بسم الله الرحمن الرحيم

Sudan University of Science and Technology

College of Graduate Studies

Assessment of Plasma Levels of Cholesterol, Triglycerides, LDL-C and HDL-C among Sudanese Menopausal Females in Khartoum State

تقييم مستوى الكوليسترول والدهون الثلاثيه والبروتين الدهني عالي الكثافة والبروتين الدهني منخفض الكثافة في البلازما لدى النساء السودانيات بعد انقطاع الطمث في ولاية الخرطوم

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By

Mawada Abbas Mohammed Abbas (B.Sc.)

B.Sc.in Medical Laboratory Sciences - Clinical Chemistry

(**Shendi University -2012**)

Supervisor:

Dr. Mariam Abbas Ibrahim

Sudan University of Science and Technology

College of Medical Laboratory Science

Clinical Chemistry Department

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بسم الله الرحمن الرحيم

{فَقُلْتُ اسْتَغْفِرُوا رَبَّكُمْ إِنَّهُ كَانَ غَفَّارًا * يُرْسِلِ السَّمَاءَ عَلَيْكُمْ مِدْرَارًا * وَيُمْدِدْكُمْ بِأَمْوَالٍ وَبَنِينَ وَيَجْعَلْ لَكُمْ جَنَّاتٍ وَيَجْعَلْ لَكُمْ أَنْهَارًا}

صدق الله العظيم

سورة نوح: 10-12

Dedication

To my mother who installed in me the good moral.

To the one who told me how to live and how to success and make me believe that if I want to gain to gain the impossible I will get it.

To

Ali Osman

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Abstract

After menopause, there is loss of ovarian function. This results in adverse changes in glucose and insulin metabolism, body fat distribution, coagulation, fibrinolysis and vascular endothelial dysfunction. This study was carried out to assess plasma; levels of cholesterol, triglycerides, LDL-C and HDL-C among Sudanese menopausal females in Khartoum state. A total of 94 participants were included in this study Forty seven were menopause women age range from 48-70 years as case group and forty seven of them were from pre menopause woman age range from 25-47 years as control group from Khartoum state during the period from April to August 2018. The estimation of serum lipid profile was done by using bio systems BTS-305 then results were analyzed by using SPSS computer program.

Statistical analysis showed a significant increase in plasma cholesterol level in menopause (mean±SD: 245.1±32.0 mg/dl) when compared to control (175.9±40.5 mg/dl) P-value = 0.000, a significant increase in plasma triglycerides level in menopause (mean±SD: 142.7±31.3 mg/dl) when compared to control (87.40±41.1 mg/dl) P-value =0.000, a significant increase in plasma LDL-C level in menopause (mean±SD) (171.2±31.3 mg/dl) when compared to control (159.1±30.6 mg/dl) P-value = 0.000, a significant decrease in plasma HDL-C level in menopause (mean±SD) (40.72±11.9 mg/dl) when compared to control (52.04±10.1 mg/dl mg/dl) P-value = 0.044.

statistical analysis also showed a significant increase in plasma cholesterol and LDL-C according to duration of menopause, for cholesterol: (mean±SD) (233.8±25.7) (239.6±25.9) (267.2±37.4) P-value=0.009, a significant increase in plasma LDL-C (153.9±44.53) (177.7±31.24) (185.2±35.78) P-value = 0.034, insignificant difference in plasma level of triglycerides and HDL-C in were found across difference age group according to duration of menopause, for triglycerides (mean±SD) (135.8±32.5) (145.8±30.6) (147.6±31.3) p-value = 0.526, for HDL-C (mean±SD) (36.94±6.49) (42.47±16.94) (43.38±8.90) P=0.256 according to duration of menopause from (1-5), (7-12), (>12) year respectively.

Results showed positive correlation between age of menopause and plasma cholesterol level (R=0.463, P-value =0.001), no correlation between age of menopause and plasma triglycerides level (R=0.186, P-value =0.210), plasma HDL-C level (R=0.220, P-value =0.137), plasma LDL-C level (R=0.206, P-value =0.165),

In conclusion: menopause women had increased level total cholesterol, triglyceride, low density lipoprotein, and the level of cholesterol, LDL-C was increased according to duration of menopause. Moreover a proportional correlation is noted between age of menopause and cholesterol level.

ملخص الدراسة

بعد انقطاع الطمث يحدث فقدان في وظيفه المبايض ينتج عن ذلك تغيير سلبي في استقلاب الجلوكوز و الانسولين ،استقلاب وتوزيع الدهون ،انحلال الفيبرين ,التخثروضعف بطانه الاوعيه الدمويه،اجريت هذه الدراسه لتقييم مستوى الكوليسترول والدهون الثلاثيه والبروتين الدهني عالي الكثافة والبروتين الدهني منخفض الكثافة في البلازما لدى النساء السودانيات بعد انقطاع الطمث في ولاية الخرطوم.تحتوي هذه الدراسة على 94 امرأة ،تم اخذ العينات من 47 امرأة بعد انقطاع الطمث تتراوح اعمارهم من 48-70 سنه كفئه دراسه وايضا 47 امرأة قبل انقطاع الطمث تتراوح اعمارهم من 25-48 سنه كمجموعه ضابطه من ولاية الخرطوم خلال الفترة من ابريل الى اغسطس 2018 تم اجراء الاختبارباستخدام طرق تحليليه لقياس مستوى الدهون وتحليل النتائج احصائيا ببرنامج التحليل الاحصائي .

اظهر التحليل الاحصائي زيادة معنويه ذات دلاله احصائية في مستوى الكوليسترول في الدم عند النساء في سن اليأس المتوسطات والقيم المعنويه كالاتي: للكوليسترول (32.0 ± 245.1) عند مقارنته بالفئه الضابطه (40.5 ± 175.9)بقيمه معنوية (0.000)، زيادة معنويه ذات دلاله احصائية في مستوى الدهون الثلاثية في الدم عندالنساء في سن اليأس(31.3±142.7) عند مقارنته بالفئه الضابطه (41.1±87.40) بقيمه معنوية (0.000)، زيادة معنويه ذات دلاله احصائيه في مستوى البروتين الدهني منخفض الكثافة في الدم في سن اليأس (31.3±171.2) عند مقارنته بالفئه الضابطه (30.6±159.1) بقيمه معنوية (0.000). انخفاضا في مستوى البروتين الدهني عالي الكثافة في الدم عند النساء عند سن اليأس (11.9±40.72)عند مقارنته بالفئه الضابطه (10.1±52.04) بقيمه معنوية (0.044).

اظهر التحليل الاحصائي ان مستوى الكلسترول ومستوى البروتين الدهني منخفض الكثافة يتأثر بمده انقطاع الطمث. للكلسترول P-value= 0.009 (37.4±267.2) (25.9±239.6) (25.7±233.8)، للبروتين الدهني منخفض الكثافة P-value= 0.034 (35.78±185.2) (31.24±177.7) (44.53±153.9) بالنسبه لمده انقطاع الطمث من (1-5)، (5-12)، (12<)، علي التوالي. وان مستوى الدهون الثلاثية ومستوى البروتين الدهني عالي الكثافة لا يتأثر بمده انقطاع الطمث:

المتوسطات والقيمه المعنويه كالاتي: للدهون الثلاثية p-value= 0.526 (31.3±147.6) (30.6±145.8) (32.5±135.8) البروتين الدهني عالي الكثافة P-value=0.256 (8.90±43.38) (16.94±42.47) (6.49±36.94) بالنسبه لمده انقطاع الطمث من (12<) ,(7-12) ,(1-5) علي التوالي

اظهرت النتائج وجود علاقه ارتباط ايجابي بين عمر اليأس ومستوى الكلسترول في الدم بقيمه معنويه (0.474) وقيمه ارتباط (0.463)، بينما لا توجد علاقه ارتباط بين عمر اليأس ومستوى الدهون الثلاثيه في الدم بقيمه معنوية (0.210) وقيمه ارتباط (0.186)، ومستوى البروتين الدهني مرتفع الكثافة في الدم بقيمه معنوية (0.137) وقيمه ارتباط (0.220)، ومستوى البروتين الدهني منخفض الكثافة في الدم بقيمه معنوية (0.165) وقيمه ارتباط (0.206).

