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ESTROGEN AND TISSUE FACTOR: EXPLORING THE INTERPLAY IN MENOPAUSAL FEMALES

GURJEET KAUR* AND VINEET AWASTHI

Amity Institute of Biotechnology, Amity University Uttar Pradesh, Lucknow Campus

ABSTRACT

The research conducted so far gives us ample of evidence that aging is also a discriminatory factor and is gender biased. Women undergo a symptomatic phase of menopause with growing age. A majority of studies indicate towards the low estrogen levels which lead to cascade of events deleterious for one's health such as cardiovascular disorders. The correlation studies have been strengthening the relation of life style disorders, genetic abnormalities and autoimmune disorders with the major risk of life ie. cardiovascular disorders. The knowledge on the factors responsible for initiating and enhancing the associated risk has improved with the growing research. The present review is an attempt to widen the perspective of research by relating it with a trans-membrane glycoprotein, tissue factor and tissue factor pathway inhibitor. Tissue factor is present on the endothelial cells and in certain events in the circulatory system. Under non favorable conditions, it triggers cascade of events thus participating in the cardiovascular disorders. Tissue factor present in the extravascular compartment, acts as a hemostatic envelope contributing to the thrombus formation when the endothelial disruption takes place. The intravascular tissue factor is known to implicate in different models of thrombosis. Reports on tissue factor pathway inhibitor have also claimed to be related with the menopausal females undergoing hormone therapy. A link between tissue factor and low estrogen levels is proposed due to their known involvement in cardiovascular disorders. This provides a connecting link between the role of tissue factor, tissue factor pathway inhibitor and cardiovascular disorders. Understanding the pathways and potential biomarkers provides a promising therapeutic target in studying the treatment after effects and strategic approach towards atherosclerosis and cardiac events in the menopausal females.

