized by change in LDL particle size and buoyancy increased the risk of CAD in postmenopausal women (Carr et al, 2000). A high level of HDL has been shown to reduce the risk of coronary heart disease (CHD) (Gordon et al, 1977). CAD was said to be due to adverse changes in plasma lipids and lipoprotein arising from reduced estrogen level (Poehlman et al, 1995). Menopause is regarded as an independent risk factor for the development of CVD in our environment due to adverse lipid changes (Igweh et al, 2005). In another study, cardiovascular effect usually attributed to menopause is likely a mere consequence of older age at menopause (Edoardo et al, 2008). Cardiovascular risk becomes higher when HDL-C is reduced while increasing the levels of TC, TG, LDL-C and VLDL-C at menopause (Srinivas, 2013; Maulik et al, 2011; Nwagha et al, 2010).

II. Materials And Methods

The data for this study was collected from the premenopausal and postmenopausal women in Abakaliki, Ebonyi State and its environs, attending the General Outpatient Clinic (GOPC) of the Federal Teaching Hospital, Abakaliki. On the average, a total of one hundred and twenty adults attend the General Outpatient Clinic of the hospital, out of which 58% are women. Two groups of women were randomly selected (a) forty (40) premenopausal and (b) sixty (60) postmenopausal women. Women on lipid lowering drugs, those on hormone replacement therapy, premature ovarian failure, long-term use of diuretics therapy, diabetics, hypertensive as well as those with evidence of thyroid diseases were excluded from the study. Also alcoholics, smokers and those with sedentary lifestyle were all excluded so as to minimize the effect of lifestyle on lipid profiles.

The study was approved by the Ethics and Research Committee of the Faculty of Medicine, Ebonyi State University, Abakaliki. Following an informed consent obtained from the participants, in English and Igbo languages, they were made to fast overnight for about 12 hours. About 5mls of venous blood were collected from each subject into plain sample containers. The samples were made to stand for minutes so as to obtain the serum. This was centrifuged, and was used for the analysis.

The total cholesterol (TC), triglycerides (TG), and High density lipoprotein (HDL) were all estimated using the enzymatic method. The serum low density lipoprotein (LDL) and very low density lipoprotein (VLDL) were calculated using the Friedwald's equation. $LDL = TC - (HDL + kTG)$ where $k = 0.46$ as the quantities were measured in mmol/L. VLDL was calculated as $TG/2.2$. The atherogenic indices were calculated as the ratio of Total cholesterol to High Density lipoprotein (TC: HDL), as well as the ratio of Low Density lipoprotein to High density lipoprotein (LDL: HDL).

Statistical analyses were carried out using one-way ANOVAs and post hoc test ascertained using Tukey's multiple comparison tests. Data were generally expressed as mean \pm SEM. Level of statistical significance were kept at $P < 0.05$ and below.

III. Results

Variations in plasma level lipid are associated with different kind of diseases notably CVD. In this study we evaluated the different lipid profile among women of pre and post menopausal age in Abakaliki metropolis. They results are explained in 3 headings namely; Changes in Total cholesterol and triglycerides predisposes CVD, alteration in HDL, LDL and VLDL level promotes CVD occurrence, and Anthrogenic index affect development of CVD.

Changes in total cholesterol and triglycerides predisposes CVD

It has been noted that the effect of changes in the level of hormones associated with menopause on the serum lipid profiles plays major role in most cardiac disorders associated with menopause (Do et al, 2000). Also to note is that the

chances of women developing CVD before menopause is less compared to their male counterparts, which is abolished after menopause (Rich-Edward et al, 1995). Our study showed a statistically significant increase in serum Total Cholesterol (TC) and Triglyceride (TG), among post-menopause when compared with pre-menopause women ($P < 0.001$) in all. The values are presented in figure 1 below.

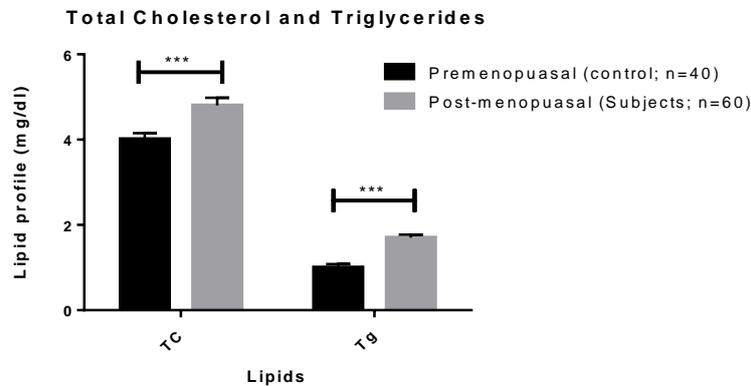


Figure 1 Bar chart showing variation of Total Cholesterol and Triglyceride among post and pre menopausal women

Such significant rise may be connected with changes in hormone as well predisposes the post-menopausal women to the risk of CVD development as suggested by Nwagha et al, 2010; Maulik et al, 2011; and Srinivas, 2013; in their studies.