خلصت هذه الدراسه على ان انقطاع الطمث يزيد من مستوى الكلسترول والدهون الثلاثيه والبروتين الدهني منخفض الكثافة وان مستوى الكلسترول والبروتين الدهني منخفض الكثافة يزداد بزياده المده الزمنيه لانقطاع الطمث علاوة على ذلك لوحظ وجود ارتباط نسبي بين مستوى الكلسترول وعمرانقطاع الطمث.

Chapter one

Chapter one

Introduction, Rationale, Objectives

1.1 Introduction

Menopause is the natural process of ageing during which a woman passes from reproductive to non reproductive phase with cessation of cyclic ovarian functions as manifested by cyclic menstruation. The transition from reproductive to non reproductive phase is the result of a major reduction in female hormonal production by the ovaries. The average age of menopause is 51 years. and less than 1% women experience it before the age of 40 years, while some undergo premature menopause at a very early age (Gayathiri et al., 2016). There are many symptoms associated with menopause. Symptoms commonly attributed to menopause include vasomotor symptoms of hot flushes and hot flashes, vaginitis, and urinary tract changes causing increases in infections and incontinence, Psychological changes such as depression, insomnia, and irritability also frequently accompany menopause Although these symptoms are not life threatening, they can be extremely disruptive in a woman's life (Marten,1993). The hormonal changes associated with menopause e.g., low plasma levels of estrogen and marked increase in follicle stimulating hormone levels exert a significant effect on metabolism of plasma lipids and lipoproteins.a number of changes that occur in the lipid profile after menopause are associated with increased cardiovascular disease risk. Lack of estrogen is an essential factor in this mechanism. After menopause, there is loss of ovarian function. This results in adverse changes in glucose and insulin metabolism, body fat distribution, coagulation, fibrinolysis and vascular endothelial dysfunction. A part from maintaining friendly lipid profile; all these are cardio protective mechanisms which are lost in menopause (Gayathiri et al., 2016). The incidence of cardiovascular disease after menopause may be partly caused by changes in the plasma lipid levels that occur following the menopausal transition (Kilim and Candala, 2013). After menopause, total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) usually increase, and these changes are accompanied by a decrease in high density lipoprotein cholesterol (HDL-C) and an increase in triglycerides (TG). In addition to these major lipid abnormalities, also modifications in size and density of these lipoprotein particles are expected to happen after the loss of ovarian hormonal production. This partially explains the increased cardiovascular risk in postmenopausal women, particularly among those with an earlier onset of

menopause (Fonseca et al., 2017), many Studies have shown that women are at a lesser risk of developing cardiovascular disease than their male counterparts before menopause, but this advantage is abolished after menopause .Data from these Study suggest that female coronary heart disease morbidity rates accelerate more quickly than do those of males after the age of 45 years.

1.1. Rationale

The risk of medical conditions increases after menopause include dyslipidemia, Lipids profile estimation help in early intervention to prevent dyslipidemia, many recent studies have investigated association between menopause and the risk of developing dyslipidemia (Matthews et al.، 2009; Fahmi et al.، 2017). And risk of cardiovascular disease, coronary heart disease (Ali et al. 2017; Gayathiri et al. 2016; Kilim and Chandala، 2013). According to the American Heart Association (1989), the number one cause of death in American women is Coronary heart disease, and women are more likely to suffer myocardial infarctions later in life than men, One in nine perimenopausal women has some type of CVD, and after the age of 65, the ratio increases to one in three.

To the best of our knowledge few published data were found regarding the impact of menopause on the level of cholesterol, triglycerides, LDL-C, HDL-C to diagnosis of dyslipidemia, that's why we attempt to do this study.

Objectives

1.3.1. General Objective

Study the assessment of plasma Levels of Cholesterol, Triglycerides, LDL-C and HDL-C among Sudanese menopausal Females in Khartoum State.

1.3.2. Specific Objective

To estimate and compare the levels of cholesterol, triglycerides, LDL-C and HDL-C in pre menopause and menopause women

To compare the levels of cholesterol, triglycerides, LDL-C and HDL-C according to duration of menopause

To correlate between the level of cholesterol, triglycerides, LDL-C and HDL-C and age of menopause women

Chapter two

Literature review

2.1 Menopause

Defined as 1 year without menses, however the ovaries production of estrogen is fail progressively. This failure often begins in the late 30 year, and most women experience near complete loss of production of estrogen by their mid-50year. The menopausal Transition is the transition from normal ovarian function to ovarian failure. The population affected by estrogen deficiency is substantial: there are approximately 70 million women in the United States beyond 50 years of age, with 2,500 to 3,500 women having their 50th birthdays each day. Although some of these women may be asymptomatic, estrogen deficiency is associated with symptom such as hot flashes, sweating, insomnia, and vaginal dryness and discomfort in up to 85% of menopausal women (Cobin et al., 2011). The menopause transition commences with the onset of first menstrual irregularity and ends 12 months after the final menstrual period. The median age at onset of menstrual irregularity is approximately 47 years, with a median age at final menses of 51.4 years (Chrvenak and Santoro, 2004). Menopause is accompanied by several physiological changes that potentially contribute to the increased risk of cardiovascular disease, including cessation of ovarian estrogen secretion, changes in body fat distribution, and adverse changes in lipid profiles. Further, menopause has been linked to the metabolic syndrome, insulin resistance, and changes in plasma adiponectin levels (Alkhoudary et al., 2013).

Perimenopause varies widely between women. Perimenopause typically lasts 4–8 years and can be characterized by variable cycle length or occasional skipped cycles in its early stage. Two or more skipped cycles (i.e. ≥60 days of amenorrhea) define the late stage, as menses become irregular they also are more likely to be anovulatory (Allshouse et al., 2015).

2.1.1 The age at which natural menopause occurs

The age at the final menstrual period holds intrinsic clinical and public health interest because the age at which natural menopause occurs may be a marker of aging and health, Later age at natural menopause has been associated with: longer overall survival and greater life expectancy and reduced all cause mortality, reduced risk of cardiovascular disease and mortality from cardiovascular and ischemic heart disease, stroke, angina after myocardial infarction, and atherosclerosis, less loss of bone density, and a reduced risk of osteoporosis and fracture but an

increased risk of breast, endometrial, and ovarian cancer, women who underwent natural menopause before age 45 years had an increased risk of ischemic heart disease that was not attenuated by use of hormone therapy. Further, early menopause has been associated with earlier decline in cognitive function. Because 40 million women in the United States alone and several hundred million worldwide experienced the menopausal transition between 1990 and 2010 due to the aging of the baby boomer generation, millions of women are undergoing or have recently undergone the menopause transition, and the timing of their final natural menstrual periods could have important clinical and health implications, because one third of women's lives is spent post menopause (Gold, 2011). Epidemiological studies suggest that the menopause is associated with increases in total cholesterol and low-density lipoprotein cholesterol (LDL-C), whereas increases in blood pressure and weight during midlife are more linear and appear to reflect chronological aging (Matthews et al.2009).

2.1.2 Menopause symptoms:

Estrogen deficiency is associated with symptom such as vasomotor symptoms, hot flashes, sweating, insomnia, and vaginal dryness and discomfort in up to 85% of menopausal women

2.1.2.1 Vasomotor symptoms

Vasomotor symptoms afflict most women during the menopausal transition, although their severity, frequency, and duration vary widely between women. Hot flashes are reported by

up to 85% of menopausal women. Hot flashes are present in as many as 55% of women even before the onset of the menstrual irregularity that defines entry into the menopausal transitionand their incidence and severity increases as women traverse the menopause, peaking in the late transition and tapering off within the next several years (Epperson et al., 2015).

