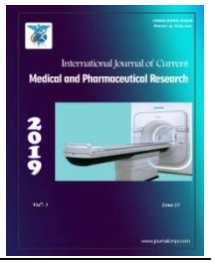
INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH
ISSN: 2395-6429, Impact Factor: 4.656
Available Online at www.journalcmpr.com
Volume 5; Issue 12(A); December 2019; Page No. 4822-4832
DOI: http://dx.doi.org/10.24327/23956429.ijcmpr201912812



Research Article

POSTMENOPAUSAL STATE –RISK FACTORS FOR METABOLIC SYNDROME

Neelima Saoji

Department of Medicine, NKPSIMS & LMH, Nagpur

ARTICLE INFO

Article History:
Received 13th September, 2019
Received in revised form 11th October, 2019
Accepted 8th November, 2019
Published online 28th December, 2019

Key words:
Postmenopausal women,Metabolic syndrome,Cardiovascular diseases,visceral obesity

ABSTRACT

There is clustering of cardiometabolic risk factors like physical inactivity,obesity,poor dietary factors,hypertension,insulin resistance,diabetes,dyslipidemia,& hypothyroidism in postmenopausal women, which has major impact on development of cardiovascular diseases(CVD) like hypertension,coronaryarterydisease,stroke& heart failure.

Menopause is actually another independent risk factor.Most of the effects are due to deficiency of estrogen making these women vulnerable to the hazards of CVD. Aging and these risk factors add to the burden of CVD.

Menopause is associated with emergence of metabolic syndrome characterised by central visceral obesity,shift towards atherogenic lipid profile,high BP& glucose intolerance with endothelial dysfunction leadingto coronary artery disease.

Women often have casual approach towards their health. They delay in seeking medical advice,lack of knowledge & societal attitudes leads to poorer outcomes,longer hospital stay which increases their cardiovascular mortality by 3-7 fold.

Most of the risk factors are modifiable.Regular screening can help in early detection & proper treatment.

INTRODUCTION

There is a high risk of cardiovascular diseases in post-menopausal women secondary to a higher prevalence of cardio metabolic risk factors. The changes in body fat distribution from a gynoid to an android pattern, reduced glucose tolerance, abnormal plasma lipids, increased blood pressure, increased sympathetic tone, endothelial dysfunction, and vascular inflammation.

Metabolic syndrome is characterized by clustering of several parameters as the diagnostic criteria which are associated with increased cardiovascular diseases (CVD) burden. By NCEP-III definition, three or more of five of the following criteria are required for diagnosis of Metabolic syndrome or Syndrome-X.

Waist circumference ≥40 inches (men) or 35(women)
BP ≥ 135/85mmHg.
Fasting TG ≥ 150 mg/dl, Fasting HDL cholesterol≤ 40mg/dl(men) or 50mg/dl(women)
Fasting Blood glucose ≥ 100mg/dl.

The above definition is most widely used as it incorporates the key features of hyperglycemia/insulin resistance, visceral obesity, atherogenic lipid profile and hypertension. The hypothyroidism is often seen as a common endocrinological disorder increasing the burden of cardiovascular disesesas it is associated with most of the components of metabolic syndrome.

Menopause is characterized by emergence of features of metabolic syndrome including an increased central body fat, a shift toward a more atherogenic lipid profile, high blood pressure & glucose intolerance[(1)].

The loss of cardioprotective effects of estrogen is implicated in the increased prevalence of cardiometabolic risk factors & thus cardiovascular diseases (CVD) in postmenopausal women.

Epidemiology

Cardiovascular diseases are the topmost cause of mortality all over the world. It has been observed that mortality from cardiovascular diseases is decreasing rapidly in the developed countries whereas, it is showing an increasing trend in developing countries[(2)].Cardiovascular diseases (CVDs) are the leading cause of mortality in India[(3)]. Ischemic heart disease and stroke are the predominant causes and are responsible for >80% of CVD deaths. There has been a rise in the prevalence of cardiovascular risk factors i.e. diabetes, hypertension, dyslipidemia, smoking, central obesity and physical inactivity & CVD mortality in India[(4)].

This increase in cardiovascular mortality is attributable to epidemiological transition secondary to rapid industrialization, urbanization and related lifestyle changes in the developing

Corresponding author:* **Neelima Saoji
Department of Medicine, NKPSIMS & LMH, Nagpur

countries. Epidemiological transition gradually progresses over a period of years from a stage of predominance of communicable diseases, malnutrition associated illnesses & low CVD related mortality through increasing prevalence of CVD & related mortality to a stage of predominance of CVD risk factors such as sedentary lifestyle, obesity, diabetes, hypertension & dyslipidemia & CVD related mortality. It progresses with the development of acountry[5].

As per the WHO records the South Asian region has one of the highest cardiovascular mortality rates in the world.[5]. Also cardiovascular epidemiology in India is characterized by high mortality rates, premature coronary artery disease, and increasing burden[6,7]. Besides, CAD risk factors show up in South Asians at a younger age compared to other populations, resulting in premature CAD[8,9]. The reasons behind this remain unclear. It has also been observed that even moderate increase in body mass index subjects South Asians to greater risk of insulin resistance and related diseases[10]. Also at any given total cholesterol or LDL level, South Asians have a greater risk of CAD than Caucasians. [11]The high prevalence of CVD mortality in India is also due to lack of measures for primary prevention of risk factors, poor control of existing risk factors, lack of awareness, inadequate access to treatment & lack of rehabilitative measures for those with CVD. Initially considered a disease of the urban affluent class, CVD prevalence has started rising in the low-income urban & rural populations of India. This change is attributable to adoption of unhealthy lifestyle with high intake of fat rich low fibre diet, low intake of vegetables & fruits, tobacco abuse, smoking and physical inactivity in people from lower socioeconomic backgrounds & rural areas[12].

Contrary to the widespread notion that CVD predominantly affect men, CVD are the leading cause of death among both men and women globally[13,14]. Besides the urban-rural differences, distinct gender differences in CVD mortality & morbidity are also well recognized.

There are distinct gender differences in various CVD related aspects such as incidence, mortality, risk-factor profiles, outcomes, and clinical presentation. CVD prevalence, incidence, and mortality rates tend to be higher for men than for women in all age groups except in the older age groups viz. > 75years. These differences have been consistently reported & found to be significant in various studies over the years and across different countries and populations[15,16,17]. After age 60, CAD cases in men increase at a regular rate, while in women the rate increases exponentially[17].

It has also been reported that women encounter their first cardiovascular events later in life than men. The INTERHEART study reported that on an average, women experience their first episode of acute coronary syndrome 9 years later than men[18,19]. The prevalent low socioeconomic status since childhood is a risk factor of coronary artery disease in postmenopausal women of developing countries like India.[80]

Also a difference in the prevalence of CVD risk factors is noted among men & women. Analysis of data from the National Health & Nutrition Examination Survey revealed that blood pressure levels are comparatively lower in women compared with men of the same age between puberty &menopause irrespective of ethnicity & that there was greater prevalence of hypertension in women aged > 60yrs as compared to men of same age[19]. Also it has been observed that premenopausal women have a favourable lipid profile with high HDL cholesterol, low triglycerides & LDL cholesterol & menopauseis characterised by a change in the lipid profile to an atherogenic one.[1]

The common cardio metabolic risk factors are physical inactivity, high fat carbohydrates, salt low fibers in diet, obesity, hypertension, diabetes mellitus, dyslipidemia, and hypothyroidism which are rampant in Indian population.

As per recent studies diabetes is more common in men than in women[13,21,22]. However, after menopause a change in the fat distribution from gynoid to android pattern occurs thus increasing visceral adiposity which induces insulin resistance thus increasing the risk of diabetes mellitus[20,21]. Various studies have demonstrated an increased prevalence of diabetes in post-menopausal women. The favourable CVD risk profile in women until menopause is attributable to the protective effects of estrogen on blood pressure, lipid profile, endothelial dysfunction, visceral adiposity & glucosetolerance[1,23,24,29].

