Menopause is a universal and irreversible part of the overall aging process which involves a woman's reproductive system. Menopause results from loss of ovarian sensitivity to gonadotropin stimulation, which is directly related to follicular decline and dysfunction causing decrease in estrogen level. Coronary artery disease is the leading cause of morbidity and mortality in men and postmenopausal women. Menopausal status increases the cardiovascular risk for women independent of age whereas natural menopause not causes an immediate increase in risk of heart disease. Cardiovascular risk factors changes occurring with menopause have been considered the biological mechanism. The risk-factor prevalence increases with advancing age and varies widely by country. Deprivation of endogenous estrogen is assumed to be a crucial factor in the increasing cardiovascular risk. Interaction of high blood pressure with other risk factors is particularly important in case of postmenopausal women. Several studies have demonstrated that lipid concentrations, body weight, blood pressure, and insulin resistance increase after menopause which may impair endothelial functions. The state of "endothelial activation," is characterized by a proinflammatory, proliferative, and procoagulatory status that favours atherogenesis. Both inflammatory processes and a disturbed lipid profile may mediate the development and progression of atherosclerosis. We focused on the relationship between hormonal status and cardiovascular risk assessed by inflammatory markers and traditional laboratory variables in women during postmenopausal status.

Keywords: Postmenopause, Coronary Artery Disease (CAD), CAD Risk Factors, CAD Biomarkers.

INTRODUCTION

Menopause is best defined as the absence of menses for twelve consecutive months. It is a physiologic phase of a woman’s life, which is due to the loss of ovarian function with subsequent deficiency of estrogen and is able to influence the quality of life of women. It is clear that coronary artery disease (CAD) incidence and prevalence are higher in postmenopausal compared to premenopausal women and impaired endothelial function predicts the development of atherosclerosis. Hence, we planned to analyze the various associated mechanisms and association between various available and prospective markers in relation to postmenopausal CAD risk.

Epidemiology of Menopause

In the developed world, mean life expectancy for women since 1900 has increased from 50.0 to 81.7 years. The average age at menopause is 51.4 years, thus women in developed countries live over one-third of their lives in the postmenopausal state. Life expectancy for women at age 50 years are quite similar throughout the world (range 27 to 32 years). Global population projections predict a marked increase in the number of postmenopausal women from 467 million in 1990 to 1,200 million in 2030. Coronary artery disease (CAD) is rare in premenopausal women but becomes increasingly prevalent after menopause. Premenopausal women have 66% lower risk of stroke and 33% lower risk of sudden cardiac death than males of comparable age and the risk increases and becomes equal to males after menopause.

Physiological Mechanisms

The postmenopausal status involves various mechanisms to increase coronary artery disease risk. Cessation of ovarian function and sex hormone deficiency are associated with metabolic disorders that increase the risk of cardiovascular disease. Estrogen exerts its vasodilator action due to nitric oxide release, calcium-antagonist like action and a smooth muscle antiproliferative effect, due to various sex steroid receptors present on arterial endothelium. The abrupt interruption of estrogen has indirect effects on lipid, carbohydrate metabolism and direct effects on vessel function. A common polymorphism in the estrogen receptor alpha has been associated with earlier onset of menopause, as has the Factor V Leiden mutation. Earlier studies on animal and human document an association between environmental psychological stress and functional hypothalamic amenorrhea. Additional factors identified for functional hypothalamic amenorrhea in humans include intense physical exercise, anorexia, bulimia, and weight loss. Biologic mechanisms linking these various forms of stress, both physical and psychological, with functional hypothalamic amenorrhea may include corticotrophin-releasing hormone (CRH) suppression of gonadotropin-releasing hormone-producing neurons in the central nervous system, resulting in impaired folliculogenesis in the ovary.
Cardiovascular Risk and Menopause

Menopause increases the risk for women independent of age. Prior to menopause, the risk of CAD for women lags behind the risk for men by approximately 10 years. After menopause, women have similar risks of CAD as men of the same age. According to the "response-to-injury" model of atherogenesis, various factors, which include hemodynamic forces and chemical agents, induce dysfunctional alterations in the overlying endothelium. This injury is then followed by the aggregation of platelets, oxidized lipids, and smooth muscle cells in the intimal layer and eventual formation of plaques. The Framingham study was pivotal in showing the relationship between menopause and increased cardiovascular mortality rate.