2.1.2.2 Vulvovaginal atrophy

Urogenital tissues are exquisitely sensitive to estrogen, and the fluctuations in estrogen that occur during the menopausal transition, followed by sustained low levels after menopause, can render these tissues fragile and cause distressing symptoms. Multiple population- and community-based studies confirm that about 27% to 60% of women report moderate to severe symptoms of vaginal dryness or dyspareunia in association with menopause. In addition to vaginal atrophy, narrowing

and shortening of the vagina and uterine prolapse can also occur, leading to high rates of dyspareunia. Furthermore, the urinary tract contains estrogen receptors in the urethra and bladder, and as the loss of estrogen becomes evident, patients may experience UI. Unlike vasomotor symptoms, vulvovaginal atrophy does not improve over time without treatment (Epperson et al., 2015).

2.1.2.3 Sleep disturbances and insomnia

Sleep quality generally deteriorates with aging, and menopause seems to add an additional, acute layer of complexity to this gradual process. Women report more trouble sleeping as they enter into the menopausal transition, and sleep has been shown to be worse around the time of menses (Epperson et al., 2015).

2.1.2.4 Adverse mood

One-fifth of the US population will have an episode of depression in their lifetime, and the women are twice as likely to be affected. Although depression is more likely to occur in young adults, with peak onset in the fourth decade of life, there is evidence that the pre menopause represents another period of vulnerability for women, Although aprevious episode of depression has been shown to confer an increased risk, women with no previous episode of depression are still 2 to 4 times more likely to experience a depressive episode during the menopause transition compared with the pre menopause. Anxiety symptoms have been found to precede depression in some instances, and anxiety may also be viewed as increasing a woman's vulnerability to a mid life depressive episode (Epperson et al., 2015).

2.1.3 Complication of menopause

Menopause Complication include osteoporosis and cardiovascular disease.

2.1.3.1 Osteoporosis

A widely accepted complication of menopause is osteoporosis and subsequent increased susceptibility to bone fractures. As the level of estrogen declines, the rate of bone loss accelerates. Osteoporosis is defined as the pathological decrease in bone mass leading to increased susceptibility to fractures after minimal trauma. It is estimated that approximately 8% of the skeleton is replaced each year through a systematic process of bone resorption and bone

formation; however, the decline of endogenous estrogen associated with menopause causes the rate of bone resorption to accelerate more rapidly than it can be replaced. There are two major forms of bone: cortical and trabecular, Trabecular bone is primarily found in the vertebrae, the pelvis and other flat bones, and in the ends of long bone. In menopausal women trabecular bone may be lost at a rate of 5% to 8% annually. Due to the rapid onset of trabecular bone mass loss, the most common types of fractures of postmenopausal women up to age 65 are Colles' (distal arm) and vertebral fractures, but the incidence of vertebral fractures continues to rise after age 65. Cortical bone loss in postmenopausal women proceeds at a slower but still significant rate of 1% to 3% annually, Hip, pelvic, proximal humerus, and proximal tibia fractures are more common later in menopause because they are composed of both trabecular and cortical bone (Marten, 1993).

2.1.3.2 Cardiovascular disease and Coronary heart disease

Although the association between CVD and menopause is controversial, CHD in young women is significantly less prevalent than it is in young men, and the incidence of CHD mortality increases in both groups as they age. However, in women the rate of this increase is much more rapid than it is in men. The result showed that most measurable risk factors for CVD were significantly lower in estrogen and estrogen and progestin users than in women who were not taking replacement hormones. These findings suggest that when women become menopausal with a subsequent decline in levels of endogenous estrogen they are at increased risk for CVD. women are more likely to suffer myocardial infarctions (MI) later in life than men. The mortality rate for women within the first few weeks post MI is twice that of men, and within the first 4 years post MI women are 25% more likely to have a second MI. While these facts are alarming, cardiovascular diseases, such as strokes and hypertension, also have a major impact on morbidity and mortality in aging women. One in nine premenopausal women has some type of cardiovascular, and after the age of 65, the ratio increases to one in three (Marten, 1993).

2.2 Lipids profile

Lipids are defi ned as organic compounds that arepoorly soluble in water but miscible in organic solvents. Lipidology is the study of abnormal lipid metabolism. An understanding of the pathophysiology of plasma lipid metabolism is usefully based on the concept of lipoproteins, the form in which lipids circulate in plasma (Crook, 2012).

2.2.1 Lipid chemistry

Lipids are ubiquitous in the body tissue and play a vital role in all aspects of life; serve as hormones or hormone precursors, aiding in digestion, providing a source of metabolic fuel and energy storage, acting as functional and structural components in cell membranes, and forming insulation to allow nerve conduction or to prevent heat loss (Ashwood et al., 2012).

2.2.2 Biomedical importance

The lipids are a heterogeneous group of compounds related to fatty acid, including fats, oils, steroids, waxes, and related compounds, They have the common property of being insoluble in water and soluble in non polar solvents such as ether and chloroform. They are important dietary constituents not only because of the high energy value of fats but also because essential fatty acids, fat-soluble vitamins, and other lipophilic micronutrients are contained in the fat of natural foods. Fat is stored in adipose tissue, where it also serves as a thermal insulator in the subcutaneous tissues and around certain organs. Nonpolar lipids act as electrical insulators, allowing rapid propagation of depolarization waves along myelinated nerves. Lipids are transported in the blood combined with proteins in lipoprotein particles. (Rodwell et al., 2018).

2.2.3 Cholesterol

Present in tissues and in plasma either as free cholesterol or combined with a long-chain fatty acid as cholesterol ester, the storage form. In plasma, both forms are transported in lipoproteins. Cholesterol is an amphipathic lipid and as such is an essential structural component of membranes, where it is important for the maintenance of the correct permeability and fluidity, and of the outer layer of plasma lipoproteins. It is synthesized in many tissues from acetyl-CoA and is the precursor of all other steroids in the body, including corticosteroids, sex hormones, bile acids, and vitamin D. cholesterol also occurs in foods of animal origin such as egg yolk, meat, liver, and brain. Plasma low-density lipoprotein (LDL-C) is the vehicle that supplies cholesterol and cholesteryl ester to many tissues. Free cholesterol is removed from tissues by plasma high density lipoprotein (HDL-C) and transported to the liver, where it is eliminated from the body either unchanged or after conversion to bile acids in the process known as reverse cholesterol transport. Cholesterol is a major constituent of gallstones. However, it have role in

pathologic processes as a factor in the development of atherosclerosis of vital arteries, causing cerebrovascular, coronary, and peripheral vascular disease (Rodwell et al., 2018).

Cholesterol is transported in plasma in lipoproteins, in the form of cholesteryl ester, and in humans the highest proportion is found in LDL. Dietary cholesterol equilibrates with plasma cholesterol in days and with tissue cholesterol in weeks. Cholesteryl ester in the diet is hydrolyzed to cholesterol, which is then absorbed by the intestine together with dietary unesterified cholesterol and other lipids. With cholesterol synthesized in the intestines, it is then incorporated into chylomicrons, Of the cholesterol absorbed 80 to 90% is esterified with long-chain fatty acids in the intestinal mucosa. Ninety-five percent of the chylomicron cholesterol is delivered to the liver in chylomicron remnants, and most of the cholesterol secreted by the liver in very-low-density lipoprotein (VLDL) is retained during the formation of intermediate-density lipoprotein (IDL) and ultimately LDL-C, which is taken up by the LDL-C receptor in liver and extrahepatic tissue (Rodwell et al., 2018).

2.2.4 Triglycerides

Triglycerides contain three fatty acid molecules attached to one molecule of glycerol by ester bonds. Each fatty acid in the triglyceride molecule can potentially be different in structure, thus producing many possible structural forms of triglycerides, Triglycerides containing saturated fatty acids which do not have bends in their structure, pack together more closely and tend to be solid at room temperature. In contrast, triglycerides, containing cis unsaturated fatty acids typically form oils at room temperature. Most triglycerides from plant sources, such as corn, sunflower seeds are rich in polyunsaturated fatty acids and are oils, whereas triglycerides from animal sources contain mostly saturated fatty acids and are usually solid at room temperature there are no charged groups or polar hydrophilic groups, making it very hydrophobic and virtually water insoluble. Because it has no charge, triglyceride is classified as a neutral lipid (Bishop et al.,2010).