KEYWORDS: ***Estrogen, Cardiovascular disorders, tissue factor, menopause***

DR. GURJEET KAUR*

Amity Institute of Biotechnology, Amity University Uttar Pradesh, Lucknow Campus

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INTRODUCTION

Ageing is a programmed physiological, morphological and psychological process irrespective of sex and species variation. The difference in the vascular biology of men and women are related to the metabolic and cardiovascular effects of sex steroid hormones as androgens and estrogens.[1]The risk factors for cardiac events rise with growing age in both sexes, but in females the symptoms are potentially expressed after the menopause.Menopause is associated with increase in weight and alteration in fat distribution in addition women with pre-eclampsia or gestational diabetes mellitus are found to increase their cardiovascular disease (CVD) risk and even more adverse lipid profile is observed at later age.[2-3] Early menopause has been related with genetic factors, lifestyle factors, Body Mass Index, chromosomal defects, epilepsy or autoimmune diseases. In the late age as compared to the male population, females are more prone to developing cardiovascular disorders and have thus become the primary cause of death when in their peri and postmenopausal stage makes it appear that females are the primary cause of death. A controversial relation of the degenerative symptoms was found to be with low estrogen in the females.[4] Estrogen or oestrogen is a primary female sex hormone responsible for the development and regulation of the female reproductive system and secondary sex characteristics. Estrogens are synthesized in all vertebrates[5] as well as some insects.[6] The three types of estrogens present in women are: E1: estrone/oestrone, is a minor female steroid sex hormone and is a weak estrogen; E2: Estradiol/oestradiol, is a primary female steroid sex hormone and is an estrogen;E3: Estriol/ oestriol, is a minor female steroid sex hormone and is a weak estrogen. The fourth E4, Esterol is produced only during pregnancy. Estrogens readily diffuse across thecell membrane. Once inside the cell, they bind to and activate estrogen receptors (ERs) which in turn modulate the expression of many genes.[7] Additionally estrogen, binds to and activate rapid signaling membrane estrogen receptors (mERs),[8-9] such as GPER30.[10] Estrogens, in females are produced primarily by the ovaries and during pregnancy by the placenta.[11] Follicle stimulating hormone (FSH) stimulates the ovarian of estrogens by the granulosa cells of the ovarian follicles and *corpus luteum*. Some estrogens are also produced by liver, adrenal glands and the breasts.[12]Apart from being major event player in CVD, estrogen has importance in the maintenance of bone, in growth and differentiation and various biological activities in the other tissues.[13] The other consequences of low estrogen are osteoporosis, Parkinson's like symptoms, depression, dementia and premature death.[14-16]One of the most sought after events that take place due to low levels of estrogen is the cardiovascular disorders.[17]In order to elevate the hormonal levels of females, the hormone replacement therapy (HRT) and estrogen replacement therapy (ERT) was prescribed by the practitioners. The data observed after the clinical trials of estrogen replacement therapy and combined hormone replacement therapy show no prevention from the early development and /or development of CVD in peri and post-menopausal females.[18] Gradual decrease in incidences of coitus, the quality of life (sex), the hypo-estrogenic state seems to contribute to certain extent in the increasing risk factor for the cardio vascular disorders and bone health.[19-21] A potential role of estrogen and testosterone therapies in multiple sclerosis hasalso been suggested. Estrogens are known to function through immune-modulatory and neuroprotective pathways thereby providing more treatment options in such diseases.[22] The fluctuating levels of estrogen during different sexual stages observed by women are also strongly correlated to the bipolar disorder.[23]A plethora of studies have been found to strongly relate these incidences and provide support to the underlying mechanism involved. But, there is always scope of investigation to come to concrete and viable conclusion. The key focus of this review is fabrication of certain promising risk factors responsible for cardiovascular disorders in ageing menopause phase in females. The effects may be regulated by a number of factors. The healthy arterial endothelial cells produce many vasodilators which are the anti-platelet agents as NO, PGI2, prostacyclin, ADP dephosphatases andother factors.[24] During vascular endothelial injury, no or negative effect on the dsysfunctional endothelium or on advanced atheromatous lesions takes place. Endothelial dysfunction has established a correlation with the circulating vWF,[25] high levels of tissue factor pathway inhibitor (TFPI).[26]Endothelial dysfunction is an event that takes place at the early stage of atherosclerosis.[27] The markers of endothelial dysfunction have supported their link with the peri and post-menopausal females. Besides this, methylation of the estrogen receptor promoter takes place resulting in low receptor expression.[28-29]The intermediary layers of the arteries are exposed thereby releasing factors as neurogenic reflex vasoconstrictors, myogenic constrictors and endothelin. **von** Willebrand Factor (vWF) sticks to the exposed collagen and binds the platelets. In the post-menopausal females, the elevated levels of vWF, FVIII and fibrinogen have been reported.[30-31]The platelets when activated are also found to release catecholamines as serotonin, ADP, calcium, thromboxane A2, epinephrine and chemokines etc in the surrounding circulatory system.[32-34]In older women, frequent events of thrombosis takes place with fluctuating estrogen levels, which are related to menopause.[35]This could relate to low levels of estrogen, being one of the factors. Estrogen known to possess antioxidant properties increases NO production thereby inhibiting the platelet aggregation.[36] Various studies support the involvement of COX 2 and its metabolites in the events which are directly or indirectly related to the estrogen imbalance (RRR).[37]The increase in cycloxygenase 2 activity leads to increased prostaglandin production and decrease in cell adhesion molecules,inflammatory factors and plasma lipoproteins. Amongst the soluble agonists ADP and TXA2 are released by the platelets which adhere to the vWF and thrombin produced by FIII ie. Tissue factor (TF), a glycoprotein. There are body of evidences supporting mechanistic link of the platelet activity and the increase in the microvesicles number in the activated blood in the recent menopausal females. It is believed that increased microvesicles in the circulatory blood are released by activated platelets and other vascular cells which contribute to the process of atherogenesis.[38-39] Increase platelet number is indicated in the recent menopausal females with increased central obesity. The adipose tissues secrete IL-6, which with other cytokines and

