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The Impact of Stress on Cardiovascular Disease in Pre- and Post-Menopausal Women

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ABSTRACT

Cardio Vascular Disease (CVD) is the number one killer and leading cause of disability among women in most of the developed countries. Several epidemiological studies indicate that women during the fertile age have a lower risk of cardiac events and the female hormone estrogen provides this natural protection. Usually, the protection fades after menopause and this risk increases gradually in the five to ten years after the female hormone estrogen begins to dwindle. Hence, postmenopausal women leaving with untreated risk factors make them vulnerable to develop myocardial infarction, heart failure and sudden cardiac death. In addition, several recently published articles have shown the effect of stress on cardiovascular system and in pathogenesis of myocardial infarction and myocardial ischemia. Moreover, the effect of stress on estrogen level has also been supported by some recently published articles. For these reasons, in this review the possible links among stress, estrogen and CVD in women have been described.

Key words: Cardiovascular disease, estrogen, menopause, stress

INTRODUCTION

Cardio Vascular Disease (CVD) is the highest single cause of mortality and morbidity in women worldwide (Solimene, 2010). It is estimated that about 8.5 million deaths among women annually are caused due to CVD and the number of death is approximately one-third of all deaths in women worldwide. In developing countries, half of all deaths of women aged 50 or above are due to heart disease and stroke (Bonita, 1996). In addition, CVD is also considered as a leading cause of disability among older women (Schenck-Gustafsson, 1996). For example, in USA within 6 years of having a heart attack, about 46% of women become disabled (AHA, 2006) and two-thirds of women who have a heart attack fail to make a full recovery (Sandmaier, 2007). However, the risk of CVD in women is underestimated as women are protected from CVD during their fertile age (Stramba-Badiale *et al*., 2002).

In the last few decades, several research articles have described the active role of estrogen in prevention of atherosclerosis and heart attacks (Kajantiea and Phillips, 2006). These research findings help us to believe that women are protected against CVD. But real fact is that, estrogen provides natural protection against CVD in women during their reproductive age (Saltiki and Alevizaki, 2007) and that protection gradually diminished after menopause. After that the risk of CVD in women gradually increases and reaches pick around the age 50 (Rosenfeld, 1992). Hence, a large number of myocardial infarctions and sudden cardiac deaths are occurred in older postmenopausal women leaving with untreated risk factors of CVD (Sparks and Frazier, 2002).

Recently published several articles have shown the impact of acute and chronic stress on pathogenesis of CVD and on estrogen deficiency as well (Chatterjee and Chatterjee, 2009). There are also extensive data that depicts that stressors make a lot of changes in sympathetic nervous system activity and disrupt homeostasis and as a consequence sudden death, myocardial infarction, myocardial ischemia are occurred (Dimsdale, 2008). In addition, the development of coronary vasoconstriction in areas of atherosclerotic plaques after mental stress has also been reported in some recently published articles. There are now well-established literatures linking increased levels of chronic stress with CVD development. For example, Barth *et al.* (2004) in one of their meta-analysis have shown that people with highly depressive symptom were more than twice as likely to have a heart attack, compared to those who had no such episodes. Besides, correlation between mental stress and onset of diabetes has also been reported. From the findings of recently published articles it can be summarized that mental stress causes diabetes by increasing glucose intolerance or insulin insensitivity (Levenson, 2006). Moreover, diabetes raises the risk of ischemic stroke and coronary heart disease in both men and women (Levitzky *et al.*, 2008; Marjani, 2010; Haque *et al.*, 2011a).

So, in this review article our main goal is to find out the relationships between stress and increased risks of CVD in pre-and post-menopausal women.

