Impact of Estradiol on Circulating Markers of Oxidative Stress among Hypertensive Postmenopausal Women with Co-morbidities

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Abstract

Background: Oxidative stress plays a key role in the pathogenesis of several age-associated diseases. The antioxidant properties of estradiol reduce oxidative stress related complications. Menopause is typified by a drop in endogenous estradiol that might subsequently affect women’s wellbeing. Materials and Methods: 100 postmenopausal women were selected and classed into four groups. Estradiol (E2) and enzymatic antioxidant status were assessed among normotensive postmenopausal women (group-1), hypertensive postmenopausal women (group-2), hypertensive postmenopausal women with diabetes (group-3) and hypertensive postmenopausal women with renal insufficiency (group-4). Kruskal-Wallis test and correlation analysis were performed using SPSS16.0 statistical software. Results: Estradiol (E2), catalase (CAT), superoxide dismutase activity (SOD), glutathione peroxidase (GPx) and glutathione-S-transferase (GST) activities were significantly decreased in hypertensive postmenopausal women with diabetes (group-3) and hypertensive postmenopausal women with renal insufficiency (group-4) compared normotensive postmenopausal women (group-1). Catalase, glutathione peroxidise and glutathione-S-transferase activities were significantly reduced in the three experimental groups compared to normotensive control. Estradiol exhibited significant positive correlations with catalase, superoxide dismutase and glutathione peroxidase. Conclusion: Elevated oxidative stress along with drop in estradiol levels in postmenopausal women seems to be aggravated by co-morbid conditions.

Keywords: Antioxidant activity, Catalase, Estradiol, Hypertension, Menopause

Introduction

The high prevalence of hypertension in elderly women is associated with aging and loss of endogenous estrogen production after menopause. Endogenous estrogens in premenopausal women mediate vasodilation and maintain normal blood pressure [1]. Estrogens such as estradiol, estrone and estriol are a family of naturally-occurring compounds that, are biochemically related, but are structurally different and vary in terms of circulating concentrations, potency, physiological activity and affinity for the various estrogen receptor subtypes [2]. Estradiol is the main ligand for human estrogen receptor and binds to estrogen receptor with greater affinity [3].

Estrogens are the natural female steroid hormones with various physiological actions. In the cells, estrogens can act as pro-oxidants and induce oxidative stress through reactive oxygen species (ROS) generation. On the other hand, estrogens can also function just the opposite way, as antioxidants by inhibition of ROS generation or neutralization of excess ROS. Both these pro-oxidative and antioxidative actions of estrogens are mediated through estrogen receptors [4]. Pro-oxidants are highly toxic to all types of biomolecules including DNA, proteins, lipids and carbohydrates and are scavenged by various antioxidants. Disturbances in pro-oxidants and antioxidants homeostasis lead to oxidative stress [5].

Through a variety of mechanisms oxidative stress may contribute to the generation and progression of hypertension. Superoxides are capable of quenching nitric oxide, thereby impairing vasodilation [6]. Increased oxidative stress is the major culprit of diabetes and its associated complications such as kidney disease [7, 8]. Reactive oxygen species play a significant role in
the pathogenesis of chronic renal failure. Reactive oxygen species are produced in abundant quantities by glomerular cells, tubular cells, vascular cells, platelets and circulating infiltrating cells such as granulocyte – monocyte – macrophage involved in renal inflammatory process, are the renal sources of ROS formation [9].

Estrogen reduces oxidative stress by increasing superoxide dismutase expression and through the inhibition of NADPH oxidase activity [10,11]. Endogenous estrogens inhibit the generation of reactive oxygen species, increases bioavailability of nitric oxide, thereby functions as powerful antioxidants [12]. Estrogen has the ability to decrease angiotensin type 1 receptor expression in vasculature and kidney; reduce angiotensin-converting enzyme expression and activity and cause the release of angiotensinogen substrate from the liver. Thus estrogen regulates the activation and suppression of the renin–angiotensin–aldosterone system and thereby maintains blood pressure [13]. Estrogen inhibits the production of ROS and proinflammatory cytokines and thus exerts antioxidant and anti-inflammatory effects. Hence estrogen deficiency may be related to oxidative stress and vascular inflammation, causing endothelial dysfunction [14]. Oxidative stress is very essential for metabolism. Reactive species control important cellular functions by acting as true second messengers. Abnormally large concentrations of these species produced under pathological conditions may lead to permanent changes in signal transduction and gene expression. Attenuation of oxidative stress to improve several disease conditions has flourished as one of the main challenges of research [15].

Women in postmenopausal state experience a decline in circulating estradiol levels. Over a period of time, this decline significantly affects women’s health and wellness. Considering the antioxidant activity of estradiol the present study was conducted to assess the estradiol and antioxidant status among normotensive postmenopausal women, hypertensive postmenopausal women, hypertensive postmenopausal women with diabetes and hypertensive postmenopausal women with renal insufficiency. Correlation analysis was performed between estradiol and oxidative stress markers among hypertensive postmenopausal women with co-morbidities.

Materials and Methods

During the study period 112 postmenopausal women who visited KTVR Hospital, Coimbatore, Tamil Nadu were selected. A written informed consent was obtained from the subjects. Institutional Human Ethics Committee clearance (HEC.2011.25) was obtained for the study. Questionnaire was distributed to elicit personal details, family history, medical history and personal habits of the participants. Menopause was confirmed by the absence of menstruation for more than two years. Subjects taking antihypertensive medications or those with blood pressure ≥140/90 mm Hg were grouped as hypertensive. Thus out of 112 subjects considered, 100 subjects were selected and categorised into four groups namely normotensive postmenopausal women (group-1), hypertensive postmenopausal women (group-2), hypertensive postmenopausal women with diabetes (group-3) and hypertensive postmenopausal women with renal insufficiency (group-4). Normotensive postmenopausal group served as the control.

