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Research Paper

Menopause and serum Lipid Profile a Review

Anyigor-Ogah CS*, Onwe PE., Obimma J., Ottah-Umahi G and Okorocha AE

Department of Medical Physiology, Faculty of Medicine, Ebonyi State University, Abakaliki, Nigeria

ABSTRACT:- Menopause is a normal physiologic process that marks the end of a woman`s reproductive life. It is the cessation of the menstrual period resulting from the eventual atresia of almost all oocytes in the ovaries. There is the cessation of cyclic ovarian functions as manifested by cyclic menstruation. It is heralded by the "climacteric" - a period in the menopausal transition when endocrine, biological and clinical manifestations of menopause begin (Burger et al, 2002). These manifestations could be sensation of heat, flushed skin and excessive sweating in what is commonly referred to as "hot flush". Changes in mood (anxiety, anger) commonly seen in menopause can lead to an elevation in blood pressure and subsequently stroke and other cardiovascular diseases (CVD). On the average, menopause occurs at the age of 51 years but less than 1% of women experience it before the age of 40 years while some other women undergo premature menopause at an early age which affect their ability to procreate (Derek, 1990). The effect of changes in the levels of hormones associated with menopause on the serum lipid profiles plays major role in most cardiac related disorders associated with menopause (Do et al, 2000). The rate of coronary heart disease (CHD) accelerates more in women than in men after the age of 45 years (Lerner et al, 1980). The incidence of CVD after menopause may be due to changes in plasma levels of lipids that usually occur following menopausal transition (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. Here we reviewed the changes in lipid profile in relation to menopause and possible control.

Keywords:- Menopause, hot flushes, atresia, lipoproteins and lipid profile.

I. INTRODUCTION

Numerous studies have shown the association between postmenopausal status and elevated levels of total cholesterol and low density lipoprotein cholesterol (Jensen et al, 1990;

Akahoshi et al, 1996). On the other hand, evidence regarding the relationship between menopause and HDL-C or TG is inconsistent (Do et al, 2000). Since both menopause and lipid profile are highly correlated with age, it remains unclear whether lipid changes at menopause are independent of age effects (Do et al, 2000). Obesity has been associated with adverse lipid profiles according to Expert Panel on Detection, Evaluation and treatment of High Blood Cholesterol in adults in 2002 (NCEP, 2002). However, Berg et al, (2004) studied lipid and lipoprotein profile in menopausal transition in relation to hormone and age and concluded that the behaviour of lipoprotein during the menopausal transition and their relationship with sex hormone and body fat distribution is still unclear. Body Mass Index (BMI) has been related to endogenous estradiol and follicle stimulating hormone (FSH) levels during menopause (Randolph et al, 2004).

Besides being a natural process, menopause could also be induced by surgical removal of the ovaries (oophrectomy), chemotherapy or high dose radiotherapy related to cancer treatment or premature ovarian failure (Barrett and Bush, 2001). Whether it occurs spontaneously or induced, the cardiovascular risk remains high. Kenemans et al, (1996) in their work on practical hormone replacement therapy, reported that women in the above group are also at risk of CVD. Sacks et al, (1992) studied hormone therapy to prevent disease and prolonged life in post menopausal women and reported that hormonal changes associated with menopause such as low plasma estrogen and high levels of Luteinizing and follicle stimulating hormones exert a significant effect on the metabolism of plasma lipids and lipoprotein. The work by Usoro et al, (2006) on the lipid profile of post menopausal women in Calabar, Nigeria, total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and atherogenic index (TC: HDL-C ratio) were significantly higher and high density lipoprotein

cholesterol (HDL-C) lower in post menopausal women and women greater than 45 years of age in comparison with premenopausal women and women between the age ranges of 25-45 years. Atherogenic alterations in lipid and lipoprotein profiles have also been found in studies of surgically induced menopause, (Lip et al 1997; Griffen et al, 1993; Wakatsuki and Sagara, 1995). Carr et al, (2000) studied the changes in LDL density across the menopausal transition and reported that alterations in the lipid profile characterized by change in LDL particle size and buoyancy increased the risk of CAD in postmenopausal women. At menopause, there is a detrimental change in lipid profile which includes an increase in LDL (Stevenson et al, 1993). A high level of HDL has been shown to decrease the risk of coronary heart disease (CHD) (Gordon et al, 1977). On the other hand, a 1% increase in LDL increases the risk of CHD by up to 2% within 6 years and a 1% decline in HDL increases the risk of CHD by up to 34% (Wallace et al, 1979; Bradley et al, 1978).