Alteration in HDL, LDL and VLDL level promotes CVD occurrence

Jan et.al, (2007) postulated that the incidence of CVD after menopause may be caused by changes in plasma levels of lipids which usually occur at this period (Jan et al, 2007). In this study we, found that at postmenopausal stage, there is a statistically significant rise in serum level LDL ($P < 0.001$) than pre-menopausal age. This result was in agreement with various finding that there is increase in LDL which accelerates CVD development (Igweh et.al, 2005 and Dowling, 2001). Our result also showed a significant reduction in HDL among postmenopausal women than pre-menopausal ($P < 0.001$). HDL is well known to be protective, so its serum level reduction predisposes individual to increase incidence of CVD. Lastly, we reported a slight increase in VLDL among postmenopausal women than pre-menopausal although not statistically significant as shown in figure 2 below.

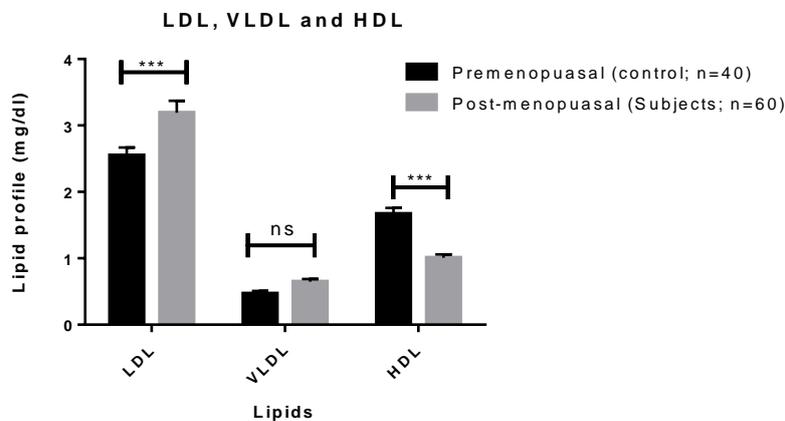


Figure 2 Bar chart showing variation of LDL, VLDL and HDL among post and pre menopausal women

Igweh et.al. (2005) postulated that there is a strong association between the risk of CAD, increased level of LDL-C and reduced levels of HDL-C (Igweh et al, 2005). It has also been shown that at postmenopausal period, women have less cardiovascular friendly lipid profiles than in premenopausal state (Dowling, 2001). The later is in agreement with our findings, these alterations in serum level LDL and HDL may predispose the post-menopausal women to high risk of CVD development especially atherosclerosis.

Atherogenic index affect development of CVD

The atherogenic indices calculated as the ratio of Total cholesterol to High Density lipoprotein (TC: HDL), as well as the ratio of Low Density lipoprotein to High density lipoprotein (LDL: HDL) gives indication to risk of CVD development. The lower the ratio the higher protective effect of the lipid profile and the reverse is the case. Our result showed that at postmenopausal age, these indices rises dramatically (Figure 3).

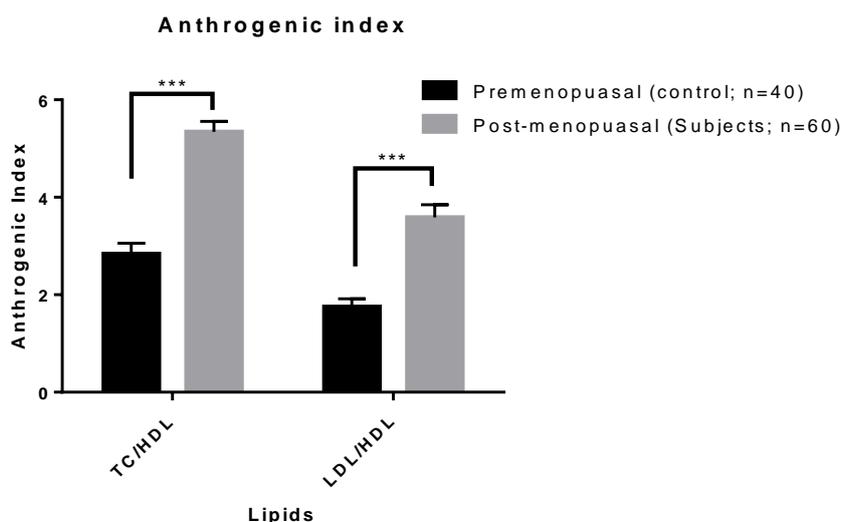


Figure 3 Bar chart showing variations in atherogenic indices among post and pre menopausal women

These may have a consequence of increase risk of CVD development. These dramatic increases in atherogenic indices were statistically significant among postmenopausal women when compared to pre-menopausal women.