2.2.5 Lipoproteins

are typically spherical in shape and range in size from 10 to 1200 nm, lipoproteins are composed of both lipids and proteins, called apolipoproteins, The amphipathic cholesterol and phospholipid molecules are primarily found on the surface of lipoproteins as a single monolayer, whereas the

hydrophobic and neutral triglyceride and cholesteryl ester molecules are found in the central or core region. Because the main role of lipoproteins is the delivery of fuel to peripheral cells, the core of the lipoprotein particle essentially represents the cargo that is being transported by lipoproteins. The larger lipoprotein particles have correspondingly larger core regions and, therefore, contain relatively more triglyceride and cholesterol ester. The larger lipoprotein particles also contain more lipids relative to protein and thus are lighter in density. The various lipoprotein particles were originally separated by ultracentrifugation into different density fractions (chylomicrons [chylos], VLDL, LDL, and HDL), which still form the basis for the most commonly used lipoprotein classification system. Apolipoproteins are primarily located on the surface of lipoprotein particles, They help maintain the structural integrity of lipoproteins and also serve as ligands for cell receptors and as activators and inhibitors of the various enzymes that modify lipoprotein particles, Apolipoproteins contain structural motif called an amphipathic helix which accounts for the ability of these proteins to bind to lipids (Bishop et al., 2010).

2.2.5.1 Chylomicrons

Chylomicrons, which contain apo B-48, are the largest and the least dense of the lipoprotein particles, having diameters as large as 1200 nm13. Because of their large size, they reflect light and account for the turbidity of postprandial plasma. Because they are so light, they also readily float to the top of stored plasma and form a creamy layer, which is a hallmark for the presence of chylomicrons. Chylomicrons are produced by the intestine, where they are packaged with absorbed dietary lipids. Once they enter the circulation triglycerides and cholesterol esters in chylomicrons are rapidly hydrolyzed by lipases and, within a few hours, they are transformed into chylomicron remnant particles, which are recognized by proteoglycans and remnant receptors in the liver, facilitating their uptake.The principal role of chylomicrons is the delivery of dietary lipids to hepatic and peripheral cells (Bishop et al., 2010).

2.2.5.2 Very Low Density Lipoproteins

Produced by the liver and contains apo B-100, apo E, and apo Cs; like chylomicrons, they are also rich in triglycerides, and the major carriers of endogenous (hepatic-derived) triglycerides (Crook, 2012).

2.2.5.3. Low density lipoprotein

It is a small cholesterol rich lipoprotein containing only Apo B. It represents about 70 per cent of the total plasma cholesterol concentration. It can be taken up by most cells, the liver by the LDL or receptor recognizes and binds apoB100. Within the cell, the LDL particles are broken down by lysosomes, releasing cholesterol. This cholesterol incorporated into cell membranes or in specifi c tissues such as the adrenal cortex or gonads and utilized in steroid synthesis. Most cells are able to synthesize cholesterol, but, to avoid intracellular accumulation, there is a feedback control system reducing the rate of synthesis of the LDL receptors. Although most of the plasma LDL is removed by LDL receptors, if the plasma cholesterol concentration is excessive, LDL particles, by virtue of their small size, can infiltrate tissues by passive diffusion and can even cause damage, as in atheroma formation within arterial walls. An alternative route of removal of LDL is via the reticuloendothelial system, collectively termed the scavenger cell pathway, which recognizes only chemically modified LDL-C, for example oxidized LDL (Crook, 2012).

2.2.5.4. Lipoprotein (a)

Lipoprotein(a) particles are LDL-like particles that contain one molecule of apo (a) linked to apo B-100 by a disulfide bond (Bishop et al., 2010).

2.2.5.5. High density lipoprotein

HDL synthesized by both the liver and intestine. the smallest and most dense lipoprotein particle, exist as either disk-shaped particles, spherical particles, Discoidal HDL typically contains two molecules of apo A-I, which form a ring around a central lipid bilayer of phospholipid and cholesterol. Discoidal HDL represent nascent or newly secreted HDL and is the most active form in removing excess cholesterol from peripheral cells. The ability of HDL to remove cholesterol from cells, called reverse cholesterol transport, is one of the main mechanisms proposed to explain the antiatherogenic property of HDL(Bishop et al., 2010).

2.2.6. Lipoprotein physiology and metabolism

The lipid absorption pathway, the exogenous pathway, and the endogenous pathway, which all depend on apo B–containing lipoprotein particles, can be viewed as means to transport dietary

lipid and hepatic-derived lipid to peripheral cells. In terms of energy metabolism (Bishop et al., 2010).

Transport of dietary (exogenous) fat: Dietary fat is secreted from intestinal cells on chylomicrons in a process that requires apolipoprotein B-48. The triglyceride in the core of the chylomicrons is hydrolyzed into free fatty acids and glycerol by lipoprotein lipase with apo lipoprotein C-II as a cofactor, producing a smaller chylomicron remnant. This remnant is removed primarily by a chylomicron remnant receptor on the liver, known as the LDL-like receptor protein, A delayed removal of chylomicron remnants may promote atherogenesis. In normal patients, postprandial triglyceride levels return to baseline within 8–10 hours after an intake ofdietary fat. In contrast, patients with coronary artery disease have been found to have both higher elevations of postprandial triglycerides after a fat load and a delayed return of the triglycerides to baseline, due to a slowed removal of chylomicron remnant particles ,A diet low in total fat and saturated fats therefore remains important in patients with coronary artery disease to decrease the amount of dietary fat that must be cleared through the exogenous lipoprotein pathway and reduce the consequent elevation in chylomicron remnant particles (Kwiterovich, 2000).

Transport of endogenous (hepatic) fat: Triglyceride rich VLDL is synthesized and secreted from the liver, a process that requires apolipoprotein B-100. In plasma, the triglyceride in VLDL is broken down into free fatty acids and glycerol by lipoprotein lipase and its cofactor, apolipoprotein C-2. This results in the production of smaller VLDL remnants and, ultimately, IDL, the final remnant particle. Some of the IDL particles are removed through the interaction of apolipoprotein E with the LDL receptor on the surface of the liver, or the triglycerides in IDL can be hydrolyzed further by hepatic lipase to produce LDL. LDL is normally removed by the interaction of apolipoprotein B-100 with the LDL receptor. If LDL is oxidized, it can enter the macrophage through the scavenger receptors, CD36 and SR-A, on the surface of the macrophage (Kwiterovich, 2000).

2.2.7 Disorders of Lipoprotein Metabolism

Disorder of lipoprotein metabolism include primary and secondary hyperlipoproteinemia , familial combined hyperlipidemia, hypercholesterolemia and hypertryglyceridemia as first:

2.2.7.1. Primary and Secondary Hyperlipoproteinemia

hyperlipidemia is evaluated by whether it is from a primary lipoprotein disorder or is secondary to a wide variety of metabolic diseases. The diagnosis of primary hyperlipidemia is made after secondary causes have been ruled out. The most commonly seen secondary causes in the first year of life are glycogen storage disease and congenital biliary atresia. Hypothyroidism, nephrotic syndrome, and diabetes mellitus are more prevalent later in childhood. Exogenous factors, such as dietary and alcohol intake, oral contraceptives, diabetes mellitus, and pharmacologic agents [e.g., steroids, isotretinoin (Accutane), and β-blockers], are the main secondary causes of hyperlipidemia in adults (Ashwood et al., 2012).