In a controlled longitudinal study by Poehlman et al, (1995) on changes in energy balance and body composition at menopause, the incidence of coronary artery disease was attributed in parts to adverse changes in plasma lipids and lipoprotein due to reduced level of estrogen. Deposition of fatty plaques on arterial walls (atherosclerosis) is a predisposing factor to CHD (Kannel,1987).Variations in the distribution of serum lipids and lipoproteins have been implicated in the aetiology of atherosclerosis and CVD. The effects of hormonal changes associated with menopause on the serum lipid levels play important role in most cardiovascular disorders associated with menopause (Do et al, 2000). Modification in the plasma concentration of lipoprotein will also modify the cardiovascular risks (Nabulsi et al, 1993). In the study done by Osakue (2013), on the serum lipid profile of postmenopausal women in Sapele, Delta State, Nigeria, ethnic and geographical variations were said to be factors affecting the lipid profiles in postmenopausal women. He obtained high levels of HDL and TC which were different from the results obtained in the Calabar study. Igweh et al, (2005), studied the effects of menopause on the serum lipid profile of normal females of South East Nigeria and reported that there was no significant difference in the total serum cholesterol and TGs between the cases and controls. However, there was a significant reduction of HDL and VLDL in the postmenopausal group as well as a marked increase in LDL in the same group. They concluded that menopause is an independent risk factor for the development of cardiovascular disease in our environment.

Edoardo et al, (2008), in a population based study of Italian women, evaluated the differences between fertile and naturally menopausal women in terms of BP, target organ damage, cardiovascular reactivity, blood lipids and glucose tolerance. They concluded that cardiovascular effects usually attributed to menopause seem to be a mere consequence of the older age of menopausal women. Srinivas, (2013), made a comparative study of lipid profile and estradiol in pre and postmenopausal women in India and reported that menopause leads to alteration in lipid profile by reducing HDL while increasing the levels of TC, TG, LDL-C and VLDL-C, hence increasing the risk of CVD. A similar study was also done by Maulik et al, (2011) in Jamnager and reported that the mean level of serum TC and LDL were significantly higher in postmenopausal women and levels significantly increased with increase in the duration of menopause. In contrast, level of serum HDL was significantly lower in postmenopausal women and level significantly decreased with increase in the duration of menopause. They also concluded that menopause is associated with altered serum lipid profile and so becomes independent risk factor for developing CVD which is in keeping with the study done by Igweh et al, (2005) in South East Nigeria.

Nwagha et al, (2010) studied the atherogenic index of plasma as a useful predictor of cardiovascular risk among postmenopausal women in Enugu, Nigeria. They concluded that menopause alters lipid profile following a statistically significant increase in TC, TG, LDLC, VLDL-C with significant decrease in HDL-C in postmenopausal women compared to premenopausal group. In the work done by Carol et al, (2009) on the lipid changes during the menopausal transition in relation to age and weight, menopausal related changes in lipid profile were said to be similar in magnitude to changes attributed to ageing. In their study, TC, LDL-C, TG and lipoprotein (a) peaked during late peri and early post menopause while changes in the early stages of menopause were all normal. Similarly, HDL-C also peaked in late peri and early post-menopause.

Menopause and Variations of Serum Lipid Profile

Current recommendations for cholesterol testing came from the Adult Treatment Panel (ATP)
III guideline. They are based on large clinical studies such as the Framingham Heart Study. For healthy adults without a cardiovascular risk factor, the ATP III guidelines recommended screening once every five years (NCEP, 2002). A lipid profile may also be ordered at regular intervals to evaluate the success of treatment with lipid lowering drugs.