Controversy exists about whether menopause increases the risk of cardiovascular disease (CVD) independent of normal aging. Some studies have demonstrated increased risk of CVD after menopause, and others have not. The large-scale primary (Women's Health Initiative) and secondary (Heart and Estrogen-Progestin Replacement Study) prevention trials assessing the effect of hormonal replacement therapy on cardiovascular events could not show a positive effect. Kok et al. suggested that it is not menopause that adversely affects cardiovascular risk but rather that cardiovascular risk factors determine the age at menopause, possibly by inducing ischemic damage in the ovaries or through direct effects on the endocrine system. They found early menopause was associated with increase in cholesterol and blood pressure. Improvements in cholesterol and systolic blood pressure were associated with a later menopause.

Metabolic Syndrome

Postmenopausal status is associated with a 60% increased risk of the metabolic syndrome, even after adjusting for confounding variables, such as age, body mass index (BMI), household income, and physical inactivity. Markers of impaired fibrinolysis [plasminogen activator inhibitors (PAI-1) and tissue plasminogen activators (tPA)] and systemic inflammation [C-reactive protein (CRP) and interleukin-6 (IL-6)], are also associated with the metabolic syndrome and appear to play a role in the pathogenesis of cardiovascular disease.

One of the most important pathophysiological components of the metabolic syndrome is insulin resistance. Insulin resistance, with inadequate compensatory hyperinsulinemia, diminishes the normal suppression of FFA arising from adipose tissue by insulin. The increased levels of FFA may impair peripheral glucose uptake, increase hepatic glucoseogenesis, and reduce hepatic clearance of insulin. Whether menopause is associated with increased insulin resistance is not clear. Several groups have shown increased fasting insulin and fasting glucose levels in postmenopausal compared with premenopausal women, which would imply worsened insulin resistance with the menopause. Lindheim et al. showed reduced insulin sensitivity (i.e. higher insulin resistance) in postmenopausal women compared with BMI-matched premenopausal women. However, others have shown no differences in insulin sensitivity in postmenopausal compared with premenopausal women.

Dyslipidemia

During the perimenopausal and early postmenopausal period, the differential determinants of risk factor change, with reduced estradiol levels, weight gain, increased waist circumference. Analysis by Claire et al. showed that total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B, triglycerides (TG), systolic blood pressure and fibrinogen were significantly higher in postmenopausal women compared to premenopausal women even after controlling for the effects of confounding variables (age, body mass index and smoking status). The plasma concentrations of cholesterol and of its main component, LDL cholesterol (total cholesterol> 250 mg/dl, LDL > 160 mg/dl or if the patient was on lipid-lowering therapy), are established risk factors for the incidence of atherosclerotic vascular complications. High density lipoprotein (HDL) cholesterol, diastolic blood pressure and blood glucose did not change with menopausal status.

In another study, bilateral oophorectomy causes a marked reduction in estrogen production and has been associated with increased CHD risk. These findings support the hypothesis that endogenous estrogens affect risk factors of CHD, including plasma lipid and lipoprotein levels.

VARIOUS RISK FACTORS AND PATHOPHYSIOLOGICAL MECHANISMS LEADING TO INCREASE CAD RISK IN POSTMENOPAUSAL WOMEN

Evaluation of CAD in premenopausal women has been overlooked, despite its being the leading killer of women in this age group, outpacing even breast cancer. CAD is found to be a multifactorial disease and it is clear that no single common pathway is likely to account for all cardiovascular events.