2.2.7.2 Familial Combined Hyperlipidemia

About 10 to 15% of patients with premature CHD have familial combined hyperlipidemia (FCHL), thus making it one of the more common forms of dyslipidemia. Patients with FCHL can have increased plasma concentrations of total and LDL cholesterol (type IIa) or triglyceride (type IV), or both (type IIb). In all cases, apo B-100 concentrations are increased. The presentation of lipoprotein patterns can vary in an indi- vidual over time (Ashwood et al., 2012).

2.2.7.3 Hypercholesterolemia

Hypercholesterolemia is the lipid abnormality linked to heart disease. One form of the disease, which is associated with genetic abnormalities that predispose affected individuals to elevated cholesterol levels, is called familial hypercholesterolemia (FH). Homozygotes for FH are fortunately rare (1:1 million in the population) and can have total cholesterol concentrations as high as 800 to 1,000 mg/dL (20–26 mmol/L). These patients frequently have their first heart attack when still in their teenage years. Heterozygotes for the disease are seen much more frequently (1:500 in the population) because it is an autosomal codominant disorder; a defect in just one of the two copies of the LDL receptor can affect lipid levels. Heterozygotes tend to have total cholesterol concentrations in the range of 300–600 mg/dL (8–15 mmol/L) and, if not treated, become symptomatic for heart disease in their 20s to 50s. Approximately 5% of patients younger than age 50 with CAD are FH heterozygotes. Other symptoms associated with FH include tendinous and tuberous xanthomas, which are cholesterol deposits under the skin, and arcus, which are cholesterol deposits in the cornea (Bishop et al., 2010).

2.2.7.4 Hypertriglyceridemia

Hypertriglyceridemia can be a consequence of genetic abnormalities, called familial hypertriglyceridemia, or the result of secondary causes, such as hormonal abnormalities associated with the pancreas, adrenal glands, and pituitary, or of diabetes mellitus or nephrosis (Bishop et al., 2010).

Chapter three

3. Material and methods

3.1 Materials

3.1.1 Study design

This is across sectional case control study.

3.1.2 Study area and period

The study was conducted in Khartoum state - Sudan. The study was carried out over 5 month (April-August2018).

3.1.3 Study population

The study was conducted on 97 Sudanese healthy female 47 healthy menopausal females as case group and 47 healthy Sudanese pre menopausal females as controls.

3.1.4 Selection Criteria

Inclusion Criteria

Menopause women in the age group of 48-70 years with natural menopause, apparently healthy pre menopause women in the age group of 25-47 years.

Exclusion Criteria

Ladies with 25-70 year, Hypertension, Diabetes Mellitus, Hepatic disease, Patients on lipid lowering medication.

3.1.5 Ethical consideration

The study was approved by the scientific committee of clinical chemistry department College of Medical Laboratory Science of the Sudan University of Science and Technology. Then a verbal informed consent was obtained from participants (Appendix I).

3.1.6 Sampling

Exactly 3ml of venous blood were collected in heparin container under Aseptic condition, centrifuged for 5-10 min then plasma was collected in plain tube and kept at -20c until use for lipid profile estimation.

3.2 Methodology

3.2.1 Estimation of cholesterol concentration using enzymatic method

Cholesterol esters react with H2Oin the presence of CHE to give cholesterol and fatty acids. then cholesterol react with O2 in the presence of CHOD to give 4-cholestenona and H2O2.2H2O2 react with phenol and 4-aminophenazone in the presence of POD to give quinonimine and 4H2O.the intensity of color formed is proportional to the cholesterol concentration in the sample. (Appendix II)

3.2.2 Estimation of Triglyceride using enzymatic method

Sample triglycerides incubated with lipoproteinlipase(lpl), liprate glycerol and free fatty acids. Glycerol is converted to glycerol-3-phosphate (G3P) and adenosine-5-diphosphate(ADP) by glycerol kinase and ATP.Glycerol-3-phosphate is then converted by glycerol phosphate dehydrogenase(GPO) to dehydroxyacetone phosphate(DAP) and hydrogen peroxide(H2O2).

In the last reaction hydrogen peroxide (H2O2) react with 4-aminophenazone(4-AP) and p-chlorophenol in the presence of peroxide (POD) to give red colored dye.

The intensity of color formed is propotional to the triglyceride concentration in the sample (Appendix III).

3.2.3 Estimation of HDL-C using enzymatic method

Very low density lipoproteins (VLDL) and low density lipoproteins (LDL-C) in the sample precipitate with phosphotungstate and magnesium ions. The supernatant contain high density lipoprotein (HDL-C). The HDLc is then spectrophotometrically measured by means of the coupled reaction: Cholesterol esters react with H2Oin the presence of CHE to give cholesterol and fatty acids. then cholesterol react with O2 in the presence of CHOD to give 4-cholestenona and H2O2.2H2O2 react with phenol and 4-aminophenazone in the presence of POD to give quinonimine and 4H2O.the intensity of color formed is proportional to the cholesterol concentration in the sample (Appendix IV).

3.2.4 Estimation of LDL-C using enzymatic method

Low density lipoprotein (LDL-C) in the sample precipitate with polyvinyl sulphate. Their concentration is calculated from the difference between the serum total cholesterol and the cholesterol in the supernatant after centrifugation. The cholesterol is spectrophotometrically measured by means of coupled reaction:

Cholesterol esters react with H2Oin the presence of CHE to give cholesterol and fatty acids. then cholesterol react with O2 in the presence of CHOD to give 4-cholestenona and H2O2.2H2O2 react with phenol and 4-aminophenazone in the presence of POD to give quinonimine and 4H2O.the intensity of color formed is proportional to the cholesterol concentration in the sample (Appendix V).

3.3 Quality control

Pathological and normal control sera of lipid profile (cholesterol, triglycerides, HDL-C, LDL-C) were measured to assure the accuracy of results.

3.4 Data analysis

Data was analyzed by using the SPSS computer program the independent T. test and Anova used for comparison (P-value< 0.05) was consider significant and Pearson correlation used for correlation.

Chapter four

4. Results

In this study 94 participant were enrolled,47 menopause female as case group and 47 pre menopause female as control to investigate the Assessment of plasma Levels of Cholesterol, Triglycerides, LDL-C and HDL-C among Sudanese menopausal Females in Khartoum State**,** data were analyzed statistically using computer SPSS program and the result were as follow:

Table 4.1: Statistical analysis showed a significant increase in plasma cholesterol level in menopause (mean±SD) (245.1±32.0 mg/dl) when compared to control (175.9±40.5 mg/dl) p-value=0.000, plasma triglycerides level in menopause (mean±SD)(142.7±31.3 mg/dl) when compared to control (87.40±41.1 mg/dl) p- value=0.000, plasma LDL-C level in menopause (mean±SD)) (171.2±31.3 mg/dl) when compared to control (52.04±10.1 mg/dl) p- value=0.000, and a significant decrease in plasma HDL-C level in menopause (mean±SD)(40.72±11.9 mg/dl) when compared to control (159.1±30.6 mg/dl) p- value=0.044.

Table 4.2: show a significant increase in plasma cholesterol and LDL-C according to duration of menopause, for cholesterol: (mean±SD) (233.8±25.7) (239.6±25.9) (267.2±37.4) P-value=0.009, a significant increase in plasma LDL-C (153.9±44.53) (177.7±31.24) (185.2±35.78) P-value = 0.034, insignificant difference in plasma level of triglycerides and HDL-C in were found across difference age group according to duration of menopause, for triglycerides (mean±SD) (135.8±32.5) (145.8±30.6) (147.6±31.3) p-value = 0.526, for HDL-C (mean±SD) (36.94±6.49) (42.47±16.94) (43.38±8.90) P=0.256 according to duration of menopause from (1-5), (7-12), (>12) year respectively.

Figure4.1: A scatter plot shows positive correlation between age of menopause and total cholesterol level (R=0.463, P-value=0.001).

Figure4.2: A scatter plot shows no correlation between age of menopause and triglyceride level(R=0.186, P-value=0.210).

Figure4.3: A scatter plot shows no correlation between age of menopause and HDL-C level(R=0.220, P-value=0.137).