Serum lipid profile is measured for cardiovascular risk prediction. It has now become almost a routine test. The test involves 4 basic parameters; total cholesterol, HDL cholesterol, LDL cholesterol and Triglycerides. It is usually done in fasting blood sample. The subject is made to undergo 12-14 hours overnight complete restriction of diet with exception of water and medication. This may hold true when the postprandial triglycerides remain elevated for several hours (Campose et al, 2005) and most reference values for serum lipids are established on fasting blood samples. Do et al, (2000) in the European guidelines on CVD and prevention in clinical practice also recommended fasting blood specimen for lipid profile in assessing cardiovascular risk.

These guidelines, however, allow total cholesterol and HDL cholesterol in the non-fasting blood specimen as there is not much difference in these lipids in fasting and non-fasting specimens. Furthermore, non-HDL-C (TC-HDL-C) which is a secondary target of therapy in adult treatment panel III may as well be used in the non-fasting state according to the third report on National Cholesterol Education Programme (NCEP) of India in 2002. Fasting state is basically essential for triglyceride estimation because it remains high for several hours after meal. If non-fasting triglyceride value is applied, LDL-Cholesterol, the main target of lipid lowering therapy, will be underestimated. These problems can be overcome by using direct LDL-C estimation in non- fasting specimen. However, the method for direct measurement sometimes also gives underestimated level of LDL-C (Saliu et al, 2005; Mora et al, 2009). Also, lack of association of non-fasting direct LDL-C with CVD in women raises querries regarding the clinical use of a direct assay for LDL cholesterol in non-fasting samples (Mora et al, 2009). Direct assays are costly and hence, add to health care cost.

In the past few years, there have been attempts aimed at simplifying blood sampling by replacing fasting lipid profile with non-fasting lipid profile since it has been found that lipids, lipoproteins and apolipoproteins were not much different in both fasting and non-fasting states. An exception to this is triglycerides which were higher in non-fasting state and all these were associated with cardiovascular risk prediction (Nordestgaard et al, 2009). However, a fasting sample is ideal if CVD role assessment is based on TC, LDL-C or non-HDL cholesterol but HDL-C, TG, TC/HDL-C ratio and apoliprotein A-1 predict CVD when measured in the non-fasting state (Mora et al, 2008). Non-fasting triglyceride levels may be even better predictor of cardiovascular risk as compared to fasting triglycerides (Bansal et al, 2007; Benne et al, 2007).

The terms "non-fasting and postprandial samples" slightly differ. In non-fasting sample, blood is collected at any time without knowledge of the time of the previous meal unlike the postprandial sample which is collected at a fixed time following a standard meal. There is usually a stepwise increase in triglycerides after fat diet, hence non-fasting triglycerides would vary depending on the time after meal with the highest levels 4-5 hours postprandial (Benne et al, 2007). The cut off levels of non-fasting triglycerides for cardiovascular risk have not yet been defined (Nigam, 2004). With regards to triglycerides, postprandial lipemia can be affected by the following factors; ethnicity, alcoholism and menopausal status, hence these factors should be evaluated in clinical practice (Ridker, 2008).

Recall of basic estimation of lipid profiles

1 Total Cholesterol Estimation:

This is done using modified Fredrickson et al, (1967) and Allain et al, (1974) methods.

The principle: Cholesterol esterase catalyses the hydrolysis of cholesterol esters into free cholesterol and fatty acids. The resulting free cholesterol in oxidized to 4-cholesten-3-one and hydrogen peroxide in the presence of an enzyme -cholesterol oxidase. Phenol and 4 -aminoantipyrine were combined with hydrogen peroxide in the presence of peroxidase to form a red quinoneimine.

Cholesterol ester + H_2O Cholesterol + FA
esterase

Cholesterol ester + O_2 Cholesterol $-3-$ one + H_2O_2
cholesterol oxidase

$2H_2O_2$ + Phenol + $4-$ amino antipyrine quinoneimine + $4H_2O$ peroxidase

HDL - Cholesterol Estimation

This is estimated using the selective precipitation and ultracentrifugation method.

Principle: This is based on the determination of HDL in supernatant after all other lipoproteins are precipitated by a mixture of phosphotungstic acid and magnesium chloride and then centrifuged at very high revolution per minute.

LDL-cholesterol and vldl-cholesterol estimation:

Chemical measures of lipid concentration have since been the most used measurement, not because they have the best correlation but because these methods are cheap and more readily available.