After menopause due to loss of this protective effect of estrogen, there is a change in body fat distribution from a gynoid to an android pattern, reduced glucose tolerance, abnormal plasma lipids, increased blood pressure, increased sympathetic tone, endothelial dysfunction, and vascular inflammation, all of which lead to an increased prevalence of cardiovascular diseases viz. atherosclerosis, Coronary artery disease, stroke as demonstrated in various studies[25-35].

Menopause thus acts as a risk factor for metabolic syndrome. There are other studies which have demonstrated that the increased prevalence of CVD risk factors & CVD in post-menopausal women is attributable to increasing age[36,37]. As aging & menopause are concurrent phenomena, it is very difficult to distinguish the consequences of estrogen deprivation from those of aging. Studying the effects of estrogen deficiency &estrogen replacement in young women with ovarian failure may help to distinguish between the effects of aging & estrogen deficiency.[37]

Further, research has shown that women experience poorer outcomes when they have a CVD event; after a stroke or MI, women tend to have longer hospital stays, increased prevalence of depression and anxiety, higher short- term mortality, greater long-term disability, and higher rates of reinfarction than men[17,18]. The poorer outcomes are attributable to a casual approach towards women‘s health in the women as well as in the society, delay in seeking medical treatment at the onset of symptoms, presentation with atypical symptoms of acute coronary syndrome, lack of awareness, inappropriate/inadequate treatment.

As compared to men, women more often have an atypical presentation of acute coronary syndrome (ACS) with atypical symptoms such as:

- Neck, shoulder, upper back or abdominal discomfort
- Shortness of breath
- Nausea orvomiting
- Sweating
- Lightheadedness ordizziness
- Unusualfatigue[37]

These symptoms are not as distressing as the classical chest pain associated with ACS; hence the diagnosis may be missed unless a high degree of clinical suspicion is observed. The

atypical presentation of ACS is attributed to microvascular disease i.e. atherosclerosis predominantly involving small blood vessels of the heart in women contrary to involvement of major vessels of coronary circulation in men. On angiography the coronaries thus appear normal with the microvascular disease being missed. This is commonly referred to as 'Syndrome X'& is commonly seen in post- menopausal women[18].

Moreover, research has shown that diabetes increases a woman's risk of developing CAD three- to seven-fold, whereas it increases a man's risk two- to three-fold. It also doubles the risk of ischemic stroke[18].

Inspite of ample evidence from research, risk for CVD remains underestimated in women even today. Studies have shown that on presentation women are less likely to be investigated for ACS, or cardiovascular risk factors. Even after investigations they tend to be undertreated for their illnesses. The lack of awareness prevails not only among the common people but also amongphysicians.

The unaddressed burden of cardiovascular risk factors in post-menopausal women amounts to the increased CVD morbidity & mortality in this population. Interestingly, almost all of these risk factors are modifiable.

A cautious approach towards women's health aimed at early detection of cardiovascular risk factors in post-menopausal women & timely intervention with lifestyle & dietary modifications & therapeutic measures wherever necessary may decrease the morbidity & mortality associated with cardiovascular diseases in women.

Majority of the data related to CVD risk factors & related morbidity & mortality in post-menopausal women is from the western countries. Research on the prevalence of CVD risk factors & CVD related morbidity & mortality in post-menopausal women in India is still in its nascency. Further research is needed to study CVD risk factors in post-menopausal women in order to formulate & implement health care policies directed towards prevention, early detection, treatment & control of CVD in this population.

Menopause is a life-changing phenomenon in a woman's life occurring after an enduring journey marked by the complexities of menarche, monthly menstrual cycles, pregnancy & motherhood. It is characterized by distressing emotional disturbances like irritability, mood swings, depression, anxiety, loss of libido; vasomotor disturbances like hot flashes, cold sweats; increased risk of fractures &cardiometabolic risk factors like impaired glucose tolerance/diabetes, hypertension, dyslipidemia, endothelial dysfunction all of which increase the prevalence of cardiovascular diseases in post-menopausal women[22].

Menopauseisdefined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. It is diagnosed retrospectively after 12 months of amenorrhoea following the final menstrual period[22].A prominent Brooklyn gynaecologist's work crucially contributed to the acceptance of menopause as a deficiency disease through his book. In the 1930s, menopause was regarded by physicians as a deficiency disease rather than a natural phenomenon[38]. In the 1960s Dr Robert A. Wilson rampantly used estrogen to treat menopausal symptoms & to protect from the increased risk for cardiovascular morbidity & mortality after menopause; however after discovering the health hazards of HRT through research such as increased risk of heart attack, stroke, breast cancer & venous thromboembolism it is now used only when indicated &verycautiously[39].

Many epidemiological studies in the 1950s-1970s revealed that the prevalence of cardiovascular diseases remains lower in women as compared to age-matched men until menopause after which there is a rise in the prevalence in women[40,41].

Some of the studies done in ovariectomised females revealed increased prevalence of CVD risk factors after castration[41]. This made researchers investigate the possibility of role of hormonal changes during menopause behind the increase in prevalence of cardiovascular risk factors& diseases in post-menopausal women.

In 1978 the Framingham study done in a cohort of 2873 Framingham women who were followed up for 24 years revealed an increased prevalence of cardiovascular diseases in post-menopausal women irrespective of whether menopause was natural or surgical[42].

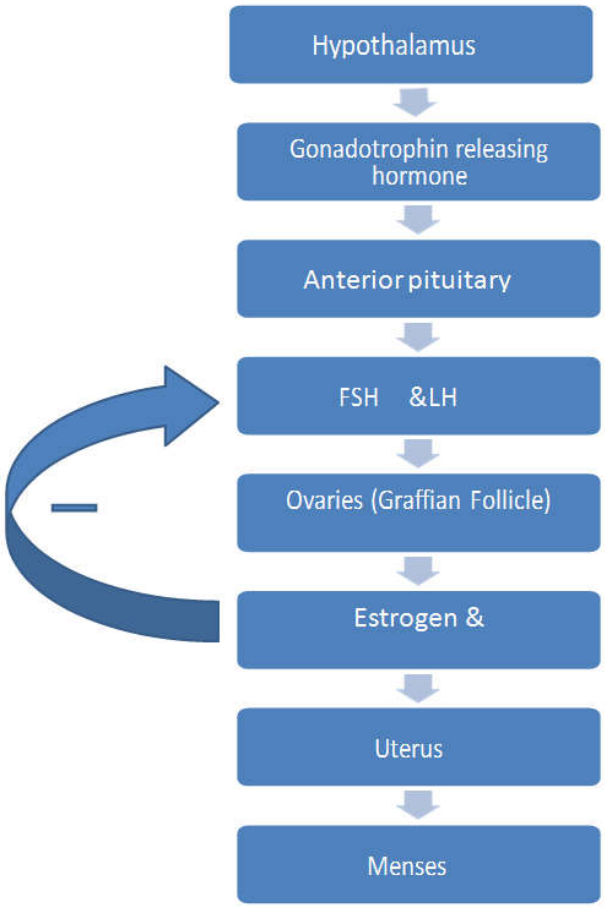
More About Menopause: *Perimenopause or climacteric* refers to the time period preceding menopause when fertility wanes and menstrual cycle irregularity increases until the first year after cessation of menses. It precedes the final menses by 2-8years with a mean duration of 4 years. It is characterized by significant endocrinologic, somatic & psychological alterations. The median age for the onset of climacteric transition is 47.5 years[22].The median age of menopause is 51 years[43]. However it has been observed that menopause occurs at an earlier age in Indian women[38,44]) thus subjecting them to the consequences of menopause at an earlier age compared to women in the industrialized world.