Obesity

Obesity and adipose tissue redistribution is another leading problem in postmenopausal women. Obesity is considered as a risk factor for CAD because of its influence on glycemic metabolism, insulin resistance, blood pressure and lipid profile. The direct relationship was stressed between body weight and all cause morbidity and mortality. A low-level chronic inflammatory state is highly associated with obesity-related disorders. Guthrie et al. reported that weight gain had a stronger influence on the development of impaired fasting glucose than menopause itself.

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Diabetes
Diabetes (positive past history of diabetes and new diabetics, fasting plasma glucose ≥126 mg/dl or two hours after glucose load ≥200 mg/dl) is the most important risk factor in women, much higher than in men. It is a well-known cause of endothelial dysfunction, vascular calcification, micro and macro-angiopathy. It may cause microvascular complications with a consequent progressive silent ischemic heart disease and diastolic failure, which is typical of elderly women.25. Menstrual irregularities are also predictive of future diabetes and may be a marker for polycystic ovary syndrome.26.

Hypertension
The hypertension (positive past history of hypertension and new hypertensives, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, based on the average of two or more readings on two or more occasions after initial screening) is considered as a risk factor, which increases the risk of reversible or non-reversible damage in defined target organ of hypertension such as left ventricular hypertrophy. It is particularly important in postmenopausal women.27.

Endothelial Dysfunction
Endothelial dysfunction which is characterized by a reduced bioavailability of vasodilators, in particular, nitric oxide (NO), whereas endothelium-derived contracting factors (eg, tPA and PAI-1) are increased, represent a key early step in the development of atherosclerosis and plaque progression.28. In addition, platelet-derived mediators, such as serotonin, induce vasoconstriction in the presence of a dysfunctional endothelium and endothelin-1.

Endothelin-1 concentrations are found to be elevated in the plasma of patients with early and advanced atherosclerosis.29. Hemodynamic forces such as shear stress may influence local endothelial homeostasis which indicates variable endothelial susceptibility and points the importance of other factors, including genetic predisposition. Thus endothelial dysfunction could potentially be used as a surrogate marker for cardiovascular disease risk in study of risk reduction therapies.30.

Oxidative Stress
The increased oxidative stress is considered a major mechanism and may serve as a common pathogenic mechanism of the effect of risk factors on the endothelium. The risk factors that are related to atherosclerosis and cardiovascular morbidity are associated with overproduction of reactive oxygen species or increased oxidative stress. By reacting with NO, reactive oxygen species may reduce vascular NO bioavailability and promote cellular damage.31.

Reactive oxygen species have been shown to activate matrix metalloproteinases, which may lead to plaque instability and rupture. Accordingly, endothelial dysfunction is partially reversed by administration of several structurally unrelated antioxidants, including superoxide dismutase, probucol, vitamin C, and glutathione.32.

Other Factors
The apparent increase in CAD risk among women with premature natural menopause seems to be secondary to confounding by smoking (Regularly using tobacco for the last 6 months) and various other factors.33.

The family history of CAD is also included as a major traditional or classical risk factor. It includes one or more family member, including parents, brothers and sisters, with documented CAD.34.

predictors of coronary artery disease extent
Coronary risk in postmenopausal women can be assessed by different tests and profile according to various mechanisms involved to cause CAD risk. It includes:

Lipid Profile
Lipoprotein subclass levels may improve the prediction of coronary artery disease (CAD) in individuals beyond the risk assessment provided by conventional enzymatically determined lipid levels. Miller et al demonstrated a significant association with HDL2 (but not of HDL3) whereas Dexel et al shown a significant association of CAD extent with both HDL2 and HDL3 cholesterol. They demonstrated the strong and independent relation of three fractions of blood cholesterol (LDL cholesterol, HDL2 cholesterol, and HDL3 cholesterol) as well as plasma triglycerides with angiographic extent of coronary atherosclerosis. The mechanism by which HDL prevents atherosclerosis is reverse cholesterol transport. Secondly, HDL prevents the oxidative modification of low density lipoprotein (LDL) and its deposition into arterial wall.35.