ESTROGEN: NATURAL PROTECTOR OF CVD IN WOMEN

Estrogen is the main sex hormone in women and is an essential part of a women's reproductive process. It also contributes to the development of secondary sex characteristics in women. Although, estrogen exists in men as well as women, it is found in higher amounts in women of childbearing age. Estrogen not only important for reproduction but also it provides natural protection against CVD in pre-menopausal women. Several research findings provide evidences that after menopause the estrogen level in women usually goes down and that hormonal change unfavorably alter the profile of some cardiovascular risk factors (La vecchia, 1992; Gensini *et al.*, 1998; Greendale *et al.*, 1999). These include increased concentrations of cholesterol, triglycerides, Low- density lipoproteins and apolipoprotein-B, reduced level of High-density lipoprotein, higher blood pressure (Dallongeville *et al.*, 1995; Mudali *et al.*, 2005; Morita *et al.*, 2006). Moreover, positive correlations between low estrogen level and insulin resistance (Carr, 2003) and calcified atherosclerotic plaques in coronaries (Christian *et al.*, 2002) have also been reported in some scientific articles.

Estrogen maintains vessel wall physiology: Estrogen plays an important role in blood circulation. It helps to maintain vessel wall physiology and to control blood flow (Lobo, 1990). Recently published scientific articles suggest that the effect of estrogen on cardiovascular health might be regulated by their receptors ERa and ERβ (Mendelsohn, 2002; Christian *et al.*, 2006; Turgeon *et al.*, 2006) which are found in the myocardium, coronary arteries (McGill, 1989), vascular smooth muscle tissues (Losordo *et al.*, 1994; Karas *et al.*, 1994) and endothelium

(Venkov *et al.*, 1996). Losordo *et al.* (1994) in one of their study have shown the correlation between severe atherosclerotic lesion in vessels and a lower expression of ERa in pre-menopausal women. Moreover, estrogen receptors have anti-hyperplastic effects on vascular smooth muscle cells, through which they maintain the thickness of the vessel wall (Turgeon *et al.*, 2006). The thickness of carotids intima media layer is an index of the risk for CVD. Inverse correlation between level of estrogen and its receptors and thickening of the vessel wall has already been proved and supported by many researchers (Sutton-Tyrrell *et al.*, 1998). But the thickening of blood vessel wall usually takes place after menopause when the estrogen level in women remains lower and thus increases the risk of CVD in them.

Estrogen produces vasodilating molecules: The endothelium is recognized as a physical barrier between blood and vascular wall. Endothelial dysfunction (partial or complete loss of balance between vasorelaxation and vasoconstriction, thrombosis and thrombolysis) is associated with pathogenesis of atherosclerosis, hypertension, coronary artery diseases and stroke (Balakumar *et al.*, 2007). But estrogen may help to prevent endothelial dysfunction by providing vasodilatory action. The vasodilatory action is mediated by producing vasodilating molecules such as NO and prostacyclines, as well as by decreasing vasoconstricting factors such as endothelin-1, renin, angiotensinogen converting enzyme and the down-regulation of the receptor of angiotensin AT1 (Mendelsohn, 2002). Besides vasodilation NO attenuates the atherogenic process by decreasing the proliferation of vascular muscle cells. Moreover, it regulates the inflammatory events by influencing the production of cytokines and decreasing the adhesion and accumulation of monocytes and platelets on the wall of the affected vessels (Chambliss and Shaul, 2002).

Estrogen prevents calcification: Estrogen deficiency also induces the calcification of atherosclerotic plaques. After menopause the level of estrogen gradually decreases and with the reduction of estrogen aortic calcification increases gradually in women (Witteman *et al.*, 1989). Several research articles provide evidence that men have twice as many calcifications on their vessels as women until the age of 60 but after this age this gender difference attenuates (Janowitz *et al.*, 1993). Actually, this research finding depicts that during reproductive age the level of estrogen in women remains higher than the men and the higher level of estrogen prevents calcification on vessels of younger women. But after menopause the production of estrogen diminishes and due to break down of natural protection, calcification initiates and/or increases on vessel of older post-postmenopausal women. Hence, estrogen level plays a vital role in maintaining vascular health of pre-menopausal women by preventing the calcification of atherosclerotic plaques on their vessels.