Age at menopause is determined genetically and not by race, socioeconomic status, lifestyle, age at menarche or number of prior ovulations & other health factors[45]. Menopause may ensue earlier in smokers, those with history of radiation exposure or chemotherapy or previous surgery e.g. B/L oophorectomy or even an ovaries sparing hysterectomy[46,47]. Alcohol consumption delays menopause. Oral contraceptive use does not affect age atmenopause.[48]

Premature menopause is defined as menopause occurring before the age of 40 years. It should ideally be defined as menopause occurring at an age less than two standard deviations below the mean estimated age for the reference population. However due to lack of reliable estimates of distribution. of age at natural menopause in developing countries, the age of 40 years is arbitrarily used as the cut-off point[49].

Causes of premature menopause include-[49]
Idiopathic
Radiotherapy orchemotherapy
Chromosomalabnormalities e.g.Turner's syndrome (45X), Klinefelter's syndrome, Fragile Xsyndrome
Viral infections e.g. mumpsoophoritis
Metabolic diseases e.g. galactosemia

Autoimmune disorders e.g. hypothyroidism, Crohn's disease, Systemic Lupus Erythematosus, Addison's disease, autoimmune polyendocrine syndrome type1.



Physiology of Menopause

Figure 1 Normal Hypothalamus-pituitary-ovarian axis

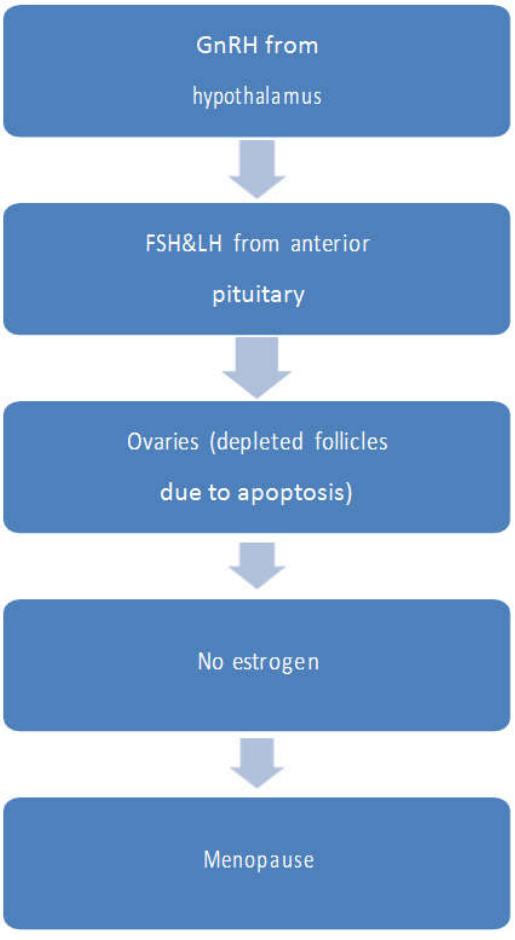


Figure 2 H-P-O axis at menopause

The Hypothalamo-Pituitary-Ovarian axis remains intact during the menopause transition. It is the depletion of ovarian follicles secondary to apoptosis that brings about menopause.

Atresia of the follicular apparatus results in cessation of estrogen, progesterone & inhibin production causing FSH levels to rise due to loss of feedback inhibition. Aromatization of ovarian and adrenal androgens (androstenedione) in the adipose tissue is the only endogenous source of low levels of circulating estrogens in post-menopausal women[(22)]

Diagnosis- complete cessation of menses for 12 months associatedwith serum FSH levels higher than 40 IU/L recorded on two separate occasions(50).

The consequences of menopause are mainly related to estrogen deficiency; absence of progesterone has no effects except for the increased risk for endometrial cancer due to unopposed action of estrogen on the endometrium. It is very difficult to distinguish the consequences of estrogen deficiency from those of aging, as aging & menopause are inextricably linked.

Studying the effects of estrogen deficiency & replacement in young women with ovarian failure may help to distinguish between the effects of aging & estrogen deficiency. In order to understand the effects of menopause we should first know the functions of estrogen.

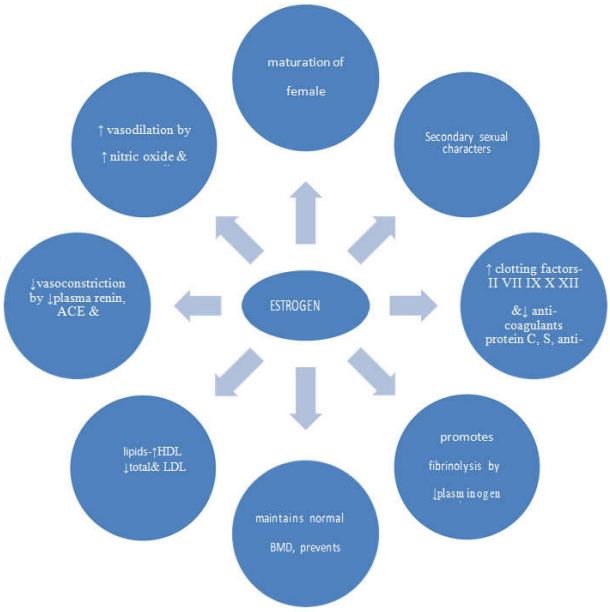


Figure 3 Functions of estrogen

Functions of estrogen-[(51)]

Maturation of the female reproductive tract (vagina, uterus & fallopian tubes) at puberty Development of secondary sexual features viz. breasts (ducts & stroma), moulding of the body contours, pubertal growth spurt of long bones & epiphyseal closure, growth of axillary & pubic hair, pigmentation of the genital region & initiation ofmenses

Lipid profile- it slightly increases triglyceride levels & decreases total cholesterol levels; increases HDL & decreases LDL cholesterol & lipoprotein A levels; thus offering protection against atherosclerosis to premenopausalwomen.

It decreases plasma renin, angiotensin- converting enzyme , endothelin-1 levels & expression of AT1 receptors for angiotensin- II; increases production of nitric oxide

&prostacyclins; all these changes promote vasodilation &retardatherogenesis.

Impairs glucose tolerance; does not affect normal sugars but diabetes may be precipitated or its control vitiated when givenexogenously Prevents resorption of bone by inhibiting the activity & number of osteoclasts & promotes the activity of osteoblasts thus maintaining normal bone mineral density & protecting againstosteoporosis.

Increases synthesis of clotting factors- II, VII, IX, X & XII, increases fibrinolytic activity & decreases the anti-coagulation factors protein C, protein S &antithrombin III. It has also been shown to promote fibrinolysis by decreasing plasminogen activator inhibitor-1 protein. Thus any imbalance between its effect on coagulation & fibrinolytic pathways may cause adverse effects more commonly increased risk of venous thromboembolism.

Increases lithogenicity of bile by elevating the cholesterol: bile salts ratio.

Exogenous estrogen may cause benign hepatomas, precipitate migraine orepilepsy.

