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# ROLE OF ESTROGEN IN CARDIOPROTECTION

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***ABSTRACT:-*** For both men and women, cardiac disease is the leading cause of death. According to statistics, cardiovascular disease strikes women 10 to 15 years later on average than it does males, and the risk may rise after menopause. This finding has generated a lot of speculation about the physiological change or changes that may occur during menopause that would explain the increased risk of atherosclerosis. The most focus has been placed on estrogen because of its ability to act as a cardioprotective medication and as an immunomodulator of the inflammation in atherosclerosis. The ability to strengthen this impact in females and activate this protection in males by therapeutic intervention may be made possible by understanding the mechanisms that result in these disparities. What this review will accomplish is: Identify the causes of atherosclerosis, examine the use of estrogen replacement medication, explain how estrogen receptors protect the heart, describe how endothelial function is affected by estrogen, and provide mechanistic-based treatment options.

**KEYWORDS:-** Estrogen, Estrogen receptors, Cardiovascular-disease, angiotensin, Postmenopausal. Mitogen-activated protein kinase (MAPK), Jun N-terminal kinase (JNK), Inducible nitric oxide synthase (iNOS).

**INTRODUCTION:-** As a sex steroid hormone, estrogen (E2) secretes mainly from the ovary and adrenal cortex. It plays the main role in reproduction as well as stress modulation (1). The leading cause of death for women is cardiovascular disease (CVD), which accounts for close to 50% of female fatalities (2). According to statistics, women experience cardiovascular disease (CVD) 10 to 15 years later on average than males do, and the risk may rise after menopause (2,3). In females, it is involved in the development of sexual characteristics. It's well known that postmenopausal women have a lower risk of cardiac arrest rather than men (4,5). Estrogen employs its various physiological roles via its receptors. These receptors are estrogen receptors alpha (ER-α) and beta (ER-β) (6). Though, another third kind of GPER has been found recently to play a noteworthy role in the cardioprotective mechanism of estrogen.

This review has generated a lot of speculation about the physiological change or changes that may occur during menopause that would explain the increased risk of atherosclerosis. Estrogen has the ability to both immunoregulate the inflammatory response in atherosclerosis and act as a cardioprotective agent (3). This review focuses on numerous pathways involved in cardioprotection mediated by oestrogen receptors in order to comprehend the role of estrogen in cardioprotection (ERs). This review also emphasises how oestrogen receptors influence the cardioprotective impact.

**Estrogen receptors (ERs)-**

The binding of oestrogen to the ERs, oestrogen receptor alpha (ER) and oestrogen receptor beta (ER), mediates the biological actions of oestrogen. Depending on how the activities of ER and ER in the target organs are balanced, oestrogen signalling is either specifically promoted or repressed. These ERs are of two types- Estrogen receptors alpha (ER-α) and beta (ER-β).

**Estrogen receptor alpha (ER-α)-**

Xue B et al. performed an experimental investigation to better understand the cardioprotective function of E2-receptors. This study also suggest the role of E2 in angiotensin II (ANG-II) induced hypertension (7). Elevated blood pressure was seen in OVX and estrogen receptor knockout (ERKO) mice following the treatment of ANG-II. The mice were subsequently given estrogen, which caused their blood pressure to drop (7). Both OVX and oestrogen receptor knockout (ERKO) mice showed raised blood pressure following the treatment of ANG-II. Once oestrogen was provided to the mice, their blood pressure reduced significantly. After the

concurrent administration of nonselective oestrogen antagonists, this cardioprotective effect of oestrogen was then reversed. Wang et al. examined the involvement of ER- in myocardial infarction (MI)(1,8). MI causes the release of proinflammatory cytokines and increases the activation of the mitogen-activated protein kinase (MAPK) family and Jun N-terminal kinase (JNK) pathway which are markers for myocardial dysfunction (1,8). Conversely, restoration of heart function is associated with activation of the extracellular-signal-regulated kinase (ERK) pathway (8). Utilizing ELISA and western blotting methods, it was discovered that ER-α increased the activation of ERK1/2 and decreased the activation of proapoptotic JNK. ER- may therefore have a significant cardioprotective effect in MI (1,8). As a result, these investigations highlight the cardioprotective function of ER-, which may be useful in the development of therapeutic medications tailored for alpha receptors.