Estrogen prevents lipogenesis: Estrogen is known to regulate adipose tissue development by both lipogenesis and lipolysis (Macotela *et al.*, 2009). Estrogen through ERa increases the expression of apoprotein genes and the LDL receptors and decreases the expression of the Lipo Protein Lipase (LPL), the enzyme that catalyzes the conversion of triglycerides into Free Fatty Acids (FFA) and glycerol (Homma *et al.*, 2000). For this reason, when circulating levels of estrogen are raised above the physiological range, adipose tissue metabolism is altered resulting in reduced lipogenic rates and fat depot size (Heine *et al.*, 2000). But after menopause the situation alters. With the reduction of estrogen levels an increase of the LPL activity is observed that helps to increase circulatory FFA and the accumulation of abdominal fat (Mayes and Watson, 2004). In addition, through Era and Er**β**, estrogen reduces the proliferation of adipocytes (Mayes and

Watson, 2004). So, their deprivation increases central obesity which is associated with a more atherogenic profile (Pascot *et al*., 2001). In addition, there is also evidence that ERs regulate the expression of other non sex steroid hormone nuclear receptors through which mediate various metabolic pathways relevant to cardiovascular disease (Turgeon *et al*., 2006).

It seems that estrogen protects the vasculature at different levels. Directly estrogen prevents atherosclerotic lesions (Turgeon *et al*., 2006), whereas by indirect actions it modulates various vasoactive (Mendelsohn, 2002), pro-inflammatory and metabolic and coagulation system factors (Saltiki and Alevizaki, 2007).

MENOPAUSE AND ITS ASSOCIATION WITH CVD

Menopause is a normal biological event that occurred in every woman during their late 40s or early 50s and marked by the end of menstrual periods. It signals the end of the fertile phase of a woman's life and it signifies the depletion of functional ovarian follicles that are responsible for estradiol production (Johnson, 1998). After menopause, with the change in the production of female hormones, risk for ischemic heart disease and cerebrovascular disease are increased which collectively are the main causes of morbidity and mortality in women of developed (Davison and Davis, 2003) and developing nations as well. Several research articles indicates menopause as a risk factor for CVD because after it the dwindled estrogen causes detrimental effect on cardiovascular function and metabolism (Ariyo and Villablanca, 2002). As a result, the incidence of CVD increases sharply after menopause. Furthermore, menopause compounds many traditional CVD risk factors, including changes in body fat distribution from a gynoid to an android pattern, reduced glucose tolerance, abnormal plasma lipids (Psaty *et al*., 1994; Paganini-Hill, 1995; Daly *et al*., 1997), increased blood pressure, increased sympathetic tone, endothelial dysfunction and vascular inflammation (Rosano *et al*., 2007).

So, from the above discussion we could say that, menopause itself not the main risk factor for CVD but it is the diminished estrogen level that increases the risk of CVD in post-menopausal women.

THE IMPACT OF STRESS ON CVD IN WOMEN

CVDs are projected to be the leading cause of death by the year 2020 worldwide (Murray and Lopez, 1997). With scientific and socio-economic developments people are gradually exposing to more and more stressful situation. And the effect of psychological stress in the pathogenesis of CVDs has been supported by many researchers (Rosengren *et al*., 2004). Several research findings support that affective disorders occur more often in women than in men. Moreover, female role models in the modern era have changed. Nowadays, they no more want to play their role as homemaker or mother only. They like to engage themselves in attractive professions, successful businesses and so on and are steadily migrating into all areas of the work force. By the same time divorce rates, disruptive family relationships are increasing. All of these abrupt changes in role and social status are combinedly forcing women towards more stressful situation (Rosch, 1984). As a result, dramatic changes in illness pattern among women are also being observed throughout the period of time.

Stress is a personal matter. Stress that is experienced by someone is usually determined by the quality and intensity of a group of variables (e.g., the dimensions of the stressor, the way to interpret the stressor, the available resources to deal with the stressor and the amount of the total strain placed on the individual) (Zimbardo, 1992). Depending on the quantity and quality of stress