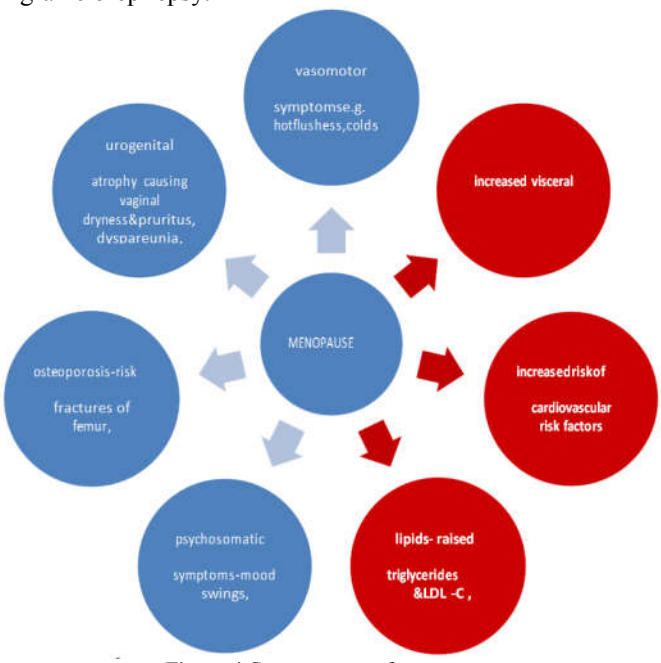


Figure 4 Consequences of menopause

Problems of Menopause

These are mainly due to estrogen deficiency.[22]

- Vasomotor symptoms – Hot flushes, coldsweats
- Urogenital atrophy- vaginal dryness & pruritus, dyspareunia, vulval shrinkage, dysuria, urinaryurgency
- Osteoporosis- owing to decreased bone mineral density & thus increased risk of minimal trauma fractures of femur, radius, hip & vertebrae
- Shift of fat distribution- from gynoid to android pattern resulting in increased visceral adipose tissue
- Thinning, dryness & loss of elasticity of skin
- Psychological- easy fatiguability, irritability, mood swings, depression, loss of libido, anxiety &dementia,insomnia.

Menopausal symptoms experienced by women vary between populations.Ina study on Indian post-menopausal women the most common menopausal symptoms reported in decreasing order of frequency were easy fatiguabilty, lack of energy (70%), cold hands & feet, rheumatology related symptoms (60%), cold sweats, weight gain, irritability & nervousness (50%), palpitations/anxiety (30%)[31].These symptomatic women suffer more from CVD.[78] There is an association of childhood socioeconomic status and coronary artery disease risk among postmenopausal women.

Cardiovascular Diseases

There is an increased risk of atherosclerosis, hypertension, coronary heart disease, heart failure and stroke in postmenopausal women.[79]In India thus there is a high burden of CVD in this population.[80] The risk factors are-

Dyslipidemia-Menopause is characterized by a change in lipid profile from normal to more atherogenic one, with increased levels of total cholesterol, low density lipoprotein cholesterol (LDL-c) and triglycerides & reduced levels of high density lipoprotein cholesterol (HDL-c) In addition to a higher LDL-c, there is a transition in LDL particles to more atherogenic smaller and more dense particles. The altered lipid profile is attributed to loss of protective effect of estrogen aftermenopause[1]. The atherogeniclipid profile further increases risk for cardiovascular diseases.

Yamamoto *et al* in their study of lipids in women reported an increase in levels of total cholesterol & mean lipoprotein(a) levels in post- menopausal women[28]. Other independent studies by Tandon *et al*, Dasgupta *et al* &Sushilkumar *et al* reported an increase in total cholesterol, triglycerides & LDL cholesterol whereas a decrease in HDL cholesterol in post-menopausal women[35,36,37,38].

Physical inactivity- is an established risk factor for cardiovascular disease[7]. Even moderate physical activity of any type e.g. sports, planned exercise, household or yard work, or occupational tasks can confer many health benefits[52].

It has also been proposed that regular physical activity may help to counteract the tendency for weight gain and changes in body composition and fat distribution that accompany aging and the menopausal transition[53].A favorable cardiovascular risk profile in postmenopausal women has been shown to be associated with daily physical activity[54].Also physical activity improves insulin sensitivity thus decreasing the risk of diabetes[55]. Alcohol consumption reduces age of menopause. Further, endothelial dysfunction, a known risk factor for cardiovascular diseases also improves with physical activity[56,57]. It is proposed that the relative physical inactivity may contribute to increased prevalence of cardiovascular risk factors in post-menopausal women.[58]

Obesity- It is a widely accepted belief that menopause is associated with weight gain. However most studies reveal that the increase in BMI after menopause is attributable to normal aging[59]. Thus midlife weight gain is not influenced by the hormonal changes of menopause. The menopause is associated with a selective increase in abdominal obesity, independent of the effect of total body obesity & age confirmed radiologically in few studies.

There are two patterns of body fat distribution observed in humans viz. android & gynoid. Android or apple shaped obesity is characterized by accumulation of fat centrally, as

intra -abdominal fat whereas gynoid or pear shaped obesity is characterized by the accumulation of fat in the gluteo- femoral region. Throughout reproductive life women have a characteristic gynoid pattern of fat distribution under the influence of estrogen.

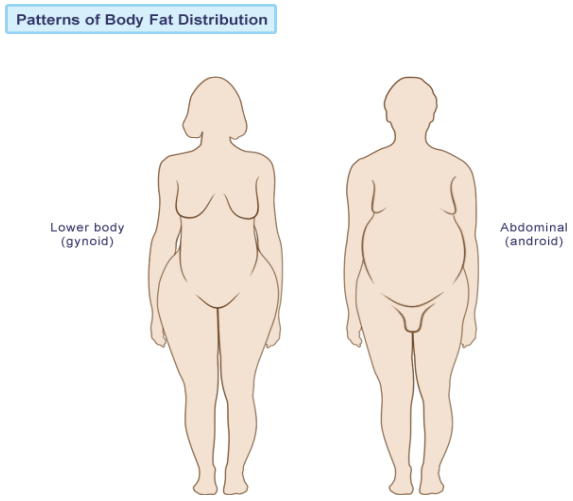


Figure 5 Patterns of fat distribution

Menopause is characterized by a shift from gynoid to android type of fat distribution due to the loss of influence of estrogen[27,28]. In men android type of fat distribution is observed under the effect of endogenous androgens. This gender difference in adipose tissue distribution may partially explain the greater CVD risk in men compared with premenopausal women[60].

Abdominal obesity has emerged as a cardiovascular risk factor independent of overall obesity[61,62]. Android fat deposition is associated with a higher risk of diabetes, dyslipidemia-hypertriglyceridemia, high Apo-lipoprotein B & small dense LDL particles, low HDL-c, hypertension, and CVD such as coronary artery disease & stroke.

Waist circumference represents both subcutaneous and visceral adipose tissue depot size and correlates closely with cardiovascular disease risk. The waist-to hip ratio is another indicator of accumulation of visceral fat which can also be quantitated by CT scanning.

Visceral adipose tissue (VAT) is directly involved in the pathogenesis of metabolic dysfunction. Normally most (85%) FFAs in the portal circulation are derived from subcutaneous adipose tissue, and <20% of total FFAs delivered to the liver or skeletal muscle originate from lipolysis of VAT.

It also releases inflammatory cytokines /adipokines (e.g. Plasminogen activator inhibitor-1, interleukin-6, tumor necrosis factor-α, retinol binding protein-4) & several metabolites including acyl-CoAs, ceramides, and diacyglycerol all of which have been implicated in the development of insulin resistance. Adipose tissue macrophages also contribute to the production of several of the adipokines.[63]

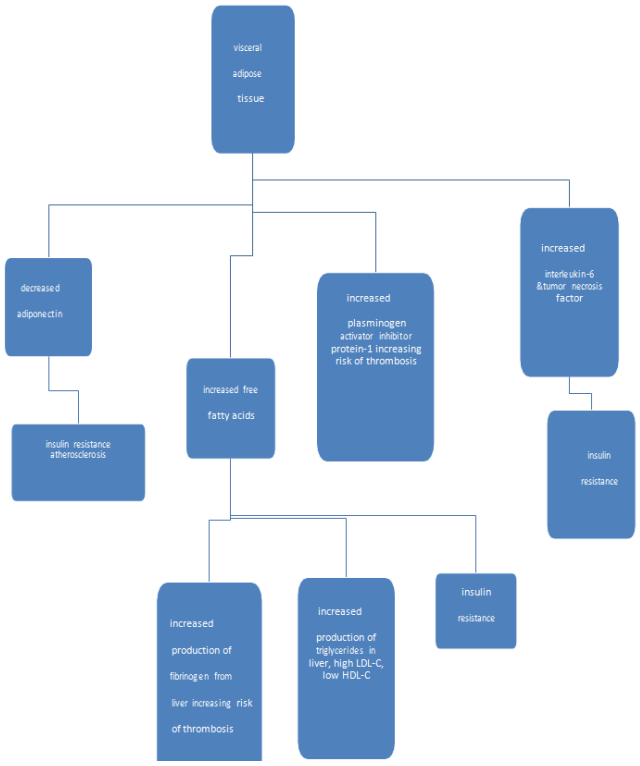


Figure 6 Effects of visceral adiposity

Chronic low grade inflammation secondary to altered adipokine secretion may adversely affect glucose & lipid metabolism & contribute to the increased risk of cardiovascular disease in individuals with visceral obesity[61].