The lipid profile does not measure LDL particles directly but instead, the calculation method of Friedwald et al, (1972) was used. It is calculated by subtracting the amount of cholesterol associated with other particles such as HDL and VLDL, assuming a prolonged fast.

(a) [illegible] = [illegible] - [illegible] + [illegible]
(b) [illegible] = [illegible]/5
K is 0.20 if the quantities are measured in mg/dl and 0.46 if in mmol/L. This has few limitations:
(a) Samples must be obtained after a 12-14 hours fast.
(b) LDL-C cannot be calculated if plasma triglyceride is greater than 4.52mmol/L (400mg/dl).
(c) Even at triglyceride levels 2.5-4.5mmol/L, this formula is considered inaccurate (Sniderman et al, 2003).

4 Triglyceride Estimation

Principle: This is based on the hydrolysis of triglycerides by lipase. The concentration of the glycerol released is a function of the enzymatic assay coupled with other reaction that terminates in the formation of a quinoemine dye. The amount of dye formed is directly proportional to the concentration of triglycerides in the sample.

Triglycerides + H_2 O Glycerol + FA
Lipase

Glycerol + ATP Glycerol − 3 − phosphate + ADP
glycerol kinase

Glycerol − 3 − phosphate + O_2 Dihydroacetone + Phosphate + glycerol phosphatase
H_2 O_2

Having discussed the various methods of assay of the lipids, it is important to state further that there are pre-analytical factors other than the fasting/non-fasting state which may affect lipid components/profiles.

A study has shown that a change from upright to a supine position resulting from dilutional effects can reduce the cholesterol levels by 10% and triglycerides by 12% (Norayana, 1996). Also prolonged application of torniquet for about 2-5 minutes can raise the cholesterol up to 15% (Young et al, 1979; Cooper et al, 1992). Reports also confirm that cholesterol level is slightly higher in winter than in summer and the reverse is the case for triglyceride (Cooper et al, 1992; Narayanan, 1993). Some disease conditions such as nephrotic syndrome increase TC, LDL-C and VLDL-C while Hypothyroidism increases LDL-C and TC (Joven et al, 1990). Infections and inflammations may reduce the level of TC and HDL-C but enhances triglycerides (Alvarez and Ramos, 1986). Nawaz et al, (2006) showed that all individual values of lipid profile in patients admitted with acute illness vary significantly during and after hospital stay, while the ratio of total cholesterol to HDL remains relatively stable. It is therefore necessary that all these factors should be kept in mind while interpreting the lipid profile results.

Management of Menopause Associated Disorders

Hormonal Replacement Therapy (HRT)

Hormone replacement therapy is the use of estrogen analogues in the management of some estrogen-related menopausal symptoms.

Routes of Administration

Hormone therapy can be administered either systematically via the oral, transdermal, topical routes, or

locally via the vaginal route in a cream, ring or tablet. Topical preparations are used only to treat vaginal system (Ponjola, 2014).

Benefits and Indications

The main reasons for treating symptoms of the menopausal transition (MT) and actual menopause are as follows:

- To provide relief of vasomotor symptoms
- To reduce the risk of unwanted pregnancy
- To avoid the irregularity of menstrual cycles
- To preserve bone
- To lower the risk of cardiovascular disease
- To improve quality of life

Factors to be considered in the Choice of Therapy

The time at which therapy should begin depends on the woman`s present complaint and medical history. A high evaluation of risk factors is also done. Whether a woman is in the MT or in the actual menopause affect the final suitable therapy. The factors that affect the final decision must be carefully weighed and include:

- Woman`s age and hysterectomy status
- Personal history
- Family history
- Smoking
- Peer and commercial influence
- Culture
- Need for Contraception
- Ethnicity
- Economic status

In May 2013, the British Menopause Society and Women's Health Concern issued updated guidelines on the use, benefits, and risks of HRT. Key recommendations include individualization of HRT, annual risk/benefit assessment, use of HRT in women with premature ovarian insufficiency, an exploration of pharmacologic alternatives to HRT, and a discussion of the benefits of phytoestrogens. In January 2014, the American College of Obstetricians and Gynecologists released an updated Practice Bulletin on the treatment of vasomotor symptoms of menopause and vaginal atrophy. They recommended the following:

- Systemic HRT with estrogen or estrogen plus progestin is the most effective treatment of VMS.
- Low-dose estrogen and ultra-low systemic doses of estrogen have a better adverse effect profile than standard doses.
- Alternatives to HRT for VMS include selective serotonin reuptake inhibitors, selective serotonin and norepinephrine reuptake inhibitors, clonidine, and gabapentin.
- Use of progestin alone, testosterone, phytoestrogens, supplements, lifestyle

Modifications are not supported by data.