appraisal neuro-neuroendocrine activation takes place and it causes a wide range of adaptive physiological and behavioral changes in an attempt to maintain homeostasis (Johnson *et al*., 1992). But, the stress response becomes maladaptive in individuals under chronic or repeated stress exposure (Von Kanel *et al*., 2001; Faragher *et al*., 2005; Ranjit *et al*., 2007) and it disrupts natural homeostasis (Haque *et al*., 2011b). There is a vast literature describing the effects of chronic stress on biological alterations which includes autonomic imbalance, endothelial dysfunction and platelet hyperactivity (Skala *et al*., 2006). Moreover, direct pathophysiological effects of chronic stress, including elevation of arterial blood pressure (Schnall *et al*., 1998), neurohumoral arousal (Theorell *et al*., 1988) and elicitation of inflammation by altering autonomic nervous system function (Tracey, 2007) has also been reported. All of these actually explain the impact of negative emotions like depression, anxiety and hopelessness on the pathogenesis of CVD in distressed people (Rozanski *et al*., 2005).

Beside chronic stress, impact of acute stress on pathogenesis of CVD has also been described by some researchers (Freeman *et al*., 1987). In recent years, some research findings have shown that acute stress causes the stimulation of Sympathetic Nervous System (SNS) that leads to a variety of effects, ranging from heart rate and blood pressure stimulation to direct effects on coronary vascular endothelium. As consequences of these effects development of myocardial ischemia, cardiac arrhythmias and fostering of more vulnerable coronary plaques and hemostatic changes occurs. All of these changes may lead one to acute myocardial infarction and sudden cardiac death (Rozanski *et al*., 1999). In below we have tried to describe the mechanisms through which stress causes neuro-endocrine changes, disrupt homeostasis and facilitates CVD especially in women.

Stress response through Hypothalamic Pituitary Adrenal (HPA) axis: First step of the stress response through HPA axis is that the environmental and psychological stresses are perceived and processed in the cerebral cortex of the forebrain (Haque *et al*., 2011b). Following the perception and processing of stressful stimuli by higher cortical and limbic forebrain structures, the paraventricular nucleus of the hypothalamus is stimulated (Sobhani *et al*., 2006). As a result hypothalamus secretes stress hormone CRH that activates the HPA axis by inducing the secretion of ACTH frim the anterior pituitary (Montoro *et al*., 2009). After that, ACTH stimulates the secretion of glucocorticoids (Smith-Rohrberg, 2000), corticosterone in rodents and cortisol in primates by the cells of the adrenal cortex (Munck *et al*., 1984; Endo *et al*., 2011). Cortisol and other glucocorticoids usually increase glucose production (Soliman *et al*., 2007), inhibit protein synthesis and increase protein breakdown, stimulate lipolysis (Desborough, 2000) and affect immunological and inflammatory responses. Besides, glucocorticoids help maintain blood pressure (Chamani *et al*., 2006) and form an essential component of the body's response to stress. Under basal (non-stress) conditions, cortisol feeds back to the pituitary and hypothalamus to suppress levels of ACTH and CRH and it is secreted with a pronounced circadian rhythm, with higher levels early in the morning and low levels late in the evening. However, under stressful conditions, the circadian variation is blunted (Foye *et al*., 1995).

Depression is a state of psychological stress. There is a lot of scientific evidence those indicates that depression has both behavioral and direct pathophysiological effects. Depression usually causes hypercortisolemia (Veith *et al*., 1994; Mahbub-E-Sobhani *et al*., 2011). Besides, significant impairments in platelet function has also been reported in depressed individuals (Laghrissi-Thode *et al*., 1997). Hence, depression may facilitate the progression of atherosclerotic plaques on vessels of depressed patients through the combine effects of hypercortisolemia and enhanced platelet function.

Moreover, psychosocial stress stimulates the production of cortisol through the activation of HPA axis (Sadeghi *et al.*, 2007; Haque *et al.*, 2011b) and sympathetic nervous system which can trigger pathophysiological mechanisms that include inflammation and altered metabolic and cardiac autonomic control (Brotman *et al.*, 2007). In addition, cortisol (glucocorticoids) increases insulin resistance (Willi *et al.*, 2002) that causes diabetes and hence increases the risk of CVD as well. Thus, these articles not only described the correlation between psychological distress and CVD events but also provided the clues to understand and treat psychological distress to reduce risk of CVD.