Visceral adiposity has been demonstrated to be inversely related to adiponectin levels[63,,64]. Adiponectin is a protein hormone secreted from adipose tissue that regulates a number of metabolic processes, including glucose metabolism and fatty acid oxidation. It decreases gluconeogenesis, increases glucose uptake, promotes lipid catabolism, β-oxidation & triglycerideclearance, prevents endothelial dysfunction & development of insulin resistance thus protecting against type 2 diabetes, obesity &atherosclerosis. Hypoadiponectinemia is an independent risk factor for the development of metabolic syndrome & diabetes mellitus. Insulin resistance and the compensatory hyperinsulinemia have been demonstrated to be independently associated with cardiovascular diseases, type 2 DM, HTN[63].

Insulin resistance & diabetes mellitus-The shift of fat distribution from gynoid to android pattern & increase in visceral fat leads to development of insulin resistance in post-menopausal women. In a study by Yang W *et al* in China, comparing prevalence of diabetes in men & women it was found that the prevalence was lower in women than in men aged <60 years, whereas higher in women in their 60s and 70s as compared to men of the same age,suggesting that the hormonal changes occurring during menopause might be associated with the risk of diabetes in post-menopausal women[64].thus increased risk of developing type 2 diabetes mellitus. The relative physical inactivity observed in this age group may also contribute to the insulin resistance.[65]Japanese study byHeianza Y *et al*, reported increased prevalence of impaired glucose tolerance after menopause[71]

Endothelial dysfunction-The endothelium is a monolayer of elongated cells lining all blood vessels. It is considered the largest endocrine organ with numerous endocrine, autocrine,

and paracrine effects that are responsible for several regulatoryfunctions[66].

Endothelial functions in health & disease-

Homeostatic properties	Dysfunctional properties
Optimize balance between vasodilation & vasoconstriction	Impaired vasodilation, increased vasoconstriction
Anti-thrombotic, profibrinolytic	Prothrombotic, anti-fibrinolytic
Anti-inflammatory	pro-inflammatory
Anti-smooth muscle proliferation	Pro-proliferative
Anti-oxidant(decreases oxidative stress)	Pro-oxidant
Selective permeability	Impaired barrier function

Vasoregulation-The endothelium releases a number of vasodilatory factors such as nitric oxide, prostacyclin and endothelium-derived hyperpolarizing factor and other vasoconstrictive factors such as endothelin- 1, thromboxane A2, angiotensin-II (through local renin- angiotensin system) and prostaglandin H2. A balance between the dilatory & constrictive factors is responsible for normal vasoregulation. These factors are released in response to local mechanical stimuli (e.g., shear stress), metabolic conditions (e.g., hypoxia), and receptor-mediated agonists (e.g., acetylcholine)[66].

Most important among the relaxing factors is nitric oxide, which is derived from the amino acid L-arginine by the action of nitric oxide synthase. It causes vasodilation locally by activating smooth muscle cell guanylate cyclase, which leads to increased production ofcyclic-GMP[66].Anti-thrombotic function & regulation of fibrinolysis.

Nitric oxide and prostacyclin together prevent platelet adhesion and aggregation thus preventing thrombus formation[67]. The endothelium also plays an important role in regulation of fibrinolysis. There are two principal determinants of fibrinolysis-tissue-type plasminogen activator (t-PA) and urokinase type plasminogen activator(t-PA),which promote fibrinolysis;andPlasminogen activator inhibitor type 1, which inhibits t-PA and u-PA and enhances formation of thrombi. In normal blood vessels, a basal level of t-PA is secreted, which prevents thrombus formation in the absence of vascular injury.[67]

Anti-atherosclerotic function
It inhibits monocyte adhesion, vascular smooth muscle cell growth, and coagulation, all of which are important in atherogenesis and rupture of atheroscleroticplaque[68].

Dysfunctional endothelium-It upregulates chemotactic and adhesion molecules for monocytes and T lymphocytes, and secretes colony-stimulating factors that induce differentiation of monocytes into macrophages, which take up modified cholesterol and produce metabolically active foam cells which take part in formation of atheroscleroticplaque[68].

It promotes platelet aggregation through decreased activity of nitric oxide and promotes coagulation through a decreased ratio of the tissue-type plasminogen activator to the plasminogen activator inhibitor-1[68].

Endothelial dysfunction is an independent risk factor for cardiovascular diseases. It is known to precede atherosclerosis [68]. Endothelial dysfunction in the coronary and brachial arteries correlates with - increasing age, male gender, hypercholesterolemia(total & LDL cholesterol, more importantly oxidized LDL), cigarette smoking, hypertension, diabetes mellitus, high-fat diet, physical inactivity, and family history of premature coronary heart disease &post menopausal status[24]. Menopause acts as a risk factor for endothelial dysfunction.[69,70,72,73,75]

Post- menopausal hypertension-There are many cross-sectional and longitudinal studies which have demonstrated higher prevalence of hypertension in postmenopausal women.[74]

Izumi Y, Matsumoto K, *et al* in their study on postmenopausal women demonstrated that the longer the duration from menopause the greater the risk of developing hypertension thus suggesting a significant contributory role of estrogen deprivation in the risk for hypertension in post-menopausal women[76].

Analyses of the NHANES III and IV studies showed that blood pressure levels were higher in men as compared to age-matched premenopausal women irrespective of ethnicity & that there was a greater prevalence of hypertension in women ≥60 years of age as compared with age-matched men thus suggesting a significant association between post- menopausal status & hypertension[20].

Factors Contributing to Hypertension in postmenopausal women

Endothelial Dysfunction

Post-menopausal status is a risk factor for endothelial dysfunction Endothelial dysfunction is characterized by an imbalance between the endothelium derived vasodilatory& constrictive factors which increases the risk of developing hypertension.

Estrogen acts as a transcription factor for the gene regulating synthesis of the endothelial isoform of nitric oxide synthase (eNOS) thus enhancing activity of endothelial nitric oxide. Impaired endothelium mediated vasodilation measured as decreased flow-mediated dilation (FMD), by high resolution ultrasound correlates well with the risk of developing hypertension. Estrogen also regulates levels and activity of endothelin, a potent endothelium derived vasoconstrictor. Further, plasma endothelin levels have been shown to be increased in postmenopausal women. Hormone therapy in postmenopausal women has been shown to reduce plasma levels of endothelin. Thus decreased activity of nitric oxide coupled with unopposed action of endothelium derived vasoconstrictors, mainly endothelin & oxidative stress contribute to the risk of hypertension in post-menopausal women.