Adverse Effects of HRT

- Bloating
- Mastodynia
- Vaginal Bleeding
- Headaches
- Thomboembolism

Contraindications to HRT

The absolute contraindications include

- Undiagnosed abnormal genital bleeding
- Known or suspected breast cancer or estrogen dependent neoplasia Venous thromboembolism
- Pregnancy
- History of stroke or myocardial infarction in the previous year Active and severe liver diseases
- Known hypersensitivity to therapy

Commonly Used Schedules of HRT

(a) Estrogen is usually given in a daily or continuous fashion. Progestogen is added to

estrogen therapy to prevent endometrial hyperplasia and carcinoma in women who have their uterus.
(b) Cyclic therapy. Continuous estrogen therapy is given and progestogen added for 12-14 days each month. This results in a predictable withdrawal bleeding following monthly cessation of progestrogen in 80% of women.
The combination product of bazedoxifen, a selective estrogen receptor modulator (SERM) and a conjugated estrogen was approved by the FDA in October 2013 and this reduces the risk of uterine hyperplasia caused by estrogens as well as preventing osteoporosis and treating vasomotor symptom.

Non-hormonal Therapy

In women who cannot be treated with estrogen or hormone therapy (because of some risk factors) or choose not to do so but suffer hot flushes, the selective serotonin re-uptake inhibitors (SSRIs) and serotonin - nor epinephrine reuptake inhibitors eg. Venlafaxin has been used to alleviate VMS. A study by Freeman et al, (2011) found that the use of SSRI in a dosage of 10 - 20mg/day can reduce and alleviate more severe hot flushes. In June 2013, the FDA approved paroxetine mesylate as the first non-hormonal therapy for VMS (hot flushes) associated with menopause. However, paroxetin increases the risk of bleeding and increased risk of serotonin syndrome (Lowed, 2013).

Alternative Medicine Phytoestrogens

Some plant sources known as phytoestrogens, do not simply mimic the effects of human steroidal estrogen but exhibit both similar and divergent action. They act like selective estrogen receptor modulators. The effects vary according to the phytoestrogen studied, cell line, tissue, species and response being evaluated (Thacker, 2011). Fermarelle is a mixture of DT56a soy derivative and ground flaxseed for oral use. It is being promoted for the treatment of menopause and prevention of bone loss and has been described as having SERM qualities, thereby reducing the safety risk involved in estrogenic-like treatments (Sonjen et al, 2007).

Soya Isoflavones

Soya isoflavones are said to be beneficial to some symptoms of menopause. They are naturally occurring compounds, and diadzein and genistein are the main isoflavones found in soy (Murphy et al, 1982).
Consumption of soy containing diadzein produce S-eqnol(7- hydroxy-3-(49- hydroxyphenyl) -chroman) which reduces some menopausal symptoms, bone loss and crow's feet skin wrinkles in menopausal women (Setchel and Clerici, 2010; Jou et al, 2008).

Management of Menopause Related Lipid Disorders

The United State Department of Health and Human Service under their National Institute of Health in 2005 defined some markers indicating a need for LDL-C reduction as shown:
Patient`s cardiac risk

High i.e. 7, 20% risk of heart attack within 10 years or an extreme risk factors Moderately high i.e. 10 - 20% risk of heart attack within 10 years +> 2 heart attack risk factors Moderate i.e. 10% risk of heart attack within 10 years and > 2 heart attack risk factors Low i.e. < 10% risk of heart attack within 10 years and 1 or no heart attack risk factors.

LDL-C reduction considered if count in mg/dl exceed	LDL-C reduction indicated if count inmg/dl exceed
70	100
100	130
130	160
160	190

1. Pharmacologic Management: Statins
- This reduces high levels of LDL Particles.
- It inhibits 3-hydroxyl-3-methylglutarylCoA reductase in the cells, the rate limiting step in cholesterol synthesis.
- There is increase synthesis of hepatic LDL receptors.
- This leads to increased clearance of LDL particles from the blood.