IV. Discussion

In the postmenopausal period, there are reduced levels of estrogen which lead to derangement of lipid and lipoprotein profiles (Bales, 2000). Estrogens have various cardio-protective mechanisms. However, these mechanisms are lost with the onset of menopause (Igweh et al, 2005). The relationship between the concentrations of lipids and their associated blood transporting lipoproteins with the development of cardiovascular disease has been proven (Cummings, 2003).

Our study indicated variations in TC, TG, LDL-C, VLDL-C and the atherogenic indices (TC: HDL-C; LDL-C: HDL-C) among postmenopausal women when compared to the premenopausal group. HDL-C was observed to be significantly lower in postmenopausal women when compared to the premenopausal group. A lower atherogenic index in premenopausal women indicates a greater proportion of HDL-C which satisfies the criteria for reduced risk of coronary heart disease (Grady et al, 1992). Postmenopausal women in our study had higher TC, TG, LDL-C, VLDL-C, atherogenic indices and a lower HDL-C. This finding may predisposes them to high risk of incidence of CVD. This agrees with the findings of Bade et al, (2014), Woodard et al, (2010) and Srinivas, (2013). Similar observations were made by Nwagha et al, (2010) who demonstrated a statistically significant increase in TC, TG, LDL-C, VLDL-C, atherogenic index and significant decrease in HDL-C in postmenopausal women. The findings in this study contradict the findings of Igweh et al, (2005) who demonstrated no significant difference in TC, TG and VLDL-C between pre- and postmenopausal women. The findings of Osakue, (2013) who demonstrated higher levels of HDL-C and TC only among postmenopausal women also contradict these findings. Numerous studies have demonstrated that high levels of HDL-C are associated with lower risk of CHD. Conversely, low levels of HDL-C are associated with a higher incidence of CHD as indicated by our findings. The lower levels of LDL-C seen among premenopausal women in this study could be attributed to the rise in HDL-C level which scavenges cholesterol esters thereby reducing its availability for the formation of LDL-C. There is a strong association between the risk of CAD, increased levels of LDL-C and reduced levels of HDL-C (Igweh et al, 2005). Higher atherogenic indices in postmenopausal period indicate smaller proportion of HDL-C. This is a measure of CAD risk. Cardiovascular risk becomes higher with increasing levels of TG (Guerin et al, 2001).

V. Conclusion

In this study, we have shown that hormonal changes associated with menopause alter the lipid profiles in women. This is evidenced by increased TC, TG, LDL-C, VLDL-C, atherogenic indices and reduced levels of HDL-C seen among postmenopausal women. The higher levels of LDL-C, atherogenic indices and the lower HDL-C levels in postmenopausal women is a risk factor for coronary artery disease.

References

- [1]. Do KA, Green JR, Guthrie EC, Dudley HG, Burger and L Dennerstein, (2000). Longitudinal study of risk factors for coronary heart disease across the menopausal transition. *American Journal of epidemiology*, 151:584-593.
- [2]. Igweh JC, IU Nwagha, JM Okoro, (2005). The effects of menopause on the serum lipid profile of normal females of South East Nigeria. *Nigerian Journal of Physiologic Science* 20(1-2): 48 - 53.
- [3]. Jan L, Shifren Isaac Schiff, (2007). Section VII- Reproductive Endocrinology 32-
- [4]. Menopause. Editors: Berek, Jonathan S. Berek and Novak's Gynecology, 14th Edition, Lippincott Williams and Wilkins
- [5]. Butler L., and Santoro N, (2011). The Reproductive Endocrinology of the Postmenopausal Transition. *Obstetrics and Gynecology Clinics of North America* 76(7): 627-635.
- [6]. Samantha MP, (2008). *Obstetrics and Gynecology*. National Medical Series for Independent Study, 6th edition. Lippincott Wilkins, pp: 335-336.
- [7]. Ponjola, C. (2014). *Menopause: Drugs, Diseases and Procedure*. Medscape References. Retrieved October 6, 2014.