Oxidative Stress

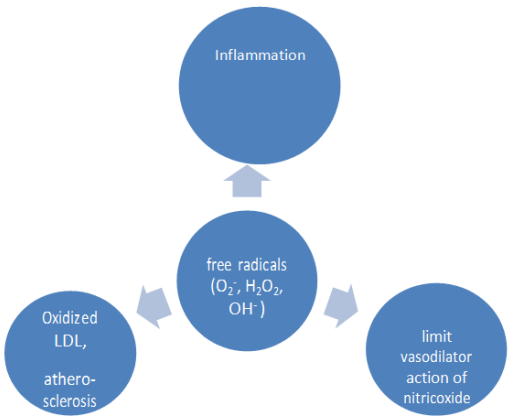


Figure 7 Effects of oxidative stress

An increase in oxidative stress can result from increased production of reactive oxygen species(ROS) viz. hydroxyl radical(OH^-), hydrogen peroxide(H_2O_2), superoxide(O_2^-) or decreased ability to neutralize these reactive molecules by anti-oxidant enzymes such as superoxide dismutase, glutathione reductase & catalase.

Estrogens have antioxidant activity. It is postulated that there is increased oxidative stress during postmenopausal period due to estrogen deficiency thus contributing to vasoconstriction and hypertension.

Renin- Angiotensinsystem

In animal studies, it has been found that 17β-estradiol prevents some of the vasoconstrictor effects of the renin-angiotensin system via reduced expression of angiotensin AT1 receptors in vessels & kidneys & also reduces plasma angiotensin-converting enzyme activity as well as circulating levels of angiotensin II. Menopause is characterized by loss of this protection. In a study, serial measurement of Plasma Renin Activity(PRA) for 9 years in men & women, showed that PRA was higher in postmenopausal women than premenopausal women. However there are a few studies which do not show any correlation between estrogen & plasma renin activity whereas others which show decreased ACE activity with

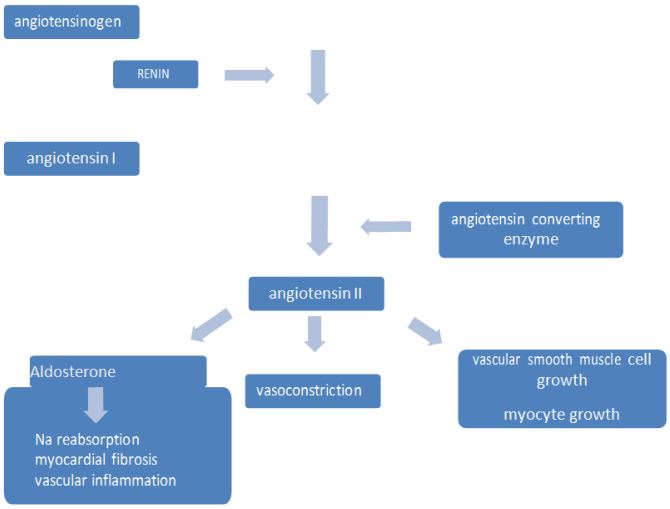


Fig 8 The Renin-Angiotensin System

Angiotensin II also stimulates synthesis of preproendothelin& additionally produces oxidative stress too. Thus, activation of the RAS may cause increase in blood pressure directly or indirectly by stimulating endothelin synthesis and oxidative stress. Menopause is associated with increased RASactivity.

Effects of estrogen on the immunesystem

After various studies, immune system activation and inflammation are now implicated in the pathogenesis of hypertension. Estrogen is a known immunomodulator with both pro & anti-inflammatory actions. Estrogen can promote B-cell activation, leading to increased antibody production (humoral immunity.[70] It is proposed that estrogen deficiency during post-menopausal state leads to inflammatory processes which contribute to the development of hypertension in post-menopausal women.

Salt Sensitivity

Salt sensitivity is known to increase with age in both sexes. It is probably mediated by impaired vasodilation of the renal circulation, secondary to reduced nitric oxide availability, increased vasoconstriction response to angiotensin II.Increased salt sensitivity is associated with an increased risk for development of hypertension and cardiovasculardiseases.

A balance between the counteracting effects of nitric oxide (NO) and angiotensin (Ang) II on pressure natriuresis, renal hemodynamics, tubular sodium reabsorption and oxidative stress determines salt sensitivity as well as hypertensive end-organ injury. Estrogens regulate the activity and expressionof NO and Ang II·It has been demonstrated that salt sensitivity increases in postmenopausal women & this increase was found to be independent of age. Estrogen therapy in post-menopausal women was found to be associated with a decrease in saltsensitivity[71].

6. Increased activity of Sympathetic nervoussystem

The shift of fat distribution from gynoid to android pattern & increase in visceral fat leads to development of insulin resistance in post-menopausal women & thus increased risk of developing type 2 diabetes mellitus**.** Insulin resistance is associated with hyperinsulinemia. Insulin has a stimulatory effect on the sympathetic nervous system probably through its actions on the arcuate nucleus.

Leptin a peptide released from adipose tissue acts on receptors in the arcuate nucleus of the hypothalamus inhibiting hunger and is commonly referred to as-the satiety hormone. Its level of production providesan index of adipose energy stores. High leptin levels decrease appetite, increase energy expenditure & enhance insulin sensitivity. In addition, leptin may regulate cardiac and vascular function through a nitric oxide–dependent mechanism. However, when obesity develops especially visceral adiposity, hyperleptinemia ensues, with evidence of leptin resistance in the brain and other tissues resulting in inflammation, insulin resistance, hyperlipidemia and a plethora of cardiovascular disorders such as hypertension, atherosclerosis, CHD, and heart failure·

Various studies suggest that leptin also stimulates the sympathetic nervous system[72]. Increased activity of the sympathetic nervous system further increases the risk of hypertension. The increase in VAT associated with menopause may induce leptin resistance & thus its complications.

Hypothyroidism-The incidence of hypothyroidism has been observed to increase with age (after 40- 50yrs of age) in females. High circulating levels of anti- thyroid antibodies have been implicated in the higher incidence of hypothyroidism[77]. The symptoms associated with hypothyroidism are very similar to the symptoms of normal aging & menopause. Thus the diagnosis of hypothyroidism may be missed due to overlapping symptoms. Hypothyroidism is associated with an increased risk of impaired endothelial function, depressed systolic function, left ventricular diastolic dysfunction at rest, and systolic and diastolic dysfunction on effort, which may compromise effort tolerance. Increased systemic vascular resistance leads to increased diastolic blood pressure thus increasing the risk for hypertension. There is also a change in lipid profile from normal to more atherogenic one in hypothyroidism[77].Thus hypothyroidism (clinical & subclinical) acts as a risk factor for cardiovascular diseases & its occurence in females timed around menopause may subject them to additional CVD risk.

Key Points

There is clustering of cardiometabolic risk factors like physical inactivity, obesity, poor dietary factors, hypertension, insulin resistance, diabetes, dyslipidemia, & hypothyroidism in postmenopausal women, which has major impact on development of cardiovascular disease s(CVD) like hypertension, coronaryarterydisease, stroke & heart failure.

Menopause is actually another independent risk factor. Most of the effects are due to deficiency of estrogen making these women vulnerable to the hazards of CVD. Aging and these risk factors add to the burden of CVD.

Menopause is associated with emergence of metabolic syndrome characterised by central visceral obesity, shift towards atherogenic lipid profile, high BP& glucose intolerance with endothelial dysfunction leading to coronary artery disease.

Women often have casual approach towards their health. They delay in seeking medical advice, lack of knowledge & societal attitudes leads to poorer outcomes, longer hospital stay which increases their cardiovascular mortality by 3-7 fold.

Most of the risk factors are modifiable. Regular screening can help in early detection & proper treatment.

CONCLUSIONS

There increased risk of cardiometabolic risk factors in postmenopausal women. This finding is supported by many previous studies done worldwide in women of different race & ethnicity. The shift of fat distribution from gynoid to android pattern, atherogenic lipid profile, and endothelial dysfunction, increased activity of sympathetic nervous system & renin angiotensin system associated with menopause predisposes this population to the risk of developing cardiometabolic risk factors & thus CVD related morbidity &mortality. Also, the relative physical inactivity in this age group may contribute to the CVD risk further thus emphasizing the need for lifestyle modifications too.