Ezetimibe:
- Reduces intestinal absorption of cholesterol,
- In combination with statins, can reduce LDL particle concentration (Brunzell et al, 2008).

Niacin (Vit B3):
- This lowers LDL by selectively inhibiting hepatic diacylglycerol acyltransferase 2,thus reducing triglyceride synthesis and VLDL secretion through a receptor HM74 (Meyers et al, 2004) and HM74A or GRP109A (Soudijn et al, 2007).

Clofibrates:
This is effective at reducing cholesterol levels. It has been associated with increased incidence of cancer and stroke mortality, despite lowering cholesterol levels (WHO trial on primary prevention of IHD with clofibrates, 1984). More recently developed and tested fibrates such as fenofibric acid has had a better record and are promoted for lowering VLDL particles.

Tocotrienols:
Some of these agents especially delta and gamma-tocotrienols are being promoted as statin alternative non-prescription agents to treat high cholesterol, having been shown in vitro to that effect. Gamma- tocotrienol appears to be another HMG-CoA reductase inhibitor, and can reduce the synthesis of cholesterol (Song and DeBoseBoyd, 2006).

Phytosterols:
These are widely recognized as having a proven LDL cholesterol lowering effect (European Food Safety Authority, 2010). Current supplemental guidelines recommended doses of phytosterols in the 1.6-3g/day range (Health Canada, EFSA, ATP III, FDA) with a recent meta-analysis demonstrating an 8.8% reduction in LDLC at a mean dose of 2.15g/day (Demanty et al, 2009).
However, plant sterols and stanols when absorbed markedly accelerates progression of atherosclerosis more than cholesterol delivered into the arterial walls by lipoprotein particles

Insulin:
This induces HMG-CoA reductase activity whereas glucagon reduces HMG-CoA reductase activity. In non-diabetics, glucagon levels are very low when insulin levels are high; however, those who have become diabetic no longer suppress glucagon output after feeding (Dinneen et al, 1995).

II. DIETARY MEASURES

The most effective approach has been minimizing fat stores located inside the abdominal cavity (Visceral body fat) in addition to minimizing total body fat. Visceral fat, which is more metabolically active than subcutaneous fat has been found to produce many enzymatic signals (Cameron and Zimmet, 2008).
An example in resistin which increases insulin resistance and circulating VLDL particle concentration, thus both increasing LDL particle concentrations and accelerating the development of Diabetes Mellitus.

III. ANTI-OXIDANTS

Ingesting anti-oxidants and reducing free radical exposure may reduce LDL`s contribution to atherosclerosis, though results are inconclusive (Stocker and Keaney, 2004). Studies have reported the benefits of green tea in reducing LDL; some studies have focused on the antioxidant qualities of the unfermented green tea compounds Known as Catechins which are thought to reduce cholesterol absorption in the gut (Norton, 2011).

IV. EXERCISE

Exercise may help reduce hot flushes. A healthy diet and regular, consistent exercise can also reduce weight gain associated with menopause. Weight-bearing exercise can protect against bone loss. Women should pursue a lifestyle that involves a balanced aerobic and weight resistance exercise programme appropriate to their age and medical conditions. Brisk walking, stair climbing, hiking, dancing, weight lifting, etc are all helpful. At least 30 minutes of exercise each day is ideal. For the purpose of reduction of weight, 60-90 minutes of exercise is preferred (Daley et al, 2011; Huang et al, 2010).

V. CONCLUSION

The old adage, "man cannot cheat nature" stands in all ramifications. Yet menopause and its associated ailment can still be reduced by tackling changes in lipid profile using allopathic medicine, herbal supplements and even physical exercises. Increased or elevated concentrations of cholesterol, LDL and reduced concentration of HDL pose a big threat to the health of the aging women. Hence there may be pronounce weight gain in most post-menopause women and control of lipid metabolism goes a long way to redress this situation.

A good knowledge of the signs and symptoms of menopause in relation to adverse changes in lipid profile may be an added advantage to its management.

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