The LDL cholesterol is found to be a strong predictor of atherosclerosis. This “LDL cholesterol” represents the non-HDL, non-VLDL fraction of plasma cholesterol and thus includes cholesterol of intermediate-density lipoproteins (IDL) (density range, 1.006 to 1.019 g/ml) besides the cholesterol of true LDL particles (density range, 1.019 to 1.063 g/ml). The IDL particles are considered particularly atherogenic because it was found that the plasma concentration of IDL particles is strongly predictive of the progression of coronary atherosclerosis. Further, Lp(a), an LDL particle with the apo(a) protein attached by a disulfide bridge, is found to be elevated in approximately one third of CAD patients. Lp(a) is particularly important in men in whom LDL cholesterol (LDL-C) is elevated.36.

Nitric Oxide
Nitric oxide (NO) is synthesized from L-arginine through catalytic activity of Nitric Oxide Synthase (NOS). NO regulates arterial tone by relaxation of vascular smooth muscle and vasodilatation. It acts as a critical factor in the pathophysiology of the vascular system through its
various actions such as preventing the oxidation of lipoproteins, down-regulating inflammatory mediators, controlling the expression of proteins involved in atherogenesis.

Coronary endothelial dysfunction is characterized by impaired NO bioavailability and found to be associated with myocardial ischemia. NO may reduce endothelial expression of several inflammatory mediators and adhesion molecules that increase plaque vulnerability, an effect that is mainly mediated by inhibition of the transcription factor nuclear factor-xB, a key regulator of various inflammatory proteins involved in atherosclerosis.

**Endothelin**

Atherosclerotic coronary arteries are prone to inappropriate constriction. One of the most potent vasoconstrictor factors produced in the arterial endothelium is endothelin-1 (ET-1), a 21-amino acid peptide. It is also released from activated macrophages and smooth muscle cells. Abundant ET-1 is present throughout the thickened intima of atherosclerotic human coronary arteries. ET-1 binds to 2 specific receptors, termed ETA and ETB in forearm. ETA receptors are located on vascular smooth muscle and mediate vasoconstriction. ETB receptors are located on both endothelial cells and smooth muscle cells, where they mediate dilation and constriction respectively.

**Oxidant/Antioxidant Status**

The increased vascular production of reactive oxygen species (ROS) plays an important role in endothelial dysfunction. Increased vascular production of superoxide anion has been demonstrated in all major conditions predisposing to atherosclerosis. The superoxide anion reacts rapidly with NO, resulting in the formation of the highly reactive and cytotoxic ONOO− and loss of the bioactivity of NO. The nicotinamide adenine dinucleotide phosphate NAD(P)H oxidase has been identified as an important vascular source of superoxide anion. Few studies have demonstrated that the coronary activity of the NAD(P)H oxidase is significantly increased in patients with coronary disease. Another potential vascular source of superoxide anion is xanthine oxidase (XO). In patients with coronary disease, increased activity of coronary and endothelium bound XO activity has been observed which may contribute to endothelial dysfunction.

Further, the major superoxide anion-degrading enzyme system is superoxide dismutase (SOD). The extracellular form of SOD (ecSOD) is highly expressed in vessel wall and is located in the extracellular space around vascular smooth muscle cells (SMCs). In patients with coronary disease, endothelium-bound ecSOD activity was shown to be reduced and closely related to impaired endothelium-dependent, NO-mediated vasodilatation, suggesting that reduced ecSOD activity may contribute to endothelial dysfunction.