Figure4.4: A scatter plot shows no correlation between age of menopause and LDL-C level(R=0.206, P-value=0.165).

Table (4. 1): Comparison of lipids profile in menopause versus pre menopause.

Parameters	Menopause (Mean±SD)	Pre menopause (Mean±SD)	P- value
T. CholestroL mg/dl	245.1±32.0	175.9±40.5	0.000
Triglyceride mg/dl	142.7±31.3	87.40±41.1	0.000
HDL-C mg/dl	40.72±11.9	52.04±10.1	0.000
LDL-C mg/dl	171.2±31.3	159.1±30.6	0.044

Independent sample T- test was used, P- value <0.05 considered significant.

Table (4.2): Comparison of mean of cholesterol, triglyceride, HDL-C, LDL-C according to duration of menopause.

Parameters	Mean±SD			*P-value*
	1-5 Years	7-12Years	<12 Years	
TC	233.8±25.7	239.6±25.9**	267.2±37.4**	0.009
TG	135.8±32.5	145.8±30.6	147.6±31.3	0.526
HDL	36.94±6.49	42.47±16.94	43.38±8.90	0.256
LDL	153.9±44.53	177.7±31.24**	185.2±35.78**	0.034

The table shows the mean± standard deviation and probability (P)

One way Anova test was used for comparison

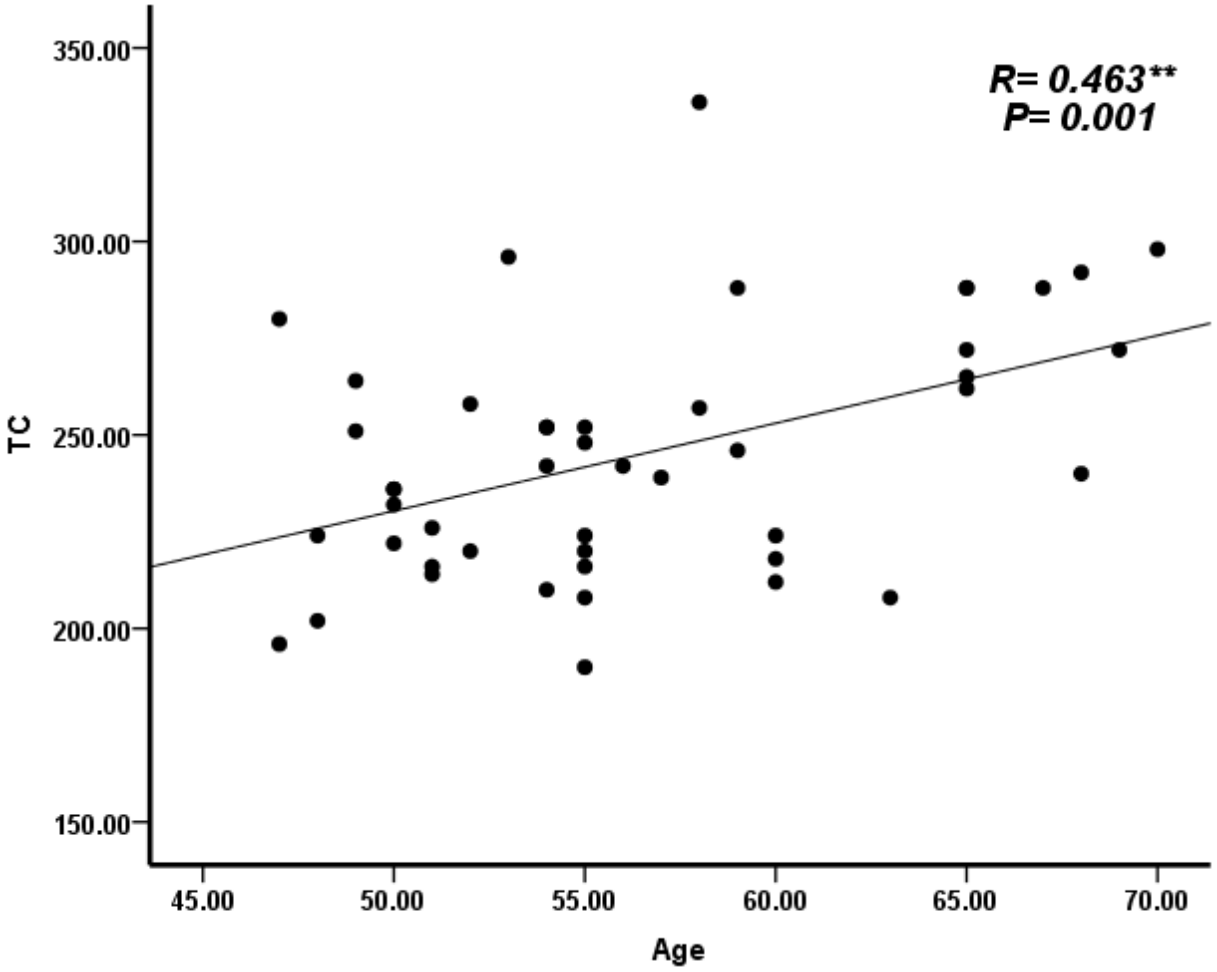

Figure (4.1): Correlation between age of menopause and T. Cholestrol level.

-**R:** Shows the Regression of Coefficient.

-**P:** Shows the Strings and Significance of Correlation.

-**X** axis: Age in years.

-**Y** axis: TC: Total cholesterol: mg/dl.