Stress response through Hypothalamic-Pituitary-Ovarian (HPO) axis: Humans have a universal response of stress via hyper-activation of the HPA axis (Mahbub-E-Sobhani *et al.*, 2008). HPA responses increase after chronic or repeated stress. As a result of chronic stress response, concentration of glucocorticoids in serum increases that evidently suppresses the HPO axis (Kalantaridou *et al.*, 2004). In fact, these articles have been provided suggestion that stress-induced ovarian impairment might potentiates atherogenesis even in pre-menopausal women, thereby predisposing these individuals to CVD (and possibly ischemic stroke) in later years (Rozanski *et al.*, 1999). Besides suppression of HPO axis glucocorticoids also induce estrogen deficiency by suppressing granulosa cell aromatase activity (Chatterjee and Chatterjee, 2009). As estrogen provides natural protection against CVD, anxiety and depression-related stress may increase the risk of CVD by reducing the production of it.

DISCUSSION

Estrogen is the vital hormone that regulates menstrual cycle and maintains the length of the fertile age in women. The diminished level of estrogen also has direct correlation with association of CVD in women (Ariyo and Villablanca, 2002). But, in the majority of the studies actually no associations have been found between current estrogen levels and the presence and severity of CVD in postmenopausal women (Barrett-Connor and Goodman-Gruen, 1995; Rexrode *et al.*, 2003). Only one longitudinal study showed that low levels of endogenous estrogen and relatively higher levels of androgens are associated with the risk for an acute myocardial infarction in post-menopausal women (Guthrie *et al.*, 2004). Whereas in several articles it has been reported that premenopausal women with lower estrogen levels had more severe atherosclerosis in their vessels (Merz *et al.*, 2003) and this provides some evidence of an increased risk for future coronary artery disease in women whose total exposure to estrogen has been lower during the reproductive years (Saltiki and Alevizaki, 2007). Besides some reports provide evidences that stress have direct impact on estrogen level. In one of the recently published article it has been stated that under stressful situation glucocorticoids produced and they reduce the number of ERs, tissue uptake of estrogen and induce estrogen deficiency by suppressing granulosa cell aromatase activity (Chatterjee and Chatterjee, 2009). Thus, it is not menopause but the level of estrogen during pre-and post-menopausal period in women is the main risk factor of CVD and stress is a vital factor that might regulate the production of estrogen and length of reproductive age in women.

Moreover, though estrogen provides natural protections against CVD in pre-menopausal women; these protective effects are usually absent in women with diabetes (Chakrabarti and Davidgea, 2009). Several research findings supported that the hyperglycemia and consequent oxidative stress observed in diabetes cause endothelial dysfunction (Stehouwer *et al.*, 1997; Schalkwijk and Stehouwer, 2005). On the other hand, one article has been described that under

normal blood glucose level estrogen increases the levels of ERa and ER, whereas high glucose reverses the estrogen effects on endothelial ER expression (Chakrabarti and Davidgea, 2009). Furthermore, correlation between mental stress and onset of diabetes by increasing glucose intolerance or insulin insensitivity has been supported by some researchers (Willi *et al*., 2002). Beside this involvement of stress hormones in the counter-regulatory response to insulin, is likely to play a role in increasing blood glucose (Levenson, 2006) has also been reported. On the basis of these findings and statements we may conclude that stress could play a vital role on production of estrogen and expression of ER in both pre and post-menopausal women and in long run it might cause CVD in women.

From the above discussion it can be conclude that estrogen is considered as the main natural protector of CVD in women especially women of reproductive age. For this, to find out an effective solution to prevent CVD in women especially in elderly women, we have to concentrate ourselves on real causes of impaired estrogen level in women of reproductive age. Because, the lower level of estrogen during fertile ages and shorter reproductive age are more dangerous than the lower level of estrogen during menopause in onset of CVD (Saltiki and Alevizaki, 2007). Moreover, research findings have been provided evidences on the impact of stress on expression of ERs and estrogen production through HPA and HPO axis regulation and/or increasing insulin resistance. Thus, leading stress free life during pre-menopausal period is more essential for women to lengthen their reproductive age and maintain higher estrogen level and that could help them to prevent or reduce the risk of CVD during their post-menopausal period.

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