**Prospective Biomarkers for Coronary Artery Disease Evaluation**

Early detection and treatment can set the stage for a lifetime of better heart health. The various other developing markers which may help in early diagnosis and intervention are as:

**C - Reactive Protein**

C-reactive protein, a marker of systemic inflammation, is a stronger predictor of future cardiovascular events. Unlike other markers of inflammation, C-reactive protein levels are stable over long periods, have no diurnal variation, can be measured inexpensively with available high-sensitivity assays, and have shown specificity in terms of predicting the risk of cardiovascular disease. It has been suggested that measurement of CRP and IL-6 concentrations may increase the predictive value of traditional lipid screening. Recently algorithms are proposed for the prediction of cardiovascular disease risk using CRP and total cholesterol/HDL-cholesterol (TC/HDL-C) or LDL-cholesterol (LDL-C) values.

**tPA (Tissue Plasminogen Activator)**

The tPA antigen acts as an independent predictor for the development of coronary and cerebrovascular events whereas this association is weakened by adjustment for other confounding risk factors, such as BMI, BP, and HDL cholesterol. There are several plausible mechanisms that may explain the observed relationship between tPA and atherothrombotic vascular disease. The increased circulating levels of tPA may reflect increased expression and enhanced plasmin-mediated breakdown of the extracellular matrix, resulting in plaque instability. In addition, tPA levels may reflect the acute phase response. Alternatively, increased tPA antigen may represent increased tPA/PAI-1 complex (because the majority of tPA circulates in this inactive, bound form) and therefore a net reduction in fibrinolytic activity which predicts CAD events in healthy subjects.

**Plasminogen Activator Inhibitor (PAI)**

According to response-to-injury hypothesis, endothelial cell injury elicits a series of cellular interactions that leads to the atherosclerotic lesions. It causes increase in PAI which has been considered as a subclinical sign of endothelial cell injury. Also, PAI-1 acts as an acute-phase protein that can rise in response to several stimuli, including cytokines such as IL-1 and TNF-α. Segarra et al. showed that the circulating levels of the endothelial cell glycoproteins PAI-1 and tPA were statistically associated with major vascular risk factors and, to a lesser degree, with an activated acute-phase response and serum triglycerides. Thus, PAI-1 could indicate a chronic endothelium activated state.

**Fibrinogen**

Fibrinogen represents an inflammatory marker that appears to be implicated in the pathophysiology and prognosis of CAD. Several atherosclerotic lesions contain...
large amounts of fibrin on the intact surface of the plaque or scattered diffusely which is associated with a decrease in fibrinolytic activity and plasminogen concentrations. It has been found that fibrin triggers cell proliferation, contributing to cell migration, and bonds fibronectin, which triggers cell migration and adhesion. The decomposition products of fibrinogen located in the inner layer can trigger mitogenesis and synthesis of collagen, attract leukocytes, and enhance permeability as well as vascular tone. In advanced atherosclerotic plaques fibrin participates in the close linkage of LDL and lipid accumulation, leading to the creation of the lipid nucleus of atherosclerotic lesions. In addition, proinflammatory cytokines, such as IL-6 and TNF-α are produced which increases the synthesis of nitric oxide (NO) and acute phase proteins, such as fibrinogen, and consequently inflammatory and prothrombotic reactions occurs.

**Fibrin D-Dimer**

Fibrin D-dimer is a product of the action of plasmin on cross-linked fibrin and therefore reflects fibrinolytic activity and fibrin turnover. Fibrin D-dimer levels are elevated in patients with established atherothrombotic vascular disease and predict arterial thrombotic events in prospective studies involving healthy, middle-aged subjects. It is possible that D-dimer levels merely reflect the underlying fibrinogen concentration; however, in the Caerphilly Study, adjustment for other CAD risk factors including fibrinogen did not affect the independent relationship between elevated D-dimer levels and the relative risk of CAD events.