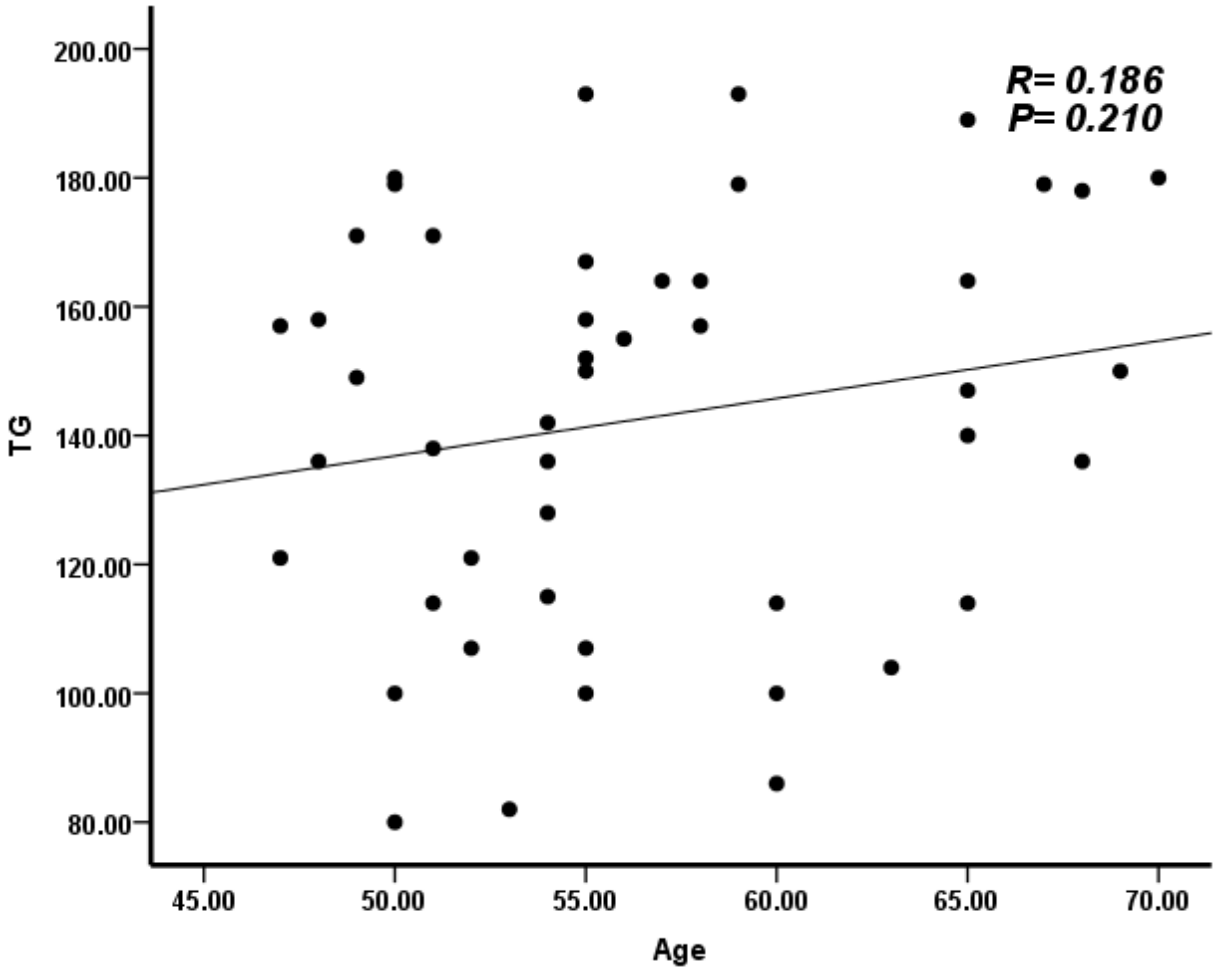

Figure (4.2): Correlation between age of menopause and triglycerides level.

-**R:** Shows the Regression of Coefficient.

-**P:** Shows the Strings and Significance of Correlation.

-**X** axis: Age in years.

-**Y** axis: triglycerides: mg/dl.

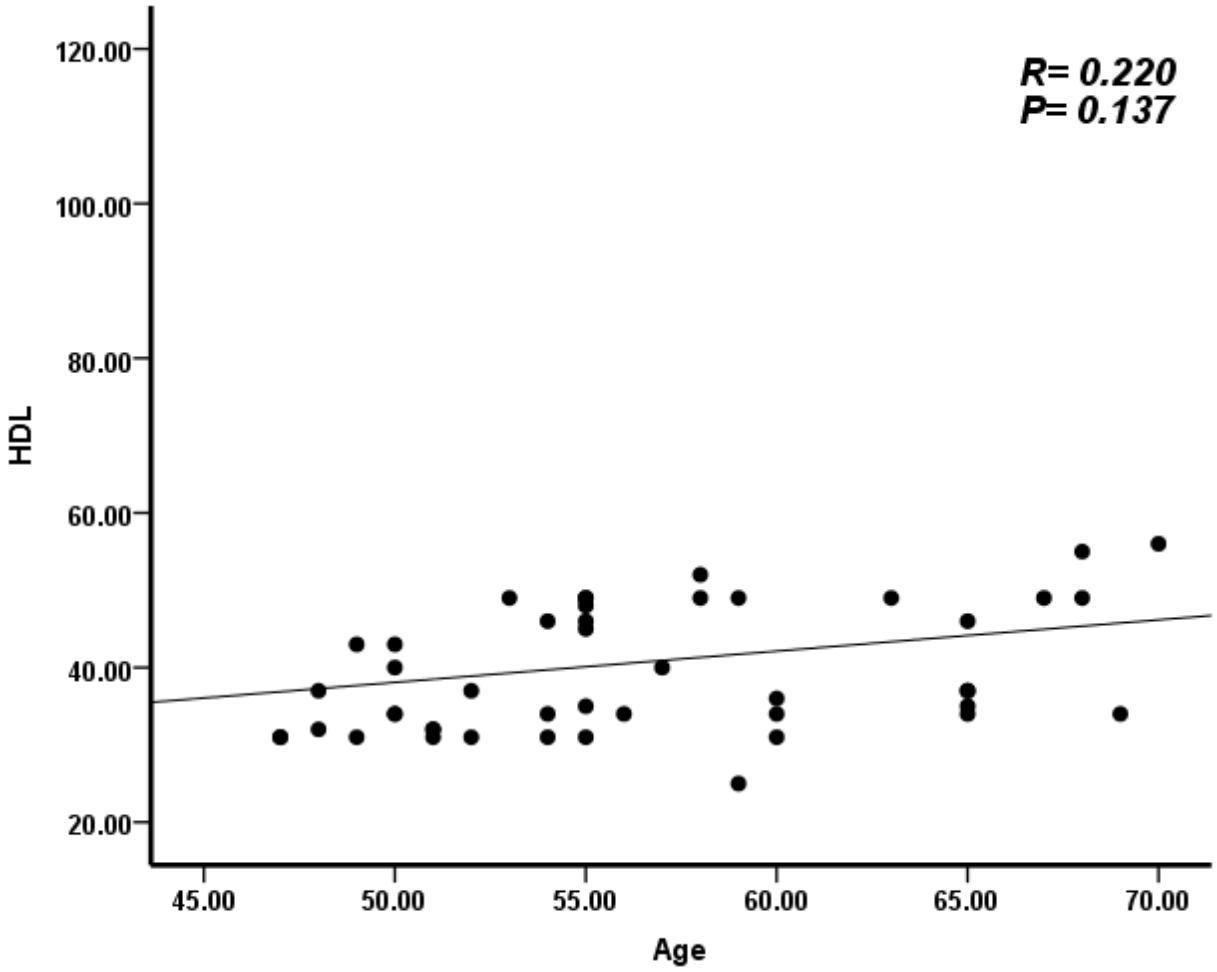

Figure (4.3): Correlation between age of menopause and high density lipoprotein cholesterol

-R: Shows the Regression of Coefficient.

-P: Shows the Strings and Significance of Correlation.

-X axis: Age by years.

-Y axis: HDL-C: mg/dl.