**Estrogen receptor beta (ER-β)-**

The cardioprotective role of ER-β has been the subject of numerous investigations. Zhu et al. (2002) investigated the impact of E2 on hypertension in one of the trials. In their research paradigm, ER-deficient mice's vascular smooth muscles displayed greater vasoconstriction and less inducible nitric oxide synthase (iNOS) generation than WT mice. On the other hand, estrogen treatment reduced vasoconstriction in E2-deficient animals (9). E2- is reported by Schubert et al. (2016) to protect against mitochondrial instability (9).

Jazbutyte et al. (2008) gave the OVX mice an E2-agonist (8-VE2) in order to clarify the function of E2- in decreasing blood pressure (10). They discovered better nitric oxide (NO)-induced vasodilation and increased expression of E2- in the aorta after 12 weeks of therapy (10). Furthermore, I/R damage activates pro-apoptotic cytochrome c, which in turn activates caspase 9, causing mitochondrial instability (11). They detected low levels of cytochrome c and high amounts of the anti-apoptotic Bcl2 protein in the OVX animals pre-treated with either E2 or ER-specific agonist (ERA) (12). Skavdahl et al. (2005) also investigated the function of E2 in cardiac hypertrophy (13). They found that animals with the genotype -/-E2- displayed the same sensitivity to stress as WT female mice when stress was induced by TAC. Also, females with the genotype -/-E2- showed a significant increase in cardiac hypertrophy, demonstrating with hard evidence how important ER- is in reducing cardiac hypertrophy (13). Skavdahl et al. (2005) elaborated on the significance of E2 on the onset of heart failure with decreased ejection fraction (HFrEF) in the same study (13). The researchers discovered that ER-KO male mice and their WT counterparts had the same heart weight to body weight (HW/BW) ratio. In contrast, the HW/BW ratio was much higher in ER-KO mice (13).

E2 has been linked to avoiding heart hypertrophy, which is a precursor to diastolic dysfunction (14). The preventive effect of E2, in particular E2-, on cardiac hypertrophy was revealed by Pedram et al. (2008) (14). They found that animals lacking E2- showed increased hypertrophy as compared to WT and E2- KO, which indicates the important role of E2- on cardiac hypertrophy, whereas E2- did not seem to play a significant role in cardiac hypertrophy after administering the animal models with ANG-II, a known potent vasoconstrictor (14).

**Cardioprotective role of estrogen-**

Estrogen receptors present hepatocytes and arterial wall (15). Estrogen reduced the influx of unsaturated fatty acid promotes the synthesis of apolipoprotein b and inhibits lipase action in hepatocytes. Despite these functions, estrogen also triggers the synthesis of LDL receptors which promotes synthesis into VLDL (16). Cardiovascular disease (CVD) is associated with an increased extent of plasma low-density lipoprotein-cholesterol (LDL-cholesterol) and less extent in high-density lipoprotein-cholesterol (HDL-cholesterol) (16). Estrogen reduced the level of LDL to a great extent and increases the level of HDL. It is due to the inhibition of LDL oxidation and not shows any interference with progestins (17). Thus, estrogen acts as an anti-atherogenic agent (18). Estrogen also reduced the level of elevated triglycerides in plasma and serum lipoprotein(a) (19). Antifibrinolytic property in blood also increased due to estrogen mediated enhanced production of plasminogen activator inhibitor 1(PAI-1) (20). Estrogen has dose dependent differential role in

insulin metabolism (21). Low dose (.625mg/day) of estrogen increases sensitivity of the insulin while high dose (1.25mg/day) causes resistance from insulin (22).

Study of mRNA expression revealed that estrogen receptors express in aortic endothelial cells. There are two different mechanisms involved in estrogen dependent regulation of endothelial function. In first mechanism estrogen dependent activation of plasma membrane bound enzymes, which is fast and non-genomic process that increases the permeability of ions channels located on the plasma membrane of endothelial cells of blood vessel. In second mechanism estrogen receptor mediated genomic expression involved (23).