**Homocysteine**

Homocysteine is a sulfhydryl containing amino acid produced by demethylation of a methionine (essential amino acid) and converts back to methionine with the help of vitamin B12 and folic acid. Therefore, folic acid and vitamin B12 deficiency can cause reduction in methylene tetrahydrofolate reductase (MTHFR) activity; leading to decrease in methionine synthesis and homocysteine accumulation. Various studies have shown that elevated total homocysteine concentration is an independent risk factor for cardiovascular diseases. Guo et al. in Fuku university (Japan) showed that the plasma level of homocysteine in patients with premature CAD was significantly higher than the control group (15.0 ± 5.7 µmol/lit versus 10.3 ± 5.1 µmol/lit, P < 0.01). Similarly, the study by Sadeghian et al showed that plasma level of homocysteine in individuals with premature CAD are significantly higher than participants without CAD (19.3 ± 1.7 µmol/lit versus 13.9 ± 0.9 µmol/lit, P = 0.005) and plasma homocysteine levels of more than 15 µmol/lit (hyperhomocysteinemia by definition) were correlated with higher risk of premature CAD.

**Osteoprotegerin**

Osteoprotegerin (OPG) is a member of the tumor necrosis factor superfamily and functions as a soluble decoy receptor for receptor activator of nuclear factor-xB (RANK) ligand (RANKL or OPG ligand). RANK is located on osteoclasts and dendritic cells. OPG is produced by a variety of tissues, including the cardiovascular system (heart, arteries, and veins), lung, kidney, bone and immune tissues. The RANK/RANKL/osteoprotegerin (OPG) system is a novel cytokine mechanism initially discovered to control bone homeostasis and later implicated in atherosclerosis and acute vascular syndromes contributes to the unstable plaque phenotype.

RANKL on ligation with its cognate transmembrane receptor stimulates chemokine release, monocyte/macrophage matrix migration, and matrix metalloproteinase activity; enhances endothelial permeability and angiogenesis; and is assumed to promote vascular calcification. In advanced lesions, RANKL is expressed by activated endothelial cells and T cells present within the plaque and is released from mast cells pericellular granula. It also exists in circulation as a biologically active molecule, making it suitable for laboratory assessment.

Upregulation of OPG is triggered by proinflammatory cytokines like IL-1α, TNF-α and IL-6 and may be viewed as part of the immunoinflammatory process in advanced plaques. OPG is also a receptor for the cytotoxic ligand TNF-related apoptosis inducing ligand (TRAIL), a potent activator of apoptosis. Serum OPG levels are also found to be positively correlated with age.

**sICAM-1 (Soluble Intracellular Adhesion Molecule)**

The impact of menopause on increased cardiovascular risk seems to be related mainly to BMI, insulin resistance, and increased total cholesterol and sICAM-1 concentrations. Anna Stefańska et al. showed that sICAM-1 values were substantially increased after menopause. They found sICAM-1 to be strongly and independently associated with BMI whereas it showed weakly inverse correlation with estradiol concentration. Soluble vascular cell adhesion molecules (VCAM-1) values were not related to any variables that change after menopause.

**CONCLUSION**

Determinants of age at menopause are incompletely understood. Current views on the relationship between menopause and cardiovascular risk assume estrogen depletion to be a causal factor. Menopause low estrogen levels may contribute to endothelial dysfunction and hence decreased nitric oxide production. Changes in sex steroids may influence inflammatory processes and lipid metabolism during the menopausal transition. The process of atherogenesis describes a possible synergism of multiple risk factors to account for the collagenous fibrous plaques in the aorta or coronary arteries. The maladaptive thickening involves an inflammatory response with monocyte recruitment, stimulation of growth factors, proliferation of smooth muscle cells, and lipid accumulation in intima superimposed onto endothelial damage to initiate atherogenesis. Thus, there is need to...
assess the cardiovascular risk in postmenopausal women in relation to hormonal imbalance and endothelial dysfunction with inflammatory markers. Thus, randomized control trials are needed to evaluate the relationship.

REFERENCES


