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Editorial

Adverse Impact of Smokeless Tobacco in Precipitating Metabolic and Cardiovascular Anomalies in Estrogen Deficient States

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Estrogens are steroid hormones which generate and regulate menstrual cycle, promote development and maintenance of female reproductive system and secondary sexual characteristics [1]. Estrogen have beneficial role on cardiovascular system [2], carbohydrate metabolism [3] and lipid metabolism [1,4] and inhibits expression of inflammatory markers [5] and maintains homeostasis [4].

In the human ovary there is a continuing decline in the number of follicles which start in fetal life. After birth several million follicles slowly declines to a few thousand as women approach menopause [6]. This denotes more than 99% of ovarian follicles undergo degenerative changes, known as 'atresia'. The condition in which ovaries become depleted of primordial follicles is referred in medical literature as 'menopause'. The hot flushes and night sweats are the most characteristic symptoms seen in 80% of women in menopause [7]. Early menopausal symptoms include, heart palpitation, shortness of breath, chest tightness, headache, joint ache, dizziness, mood swings, irritability, insomnia, anxiety, poor sleep pattern, forgetfulness, difficulty in concentration. As year passes changes in hormone production affects various parts of body in particular bones (osteoporosis), cardiovascular system (stroke and congestive heart failure) and the urogenital system [8]. Hormone replacement therapy (HRT) has been found effective in alleviating the majority of symptoms of menopause. However, several clinical studies and meta-analysis has reported increased risk of stroke, sudden death, breast and endometrial hyperplasia which constraints use of HRT [9-12].

South East-Asia is the hub of smokeless tobacco users, estimating nearly 250 million users [13]. The different forms are chewed, sucked or applied to teeth or gums [14,15]. In 2010, the Global Adult Tobacco Survey (GATS) has put forth the worrying statistic that Indian tobacco usage in women has doubled in the last five years. The survey revealed that one in five women in central India and one in three women in eastern consumes tobacco [16]. The relative risk of mortality from smokeless tobacco (popular among women) was 1.35 among women and 1.22 among men [17]. This renders teeming number of women using tobacco potentially predisposed to various diseases [18]. The adverse impact of smokeless tobacco on cardiovascular disorders and diabetes mellitus has been demonstrated in humans [19]. There are reports that suggest that smoking in women results in early menopause [20]. So it was imperative to postulate that the post menopausal women consuming smokeless tobacco will be at higher risk to suffer from cardiovascular and metabolic complications. This data prompted my laboratory to further investigate the detrimental outcomes of the use of smokeless tobacco in peri-menopausal and post menopausal state in appropriately designed studies in rodents.

We initiated the investigation in 2011 with a study wherein we assessed the impact of oral exposure of aqueous extract of smokeless tobacco (AEST) 96 mg/Kg/day (nicotine content 8.693%) in bilateral ovariectomy (OVX) (estrogen deficient) induced vascular (viz. vascular reactivity, triglyceride, cholesterol, vascular collagen), vascular endothelial (serum nitrite-nitrate levels) and metabolic derangements (viz. insulin, blood glycosylated hemoglobin) in female Wistar rats. Further, we explored the effect of resveratrol in this milieu [21].