Vascular smooth muscle cells (VSMCs) mediated plaque formation is common in atherosclerosis (24). The plaque formation induced by various stimuli like hypertension, injury in endothelial cells, diabetes mellitus, and dyslipidemia. In the responce of endothelial injury, various kinds of cells like, endothelialcell, platelets, and inflammatory cells mediated cytokines and growth that have pleiotropic effects. These growth factors and cytokines have potentiality to promote the changes of VSMC from the inactive contractile state to the mobile synthetic state (25). E2 prevents the VSMC migration and proliferation and alter the risk of atherosclerosis through the ER α mediated suppression of these cytokines and growth factors (26,27). VSMC calcification is common in old age, atherosclerosis, diabetes and renal disorder and is also associated with advanced CVS disorders. Estrogen also reduced the vascular calcification through the estrogen receptor α mediated trans activation of gas-6 gene which regulate the calcification of vascular endothelial cells via modulating Akt pathway (28). Prostaglandin synthase is an enzyme responsible for synthesis of prostacyclin, prostacyclin is a prstenoid, synthesize and secrete from endothelial cells has dual role, one of anti arthogenic property due to its inhibitory effects on pletlets aggregation and another as a vasodilator. Estrogen was increased the synthesis of prostaglandin synthase that promote the increase level of prostacyclin (23,29,30) Thromboxane A2 (TXA2) is an eicosanoid secrete from platelets, acts as a vasoconstrictor as well as associated with platelets aggregation. Increase level is common in CVS pathophysiological condition, like atherosclerosis. Estrogen inhibits the expression of TXA2 (30).

Endothelial nitric oxide synthase (eNOS) derivednitric-oxide (NO), produced in endothelial cells and acts as a vasodilator (31). A peptide hormone relaxin (insulin like family) secreted from mammalian corpus leutium play important role in reproductive physiology and in cardio blood vascular system via upregulation of inducible nitric oxide synthase (iNOS) in endothelial cells (32). Production of platelets and endothelial cell derived cell adhesion molecules (CAMs) like P-selectin increased in hypercholestremia, and in the influence of LDLoxidation. In blood stream such condition causes atherocleortic acivity due to attachments of platelets and leukocytes. LDL oxidation promotes synthesis of P-seleclinand inhibition of NO production through the inhibition of eNOS up-regulation. In atherosclerosis, estrogen treatment induced the production of NO through the up regulation of both eNOS (33)activity and relaxin mediated upregulation of iNOS (34). P-seleclin like cell CAMs inhibited by the action of estrogen. Expression of vascular cells adhesion molecule -1(VCAM-1) and E- selectin increased in the influence of cytokines like interleukin-1 (IL-1). IL-1 inhibited in the influence of estrogen which causes decreased the expression of VCAM-1and E- selectin (35).

5-hydroxytryptamine (5-HT) or serotonin, an amino acid derived neurotransmitter has the property of vasodilatation (36). Estrogen treatment increase serotonin in blood plasma (37,38).

Homocysteine is a sulphur containing protein derived from the metabolic pathway involved in methionine and cysteine pathway. Hyperhomocysteinemea is a situation in which the concentration of homocysteine, crosses it limit (5-12mmol/l). Hyperhomocysteinemea is associated with the CVS disorders like coronary heart disease (CHD), ischemia, peripheral vascular disease. Treatment of estradiol reduced the homocysteine concentration of plasma (39,40).

**CONCLUSION:-**

With a complicated mode of action, estrogen appears to play a cardioprotective role in cardiovascular disorders.

This article's goal was to provide a complete knowledge of estrogen's new role. The studies mentioned in this article present us with strong pieces of evidence towards the cardioprotective role of estrogen with a positive impact on infarct size, cardiac hypertrophy, hypertension, heart failure, etc. A major limitation of this article is that all the studies included in this review are animal based, thus, there is a need to develop human studies to extrapolate these findings. Therefore, this review recommends future studies focus on an estrogen regimen that would be beneficial to both male and female. Hence, this analysis suggests that future research concentrate on an estrogen regimen that would be advantageous to both men and women. Elevated levels of estradiol provide significant cardioprotective roles, according to the most popular idea about the pathophysiology of cardiovascular illnesses.

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