thrombopoeitin act synergistically in the megakaryocytes and lead to increase in the platelet number and hsCRP, an acute phase hepatic protein.[40]Another study indicates platelet progeny production in the circulatory system. The anucleated platelets have been shown to produce progeny and bring about changes in the biomass and morphology, a very unlikely behavior not observed in the past. The multiple bodies produced are anchored with a delicate shaft which can be easily broken down during the processes involved in the isolation. This ultimately leads to increased number of platelets in the circulatory system. These originated platelet bodies are also known to increase the protein synthesis even when stored in plasma or whole blood under *ex- vivo*conditions for several days. The women after menopause were found to have low platelet count and higher platelet activation due to higher beta thromboglobulin levels as compared to young woman.[41] One of the speculated reasons could be low estrogen levels in the post- menopausal females. The megakaryocytes were reported to be differently regulated on administration of different concentrations of testosterones and thus the platelet function was found to be different gender wise and ultimately prone to thrombotic events. This was further supported by a study which showed estrogen receptor b and androgen receptor being present in the platelets.[42] Variations in the platelet morphology and functions associate with the adverse vascular changes and support early onset of the atherogenesis, a major event in the cardiovascular disorders.[43] On the other hand, Tissue Factor (TF), a trans-membrane glycoprotein essential for Factor VII-TF complex formation and thus catalytic active which triggers the coagulation cascade. TF can be membrane integrated localized in the endothelial lining of the arteries or in the circulatory system. Under normal health conditions the TF is enveloped in an inactive (cryptic) form in the cells which are not directly in contact with blood.[44-46]At the time of vascular injury the sub endothelial TF gets exposed (decryption of TF) to the circulatory system and ultimately produces clot.[47]Monocytes and endothelial cells are known to expressTF under diseased conditions.[48-49] The TF activity in endothelial and mesothelial cells is also known to be enhanced by Plasmin.[50] There is a gap of study to support whether the membrane integrated endothelial TF gets activated and its conversion from cryptic to decryptic form allows it to enter into the circulatory system or TF is additionally synthesized into the other cellular bodies of the connective tissues under the adverse physiological conditions and released into the circulatory system. Some reports suggest that TF is present on the unstimulated blood platelets and monocytes whereas others clearly state that platelet devoid of monocytes or activated platelets do not show TF activity on the surface of the platelets when LPS or activated complement factors are used as a stimulant.[51] TF activity in the peripheral mononuclear cells can be suppressed by phenol and its derivatives,[52-53] some proteins present on the surface are sometimes mistaken for TF.[54] This group specified TF expression by monocytes under the *in vivo* conditions. When activated platelets are associated with the activated monocytes they are mistaken to express TF under various pathophysiological conditions. The microvesicles originated from activated monocytes carrying TF fuse with the activated platelets through P-selectin binding and PSGL-1 present on the microvesicles. The TF binding to platelets thus makes the platelets thrombogenic in nature. In 1995, Quirk SM et al have shown that E2 may induce TF mRNA by stimulating multiple pathways including PKC and Jun and Fos and also by generating thrombus in the uterus.[55]Tissue factor pathway inhibitor (TFPI) is a known anticoagulant, and is synthesized mainly by the vascular endothelium. It is in bulk (80-85%) associated with the endothelial cell surface, 15-20% in the plasma and approx. 3% is found in the blood platelets.[56-57] Various studies have been conducted to relate TFPI and symptomatic diseases. TFPI activity and Activated Protein C resistance are found to be related to the coronary heart disease risk in women.[58] TFPI which is an anticoagulant and anti - thrombotic protein is a promising area of investigation when studied in context to post and peri menopausal female. TFPI inhibits FXa and TF- FVIIa by binding and acting on its substrates FIX and FX in the process of coagulation. It co-localizes with TF in endothelial cells, macrophages and vascular smooth muscle cells and acts in regulating the atherosclerotic plaque. Increased TFPI levels in medial vascular smooth muscle cells might be involved in preventing arterial thrombosis.[59]Women receiving HRT are reported to have reduced TFPI levels suggesting a link between estrogen and TFPI.[60] Oestrogens are known to down regulate TFPI at the mRNA level mediating through ERα and the genomic pathway.[61] The ERαbinds to the half sites of the ERE located in the 5'- flanking region of TFPI gene and mediate the transcriptional regulation of TFPI gene by the oestrogen in the MCF7 cells.[60-62] These studies lead to investigate more about the TFPI and TF released by the Smooth muscle cells. Oral administration of 17α-ethvinylestradiol reduced the TFPI activity to significant level in ovariectomized rats.[63] It indicates that regulation of TFPI might be of some importance in the menopausal females in delaying CVD. The inhibition or low levels of estrogen reduce the production of Angiotensin II which has a dominant role in regulating blood pressure and the growth of smooth muscle cells. It is already known that during vascular injury, SMCs also undergo vasoconstriction by production of myogenic vasoconstrictors. It was observed that ERα mediated the innate immune response and /or microglial activation as well as increased IL-6 production induced due to ischemia or aging females.[64]The SMCs might not proliferate and/ or migrate to the injured endothelial lining site during CVD, thereby resulting in the maximal damage in the absence of estradiol. This may also result in the delay of CVD onset symptoms for a short period of time and cause minimum damage to the arterial walls. AHA (American Heart Association) has taken major initiatives in recognizing and improving the health of elderly females. In the developing and underdeveloped countries the elderly women health issues are yet to be given importance and addressed with a respectable perspective. In the interest of women health, the focus of research is expected to be pin pointed towards the triggering factors which cause CVD, a major health issue in the aging females.

CONFLICT OF INTEREST

Conflict of interest declared none

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Reviewers of this article

Dr. Samir Sharma, Ph.D

Associate Professor, Department of Biochemistry, University of Lucknow, Lucknow.

Asst. Prof. Dr. Deepansh Sharma, M.Sc, M.Phil, Ph.D.

Assistant Professor, School of Biotechnology and Bioscience, Lovely Professional University, Phagwara, Punjab, India

Prof.Dr.K.Suriaprabha

Asst. Editor , International Journal of Pharma and Bio sciences.

Prof.P.Muthuprasanna

Managing Editor , International Journal of Pharma and Bio sciences.

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