The outcomes established decreased levels of serum estradiol upon AEST exposure which may be said to be amenable to stimulation of 2-hydroxylation pathway of estrogen metabolism by tobacco via cytochrome P450 isoenzymes CYP1A1 and CYP1A2. Thoracic aortic reactivity is a strong marker for atherosclerosis. The study revealed that OVX and AEST reduced aortic reactivity denoting a higher risk for atherosclerosis and stroke. We found increase in aortic collagen levels upon AEST exposure, which was attributed to estrogen deficiency, leading to aortic stiffness. Estrogen is a known inducer of NO synthase, thus contributing to the vascular relaxation. OVX rats displayed decreased serum nitrate-nitrite levels. Moreover, AEST exposure caused further exacerbation of this deficit. Treatment with 17-β estradiol (50 μg/kg/day, s.c.) and resveratrol (50 mg/kg/day, p.o.) for 60 days significantly increased serum nitrate-nitrite levels and prevented rise in collagen level. We encountered reduction in serum insulin levels in the OVX rats. However, AEST exposure increased insulin levels in dictating hyperinsulinemia. Resveratrol decreased AEST induced hyperinsulinemia, much below that of 17-β estradiol treated animals. The study exposed that estrogen deficiency and AEST exposure caused exacerbated impairment of carbohydrate metabolism (rise in serum glucose and glycosylated hemoglobin levels and impaired glucose tolerance) and lipid metabolism (rise in serum cholesterol and triglycerides). This effect was attenuated by 17-β estradiol and resveratrol treatments.

This investigation provides compelling preclinical evidence on the detrimental outcomes of AEST on vascular and metabolic parameters in estrogen deficient state. However the study left us with several questions on molecular mechanisms of resveratrol considering its silent mating type information regulation 2 homolog 1 (SIRT 1) modulating potential. Further, ovariectomy did not induce peri-menopausal state prior to menopause as naturally encountered.

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Ovariectomy (OVX) has been the most conventional generally used model for menopause research in animals. However, the drawbacks are, lack of resemblance to natural, transitional menopause [22,23], sudden fall in ovarian hormones [24] and depletion of several other hormones that may play an essential roles in menopause and signaling in the brain [25-27] thus placing restriction on making use of the OVX model. The limitation of the OVX model drove us to search a suitable model which was more akin to human menopause. The induction of menopause by 4-vinylcyclohexene diepoxide (VCD) was considered as a valid model of menopause [28,29], due to advantages like no surgical interventions and genetic alteration, maintenance of intact ovarian tissue and analogous estrous cyclicity and fluctuations in estrogen, LH and FSH levels as in human menopause [30,31]. VCD is an industrial chemical and has been shown to selectively destroy primordial and primary ovarian follicles in mice and rats [32,33]. The VCD induced menopause is used primarily to study cardiovascular and metabolic diseases associated with menopause [34]. The above advantage and the degree to which it replicates human menopause made the VCD model a principle choice for use in studies of menopause and hormone replacement therapy, surpassing the conventional models. Considering the above advantage and the shortfalls of prior studies, in 2012, we designed investigations to evaluate the influence of smokeless tobacco on cardiovascular and metabolic parameters in 4-vinylcyclohexene diepoxide (VCD) induced ovotoxicity in female rats. We have initiated research to explore the potential benefits of stilbene derivatives resveratrol and pterostilbene in abrogating the detrimental outcomes.

Resveratrol (trans-3,5,4-trihydroxystilbene) has been shown to be an antioxidant, cyclooxygenase inhibitor, peroxisome proliferator-activated receptor alpha activator, endothelial nitric oxide synthase inducer and SIRT 1 activator [35]. While, Pterostilbene (trans- 3, 5-dimethoxy- 4'- hydroxystilbene), is a dimethylated analog of resveratrol, which is known to have anticancer, anti-inflammatory and antioxidant properties [36]. The enhanced lipophilicity and increased membrane permeability of pterostilbene is due to dimethyl ether structure, resulting in better pharmacokinetic profiles as compared to resveratrol [37].

Currently my lab after standardizing the VCD induced model of peri-menopause and menopause in female rats has run the pilot studies to substantiate the impact of Smokeless tobacco in VCD induced estrogen deficient states. This pilot study has reiterated the outcomes of our previous study that AEST triggered aberrations as reflected by deranged metabolic and cardiovascular markers. The ongoing investigations are exploring the impact of resveratrol and pterostilbene on this dual onslaught in the rats by trailing and profiling markers of metabolic derangements and cardiovascular risk. This will generate empirical data substantiating the impact of smokeless tobacco as a major risk factor in peri-menopausal and menopausal states in females.

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