Hence it is essential to screen post-menopausal women for cardiometabolic risk factors irrespective of presence of symptoms; this will facilitate early detection of these risk factors & timely intervention which may help us in minimising CVD related morbidity & mortality in this population. Further, it is necessary to bring about awareness regarding menopause & related health problems in postmenopausal women which may change their attitudes & make them realize the importance for early health screening & seeking timely medical help whenever necessary.

References

1. Carr MC. The emergence of the metabolic syndrome withmenopause.J ClinEndocrinolMetab. 2003; 88:2404–2411.
2. Institute of Medicine. Fuster V, Kelly BB, editors. Promoting cardiovascular health in developing world: a critical challenge to achieve global health. Washington, DC: National Academies Press; 2010.
3. World Health Organization. Global Status Report on non- communicable diseases 2014. Geneva: World Health Organization; 2014.Available from: http://www.who.int/nmh/publications/ncd-status-report-2014/en/
4. Gupta R. Coronary heart disease in India: From epidemiology to action. Fortis Medical J.2009;2:9–18.
5. Gaziano TA, Gaziano JM. Epidemiology of cardiovascular disease.Kasper DL, Hauser SL, Jameson JL, editors. Harrison's principles of internal medicine, 19th ed. New York: McGraw Hill, 2016; p. 266e1–266e5.
6. World Health Organization. Non-communicable diseases country profiles. Geneva: World Health Organization; 2014. Available from: http://www.who.int/nmh/publications/ncd-profiles-2014/en
7. Yusuf S, Hawken S, Ounpuu S, *et al*. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364:937–952.
8. Gupta R, Guptha S, Sharma KK, Gupta A, *et al*. Regional variations in cardiovascular risk factors in India: India Heart Watch. World J Cardiol. 2012; 4:112–120.
9. Joshi P, Islam S, Pais P, *et al*. Risk factors for early myocardial infarction in south Asians compared with individuals in other countries. JAMA.2007;297:286–94.
10. Chandalia M, Abate N, Garg A, *et al*. Relationship between generalized and upper body obesity to insulin resistance in Asian Indian men. J ClinEndocrinolMetab. 1999; 84:2329–2335.
11. Forouhi NG, Sattar N. CVD risk factors and ethnicity – a homogeneous relationship? Atheroscler.2006;7(1):9-11.
12. Prabhakaran D, Jeemon P, Roy A. Cardiovascular diseases in India current epidemiology and future directions. Circulation. 2016; 133:1605-1620.
13. Blauwet LA, Redberg RF. The role of sex-specific results reporting in cardiovascular disease. Cardiology in Review. 2007;15(6):275–278.
14. Jackson G. Gender differences in cardiovascular diseaseprevention. Menopause International. 2008; 14(1):13–17.
15. Lawlor DA, Ebrahim S, Davey SG. Sex matters: Secular and geographical trends in sex differences in coronary heart disease mortality. BMJ. 2001;323(7312):541–545.
16. Allen J, Szanton S. Gender, ethnicity and cardiovascular disease. J CardiovascNurs. 2005;20(1):1–6.
17. Pilote L, Dasgupta K, *et al*. A comprehensive view of sex-specific issues related to cardiovascular disease. CMAJ. 2007; 176(6):S1– S44.
18. Lori M, *et al*. Cardiovascular disease in women.Circulation.1997;96:2468-2482.
19. Anand SS, Islam S, *et al*. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. Eur Heart J. 2008;29(7):932–940.
20. Go AS, Mozaffarian D, Roger VL, *et al*. Heart disease and stroke statistics – 2013 update: a report from the American Heart Association. Circulation.2013;127:e6–e24.
21. Regitz-Zagrosek V. Therapeutic implications of the gender-specific aspects of cardiovascular disease. Nat Rev Drug Discov. 2006; 5(5):425–438.

22. RoetersvanLJE,WesterveldHT,ErkelensDW,etal.Riskfa ctorsforCoronary heart disease: Implications of gender. Cardiovascular Research. 2002;53 (3):538–549.
23. Poehlman ET, Toth MJ, Gardner AW. Changes in energy balance and body composition at menopause: a controlled longitudinal study. Ann Intern Med. 1995;123:673–675.
24. Van der LJ, Annemarie M. *et al*. Age-related differences in abdominal fat distribution in premenopausal and postmenopausal women with cardiovascular disease. Menopause.2013; 20(4): 409–417.
25. WHO. Research on the menopause. WHO technical report series866.Geneva: World Health Organisation; 1996. Availablefrom:http://apps.who.int/iris/bitstream/10665/41841/1/WHO_TRS_866.pdf
26. Mendelsohn ME, Karas RH. The protective effects of estrogen on cardiovascular system. N Engl J Med. 1999; 340:1801–11.
27. Taddei S, Virdis A, Ghiadoni L, *et al*. Menopause is associated with endothelial dysfunction in women. Hypertension. 1996;28:576–582.
28. Yamamoto A, Horibe H, Mabuchi H, *et al*. Analysis of serum lipid levels in Japanese men and women according to B.M.I Increase in risk of atherosclerosis in postmenopausal women. Research group on serum survey. Atherosclerosis.1999;143(1):55–73.
29. Tchern of A, Calles-Escandon J, Sites CK, Poehlman ET. Menopause, central body fatnessandinsulinresistance; effects of hormone replacement therapy. Coronary A disease. 1998;9(8):503–11.
30. Florence A, Tremollieres, *et al*. Coronary heart disease risk factors and menopause: a study in 1684 French women. Atherosclerosis. 1999;142(2):415–23.
31. Rosano GM, Vitale C, Marazzi G, Volterrani M. Menopause and cardiovascular disease: The evidence. Climacteric.2007;10:19–24.
32. WHO.Global burden of disease 2004 data.Genevaq: World health organization;2004. Available from :http://www.whoint/healthinfo/global_burden_disease/GBD_report_2004update_fullpdf
33. Sharma S,Bakshi R,Tandon VR,Mahajan A .Menopause and cardiovascular diseas.JK Sci.2008;10:1-2.
34. Sharma S, Bakshi R, Tandon VR, Mahajan A. Postmenopasual obesity. JK Sci.2008;10:105–6.
35. Tandon VR, Mahajan A, Sharma S, Sharma A. Prevalence of cardiovascular risk factors in postmenopausal women: A rural study. J Midlife Health. 2010; 1(1):26–29.
36. Dosi R, Bhatt N, Shah P, Patel R. Cardiovascular disease and menopause. J ClinDiagn Res. 2014; 8(2):62–64.
37. Dasgupta S, Salman M, Lokesh S, D Xaviour, S YaseenSaheb, BV Ravi Prasad, Biswanath Sarkar. Menopause versus aging: The predictor of obesity and metabolic aberrations among menopausal women of Karnataka, South India. *J Midlife Health*. 2012; 3(1):24–30.
38. Kumar S, Shah C, Oommen ER. Study of cardiovascular risk factors in pre and postmenopausal women. IJPSR. 2012;3(12):560-570.
39. Chandiok K, Joshi S, Mondal PR. Menopausal status and cardiometabolic risk: A cross sectional study from Haryana state, India. Hum Biol Rev. 2016; 5(1):104-116.
40. Lee JS, Hayashi K, Mishra G, *et al*. Independent association between age at natural menopause and hypercholesterolemia, hypertension, and diabetes mellitus: Japan nurses‘ health study. J Atheroscler Thromb.2013;20:161–169.
41. Pearson JD, Morrell CH, Brant LJ, *et al*. Age-associated changes in blood pressure in a longitudinal study of healthy men and women. J GerontolABiolSci Med Sci.1997;52:M177–183.
42. Jean C, McSweeney, Marisue C, *et al*. Women‘s early warning symptoms of acute myocardial infarction. Circulation. 2003;108:2619- 2623.
43. Singh A, Kaur S, WaliaI. A historical perspective on menopause and menopausal age. Bull Indian InstHist Med Hyderabad. 2002;32(2):121-35.
44. Avis, Stellato *et al*. Is there a menopausal syndrome? Menopausal status & symptoms across racial/ethnic group. SocSci Med. 2001;52(3):345 – 356.
45. Marshal. The physiology of reproduction. JAMA.1911;LVI(7):533.
46. Bayliss WM, Starling EH. The mechanism of pancreatic secretion.JPhysiol. (1902);28 (5): 325–53.
47. Levin ER, Hammes SR. Estrogens and progestins. Ch. 40 in: Brunton L, Chabner B, Knollmann B editors. Goodman and Gilman‘s the pharmacological basis of therapeutics, 12th ed. New York: McGraw Hill, 2011; p.1060-66.
48. Herrington DM. Hormone replacement therapy and heartdisease. Circulation. 2003;107:2-4.
49. Furman RH. Coronary heart disease and the menopause. In: Ryan KJ, Gibson DC, editors. Menopause and aging: summary report and selected papers from a research conference on menopause and aging. Washington, DC: United States Government Printing Office, 1973; p.39-55.
50. WHO. Research on the menopause. WHO technical report series670.Geneva: World Health Organisation; 1981. Available from:http://apps.who.int/iris/bitstream/10665/41526/1/WHO_TRS_670. pdf
51. Gordon T, KannelWB, *et al*. Menopause and coronary heart disease, The Framingham Study. Ann Intern Med. 1978;89(2):157-61.
52. Kato I, Toniolo P, Akhmedkhanov A, *et al*. Prospective study of factors influencing the onset of natural menopause. J ClinEpidemiol. 1998; 51(12):1271–1276.
53. 53.Singh M. Early age of natural menopause in India, a biological marker for early preventive health programs. Climacteric.2012;15(6):581–86.
54. Gold EB, Crawford SL, Avis NE, *et al*. Factors related to age at natural menopause: longitudinal analyses from SWAN. Am J Epidemiol. 2013; 178:70–83.
55. McKinlay SM, Bifano NL, McKinlay JB. Smoking & age at menopause in women. Ann Intern Med. 1985; 103(3): 350 –356.
56. Wallace WH, Shalet SM, Crowne EC, *et al*. Ovarian failure following abdominal irradiation in childhood: natural history & prognosis. ClinOncol(R CollRadiol). 1989;1(2):75-79.