- [8]. Henshaw, SK. (1998). Unintended pregnancies in the United States, *Family Planning Perspective*, 30(1): 24–9, 46.
- [9]. Lenton, EA., Krester, DM., Woodward, AJ., Robertson, DM., (1991). Inhibin concentrations throughout the menstrual cycles of normal, infertile and older women compared with these during spontaneous cycles. *Journal of Clinical Endocrinology and Metabolism*, 73(6): 1180–1190.
- [10]. Santoro N., and Randolph JF Jr, (2011). Reproductive hormones and the menopause transition. *Obstetrics and gynecology Clinics of North America*, 38(3): 455–466.
- [11]. Smith, KE., and Judd, HL. (1994). Menopause and postmenopause. In: De Cherney AH, Pernal ML, eds. *Current obstetric and gynecologic diagnosis and treatment*. 8th. ed. Appleton and Lane: 1994: 1030–1050.
- [12]. Rich-Edward, JW., Manson, JE., & Hennekens, CH. (1995). The primary prevention of coronary heart disease in women. *New England Journal of medicine*. 332(20), 1758–1766.
- [13]. Campose H, Khoo C, Sacks FM, (2005). Diurnal and Acute Pattern of Postprandial
- [14]. Apolipoprotein B-48 in VLDL, LDL and IDL from Normolipidemic Human.
- [15]. *Atherosclerosis*, 181: 345-351.
- [16]. Superko, HR., Nejedly, M., & Garrett B, (2002). “Small LDL and its clinical importance as a new CAD risk factor: a female case study”. *Progress in cardiovascular nursing* 17(4): 167–173.
- [17]. Guerin, M., Legoff, W., Vantol, A., Steiner, G., & Chapman, MJ. (2001). Proatherogenic roles of elevated CE transfer from HDL to VLDL and dense LDL in type 2 diabetes. *Arteriosclerosis, Thrombosis and vascular Research*, 21: 282–287.
- [18]. Cummings KC, (2003). Lipid and cardiac risk profiles. *Clinical Chemistry*, 47: 407-409.
- [19]. Dowling EA, (2001). How exercise affects lipid profiles in women. *The Physician and Sports Medicine*, 29(9): 45-47.
- [20]. Carr MC, KH Kim, Zambon, ES Mitchel, NF Woods, CP Cassazza, JO Purnell, JE
- [21]. Hokanson, JD Brunell and RS Schwantz, (2000). LDL Density across the Menopausal
- [22]. Transition. *Journal of Investigational Medicine*, 48: 245-258.
- [23]. Gordon, T., Castelli, WP., Hjortland, MC., & Kannel, WF. (1977). HDL as a protective factor against CHD. *The Framingham study; American Journal of Medicine*, 62:701–714.
- [24]. Poehlman, ET., Toth, MJ., & Gardner, AW. (1995). Changes in energy balance and body composition at menopause: a controlled longitudinal study. *Annals of Internal Medicine Journal*, 123:673–675.
- [25]. Edoardo C, Valerie T, Sandro C, Anna B, Laura S, Federicia G, Mario S, Martins G, Bortolo M, Alberto M, Daniel D and Achille CP, (2008). Menopause does not affect blood pressure and risk profile, and menopausal women do not become similar to men. *Journal of Hypertension*, 26: 1983-1992.
- [26]. Srinivas, RK., & Srinivas, RC. (2013). A comparative study of lipid profile and oestradiol in pre and post menopausal women; *Journal of clinical and diagnostic research* 7(8): 1596–1598.
- [27]. Maulik, SV., Annp, MV., Hitesh, AJ., Chirag, VS., & Varsh, SJ. (2011). A comparative study of serum lipid profile between pre- menopausal and postmenopausal women, *National Journal of Integrated Research in Medicine*, 3(1): 43-45.
- [28]. Nwagha, UL, Ikekpeazu, EJ., Ejezie, FE., Neboh, E E., & Maduka, IC. (2010). Atherogenic index of plasma in postmenopausal women in Enugu, Nigeria. *Africa Health Science Volume*. 10(3): 248–252.
- [29]. Bales, AC. (2000). In search of lipid balance in older women; *New studies raise questions about what works best. Postgraduate medicine*. 108 (7): 57-72.
- [30]. Grady, D., Robin, SM., Petitti, DB., Fox, CS., Black D., Ettinger, B., Ernster, VL., & Cummings, SR. (1992). Hormone therapy to prevent disease and prolong life in postmenopausal women. *Annals and Journal of Epidemiology*, 142:841-875.
- [31]. Bade G, Sheh S, Nahar P, Vaidya S. (2004). Effects of Menopause on Lipid Profile in Relation to Body Mass Index. *Chronicles of Young Scientists*. 5: 20-24.
- [32]. Woodard, GA., Brooks, MM., Barinas – Mitchell, E., Mackey, RH., Mathews, KA., & Sutton–Tyrrell, K. (2010). Lipid, menopause and early atherosclerosis in study of women Health across the Nation; *North American Menopause Society*, 18(4):376:384.
- [33]. Osakue, DI. (2013). Serum lipid profile of postmenopausal women in Sapele, Delta State, Nigeria. *Journal of Medical Research*, Volume.1(1), pp 9–13.