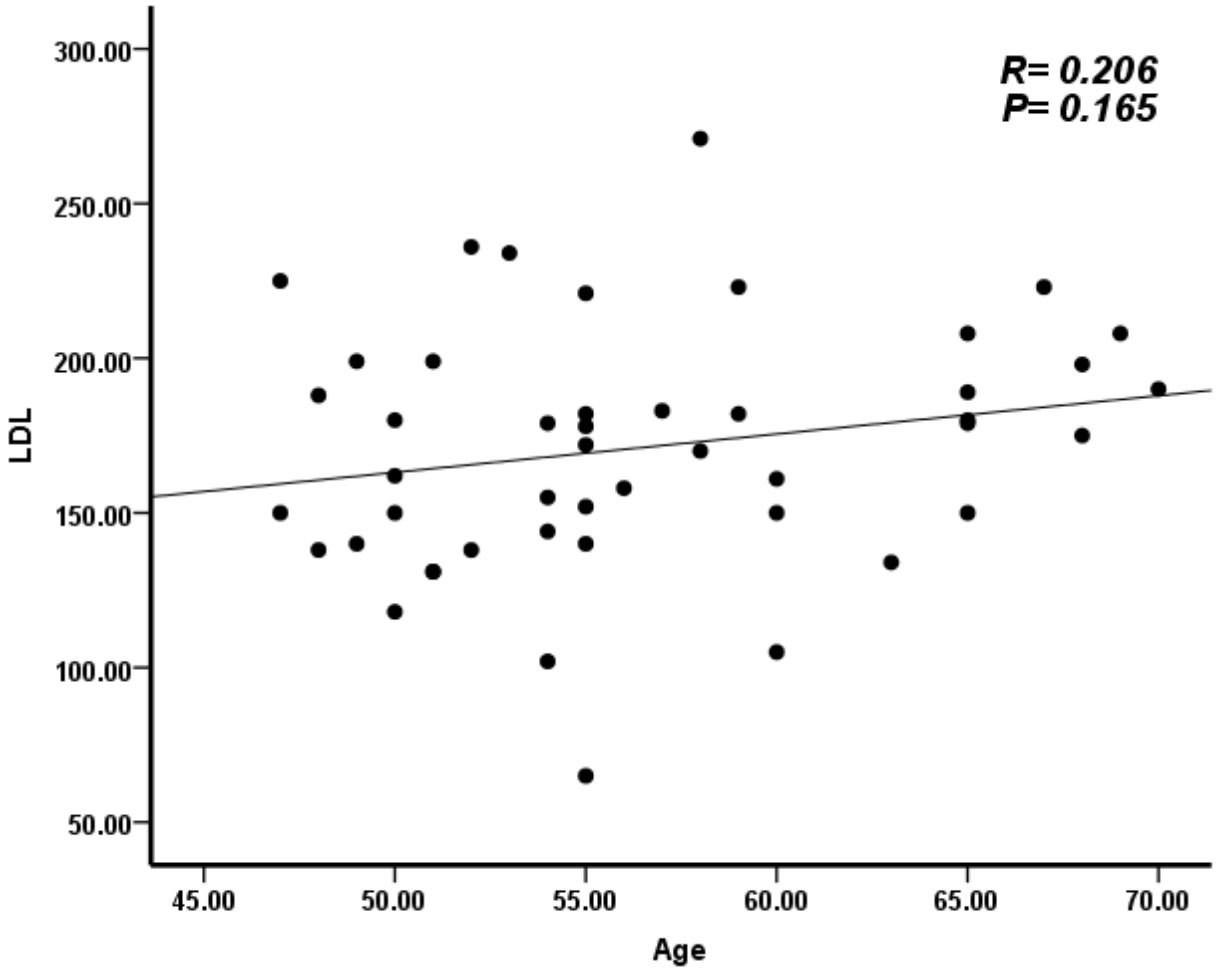

Figure (4.4): Correlation between age of menopause and Low density lipoprotein cholesterol

-R: Shows the Regression of Coefficient.

-P: Shows the Strings and Significance of Correlation.

-X axis: Age in years.

-Y axis: LDL-C: mg/dl.

Chapter five

5. Discussion, conclusion and recommendations

5.1 Discussion

Dyslipidemia in menopause is a known feature in women, which may lead to significant increase in the development of cardiovascular disease (GayathIri et al., 2016).

According to results of this study; levels of cholesterol, triglycerides, and LDLc were significantly increased in menopause, while HDLc was significantly decreased.

This results are in agreement with study done by (Ali et al., 2017), (GayathIri et al., 2016), (Fahmi et al., 2017). who compared lipid profile in pre menopause and post menopause women they concluded that levels of cholesterol, triglyceride, LDL-C were a significantly higher in menopause than control group and level of HDL-C is a significantly decreased in menopause compared with control group.

Our study showed that health state and regular production of estrogen by ovaries in pre menopause have plasma lowering action of cholesterol, triglycerides, LDL-C, and protected pre menopause women from dyslipidemia. menopause is reduction of female reproductive system due the physical, pathological or surgical removal of any female reproduction system parts making broad hormonal change that affect normal metabolism and body functions making post menopausal female at risk factor for serious metabolic disease as dyslipidemia, Menopause substantially increase cardiovascular risk in the female sex, promoting modifications on lipid metabolism and circulating lipoproteins. Lipoprotein sub fractions shift after menopause towards a more atherogenic lipid profile, consisted of hypertriglyceridemia, lower levels of high density lipoprotein.

Current study also showed correlation between age of menopause and level of cholesterol, triglyceride, HDL-C, LDL-C.

Our results showed positive correlation between age of menopause and cholesterol level, this results in agreement with study done by (Ali et al.,2017), (Fahmi et al. 2017).who correlate between lipid profile and age of menopause.

Our result showed that increase age correlate with increase cholesterol level, thus mean increase age have a significant role in the metabolism and distribution of cholesterol and increase risk of dyslipidemia.

According to result of our study the levels of cholesterol and LDL-C was significantly increased according to duration of menopause and the levels of Triglycerides and HDL-C was insignificantly increased. This study also showed no correlation between age of menopause and triglycerides, HDL-C, LDL-C to the best of our knowledge no pervious study have results regarding this correlation.

5.2 Conclusions

1. The level of total cholesterol, triglycerides, low density lipoprotein are increased in menopause women while the level of HDLc is decreased.
2. The level of total cholesterol is positively correlated with age of menopause and the level of Total cholesterol and low density lipoprotein are positively correlated with duration of menopause.

5.3 Recommendations

1. Evaluation of lipid profile is helpful to prevent cardiovascular diseases in menopausal women.
2. For reliable results further study with large sample size to assessment plasma Levels of Cholesterol, Triglycerides, LDL-C and HDL-C among Sudanese obese menopausal Females.
3. Further study to investigate the impact of menopause on the levels of cholesterol, triglycerides, LDL-C. HDL-C regarding the inclusion of BMI Are recommended to be done.

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Appendices

Appendix I

Informed consent

الموافقة المستنيرة

انا الباحثة مودة عباس محمد عباس من كلية علوم المختبرات الطبية قسم الكيمياء السريرية ، جامعة السودان للعلوم والتكنولوجيا ، اقوم بدراسة علمية بحثية لنيل درجة الماجستير بعنوان تأثير انقطاع الطمث على مستوى الكلسترول والدهون الثلاثيه والبروتين الدهني عالي الكثافة والبروتين الدهني منخفض الكثافة بين النساء السودانيات في ولاية الخرطوم.

وفقا للدراسات سابقة فان تناقص البروتين عالي الكثافة وزياده تركيز الكلسترول والدهون الثلاثيه والبروتين الدهني منخفض الكثافه يتناسب مع انقطاع الطمث.

لقد قمنا باختيارك لتشاركينني هذا البحث العلمي لانك تنطبق عليك كل شروط الشخص التي يمكن ان يكون ضمن المشمولين في الدراسة (انثى ليس لديها سكري او ضغط الدم ، لا تتناول اي ادوية تاثر ع الدهون ، غير مصابه بمرض في الكبد ، غير مصابة بمرض في القلب لا تعاني من نزيف رحمي) .

خلال الدراسة سوف نقوم باخذ3 مل من الدم لاجراء تحليل مستوى الكلسترول والدهون الثلاثيه والبروتين الدهني عالي الكثافة والبروتين الدهني منخفض الكثافة وهذا يتطلب الصيام من 12-14 ساعه للحصول على نتائج سليمة وايضا **ساقوم بطرح بعض الاسئلة التي تتعلق بالعمر والمدة الزمنية لانقطاع الطمث**.

علما بان سحب العينة قد يؤدي الى احداث بعض الالم وقد يؤدي ايضا الى ظهور ورم في منطقة الحقن قد يتفشى بمرور ساعات ، وظهور كدمات زرقاء وسوف نعمل على تفادي كل هذة المضاعفات.

بعد الموافقة منك واخذ المعلومات التي تتعلق بالعمرو المدة الزمنيه لانقطاع الطمث والاجابة على جميع الاسئلة المطلوبة في البحث ، سوف يتم اخذ العينة والعمل على تحليلها وسيتم اخبارك بالنتائج التي حصلنا عليها خلال شهرين من زمن سحب العينة ، والتي سوف تكون في سرية تامة ولن يطلع عليها احد غير العاملين في البحث بدون الاشارة الى محددات الهوية ، علما بان اشتراكك سيكون طواعية ويمكنك الانسحاب من الاشتراك في اي وقت تشائين دون اي خسائر، ونحيطكم علما انه لن تكون هناك اي عوائد مالية نتيجة اشتراكك ، ويمكنك الاتصال على الباحث في الرقم ..... في اي وقت للمزيد من المعلومات خلال فترة البحث .

اقرار المشاركة :

لقد اطلعت على المعلومات الحالية والتي تم شرحها لي واتيح لي فرصة طرح الاسئلة عنها كما شئت، ولقد تلقيت الاجابات الوافيه عن كل الاسئلة ، وانا اقر بالموافقة على المشاركة طواعية في هذة الدراسة واعلم بحقي في التوقف عن المشاركة في اي وقت دون ان يؤثر ذلك على حقوقي الاخرى او الاستفادة من نتائج هذة الدراسة.

توقيع المشارك : _____

ت- المشارك : .....

توقيع الباحث: _____