57. Bines J, Oleske DM, Cobleighet MA. Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. J ClinOncol. 1996;14(5):1718-1729.
58. Zikovic TB,VuksanovicM, Jelic MA, *et al*. Obesity and metabolic syndrome during the menopausetransition in Serbian women. Climacteric. 2011; 14:643–648.
59. Kohl HW 3rd. Physical activity and cardiovascular disease: evidence for a dose response. Med Sci Sports Exerc. 2001;33(6 Suppl):S472– 483.
60. Sternfeld B, Bhat AK, Wang H, *et al*. Menopause, physical activity, and body composition/fat distribution in midlife women. Med Sci Sports Exerc.2005;37:1195-1202.
61. Colpani V, Oppermann K, Spritzer PM. Association between habitual physical activity and lower cardiovascular risk in premenopausal, perimenopausal and postmenopausal women: a population-based study. Menopause. 2013; 20:525–531.
62. Joen CY, Lokken RP, Hu FB, van Dam RM. Physical activity of moderate intensity and risk of type 2 diabetes: a systematic review. Diabetes Care. 2007;30:744–752.
63. Harvey PJ, Picton PE, Su WS, *et al*. Exercise as an alternative to oral estrogen for amelioration of endothelial dysfunction in postmenopausal women. Am Heart J.2005;149:291-7.
64. Crawford SL, Casey VA, Avis NE, McKinlay SM. A longitudinal study of weight and the menopause transition: results from the Massachusetts women's health study. Menopause. 2000; 7:96–104.
65. Sutton-Tyrrell K, Zhao X, Santoro N, *et al*. Reproductive hormones and obesity: 9 years of observation from the study of women's health across the nation (SWAN). Am J Epidemiol. 2010; 171:1203 – 13.
66. Toth MJ, Tchernof A, Sites CK, Poehlman ET. Effect of menopausal status on body composition and abdominal fat distribution. Int J ObesRelatMetabDisord. 2000;24:226–231.
67. KrotkiewskiM, Bjorntorp P, Sjostrom L, Smith U. Impact of obesity on metabolism in men and women: importance of regional adipose tissue distribution. J Clin Invest. 1983;72:1150–1162.
68. KannelWB, Cupples LA, Ramaswami R, *et al*. Regional obesity and risk of cardiovascular disease; the Framingham Study. J ClinEpidemiol. 1991; 44:183–190.
69. Ferrante AW Jr. Obesity induced inflammation: a metabolic dialogue in the language of inflammation. J Intern Med. 2007; 262(4):408-414.
70. Kim HM, Park J, Ryu SY, Kim J. The effect of menopause on the metabolic syndrome among Korean women: the Korean national health and nutrition examination survey. Diabetes Care. 2007; 30:701–706.
71. Heianza Y, Arase Y, Kodama S, *et al*. Effect of postmenopausal status and age at menopause on type 2 diabetes and prediabetesinJapanese individuals. Diabetes Care. 2013; 36(12): 4007–4014.
72. Vane JR, Anggard EE, Botting RM. Regulatory functions of the vascular endothelium. N Engl J Med. 1990; 323:27-36.
73. Sherman D, Loscalzo J. Endothelial dysfunction and cardiovascular disease. Cardiologia. 1997; 42:177–87.
74. Zanchetti A, Facchetti R, Gesana GC, *et al*. Menopause-related blood pressure increase and its relationship to age and body mass index: the SIMONA epidemiological study. J Hypertens. 2005; 23:2269–2276.
75. Poehlman ET, Toth MJ, Ades PA, Rosen CJ. Menopause-associated changes in plasma lipids, insulin-like growth factor 1 and blood pressure: a longitudinal study. Eur J Clin Invest. 1997;27:322–326.
76. Izumi Y, Matsumoto K. Effect of age at menopause on blood pressure in postmenopausal women. Am J Hypertens. 2007; 20(10):1045-50.
77. Biondi B, Klein I. Hypothyroidism as a risk factor for cardiovascular disease. Endocrine. 2004;24(1):1-13.
78. Cagnacci A, CannolettaM, Palma F, *et al*. Menopausal symptoms and risk factors for cardiovascular disease in postmenopause. Climacteric. 2012;15(2):157–162.
79. Giampaoli S, Panico S, Meli P, *et al*. Cardiovascular risk factors in women in menopause. Ital Heart J Suppl.2000;1(9):1180–1187.
80. Lawlor DA, Davey Smith G, Ebrahim S. Association between childhood socioeconomic status and coronary heart disease risk among postmenopausal women: Findings from the British women's heart and health study. Am J Public Health. 2004;94(8):1386–1392.
81. Das J,Sharma JD, Mazumdar S,*et al*.Dyalipidemia in postmenopausal women: A case control study. Chhatragram Maa-O- Shishu Hosp Med College. J 2013; 12(2):7-12.
82. Hamad F,Dahhan A,Lamia F, Naama M AI, Disher A.Lipid profile and postmenopausal status. Al-Kindy col Med J.2008;4(1):8-12.
83. La H,Pa C,Morocho N, Alvarado M,Chavez D, Huc A. The metabolic syndrome among postmenopausal women in Eucador. Gynecol Endocrinol. 2006; 22(8)447-54.
84. Bulliyya G.Risk of coronary heart disease in women after menopause. J Indian Med Assoc.2001;99(9):478-82,48

****