Blood was drawn from each of the subjects through venipuncture. 2ml blood was collected in serum separator tubes and serum was separated for the assessment of estradiol levels. 2ml of blood was collected in EDTA vacutainers and plasma was separated through centrifugation. Activities of enzymatic antioxidants were assessed in the plasma of the selected subjects.

Estradiol levels were assessed in the selected subjects by enzyme linked fluorescent assay. Enzymatic antioxidant activities were assessed by spectrophotometry. Catalase activity was estimated by the method of Luck [16]. The superoxide dismutase activity was assessed by Beauchamp and Fridovich method [17]. Glutathione peroxidase activity was estimated spectrophotometrically by the method of Rotruck et al. [18]. Glutathione-S-transferase activity was estimated in plasma photometrically by the method of Habig et al. [19].

Kruskal-Wallis test were performed to compare selected biochemical parameters among the four groups of participants. Correlation analysis was performed using Spearman’s rank correlation. p values <0.05 were considered significant. Statistical analysis was performed using SPSS16.0 statistical software for windows.

Result

The levels of estradiol in the participants are shown in Figure 1.

Estradiol (E2) levels were significantly decreased in hypertensive postmenopausal women with diabetes (group-3) and hypertensive postmenopausal women with renal insufficiency (group-4) compared to normotensive postmenopausal women (group-1).

Estradiol (E2) levels were significantly decreased in hypertensive postmenopausal women with renal...
insufficiency (group-4) compared to normotensive postmenopausal women (group-1), hypertensive postmenopausal women (group-2) and hypertensive postmenopausal women with diabetes (group-3). Hypertensive postmenopausal women (group-2) showed no significant difference in estradiol level compared to normotensive postmenopausal women (group-1) and hypertensive postmenopausal women with diabetes (group-3). A significant decrease in estradiol level was observed in hypertensive postmenopausal women with diabetes (group-3) compared to normotensive postmenopausal women (group-1).

Fig 1: Estradiol levels in normotensive and hypertensive postmenopausal women with and without diabetic and renal insufficiency

![Fig 1: Estradiol levels in normotensive and hypertensive postmenopausal women with and without diabetic and renal insufficiency](image)

The enzymatic antioxidant activities in the participants are shown in Table 1. Catalase (CAT), superoxide dismutase activity (SOD), glutathione peroxidase (GPx) and glutathione-S-transferase (GST) activities were significantly decreased in hypertensive postmenopausal women with diabetes (group-3) and hypertensive postmenopausal women with renal insufficiency (group-4) compared to normotensive postmenopausal women (group-1).

CAT, GPx and GST activities were significantly reduced in the three experimental groups compared to normotensive control. Hypertensive postmenopausal women (group-2) showed no significant difference in SOD activity compared to normotensive postmenopausal women (group-1) and hypertensive postmenopausal women with diabetes (group-3).

CAT, SOD and GPx activities were significantly decreased in hypertensive postmenopausal women with renal insufficiency (group-4) compared to normotensive postmenopausal women (group-1), hypertensive postmenopausal women (group-2) and hypertensive postmenopausal women with diabetes (group-3). There was no significant difference in GPx activity between hypertensive postmenopausal women (group-2) and hypertensive postmenopausal women with diabetes (group-3).

Estradiol exhibited significant positive correlations with CAT (Figure 2), SOD (Figure 3) and GPx (Figure 4) in the experimental groups of participants.
Fig 2: Correlation between estradiol and catalase among hypertensive postmenopausal women with and without diabetic and renal insufficiency

$r_s = 0.350$
$p = 0.002$
$n = 75$

$r_s$ – Spearman’s rank correlation coefficient
$p$ value $<0.05$ are statistically significant
$n$ – Experimental groups of participants

Fig 3: Correlation between estradiol and superoxide dismutase among hypertensive postmenopausal women with and without diabetic and renal insufficiency

$r_s = 0.405$
$p = <0.001$
$n = 75$

$r_s$ – Spearman’s rank correlation coefficient
$p$ value $<0.05$ are statistically significant
$n$ – Experimental groups of participants

Fig 4: Correlation between estradiol and glutathione peroxidase among hypertensive postmenopausal women with and without diabetic and renal insufficiency

$r_s = 0.350$
$p = 0.002$
$n = 75$
Table 1: Plasma enzymatic antioxidant activities in normotensive and hypertensive postmenopausal women with and without diabetic and renal insufficiency

| Parameters | Group 1 (n = 25) | Group 2 (n = 25) | Group 3 (n = 25) | Group 4 (n = 25) | Group 1 vs 2 (p) | Group 1 vs 3 (p) | Group 1 vs 4 (p) | Group 2 vs 3 (p) | Group 2 vs 4 (p) | Group 3 vs 4 (p) |
|------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| CAT*(U/ml) | 72.3 (69.6-76.6) | 63.1 (58.9-71.7) | 52.1 (48.1-56.5) | 44.7 (41.8-48.3) | 0.004           | <0.001          | <0.001          | <0.001          | <0.001          | 0.003           |
| SOD*(U/ml) | 3.8 (2.6-5.8)    | 3.2 (3.0-4.2)    | 3.00 (2.1-3.3)   | 1.40 (0.8-2.1)   | 0.460           | 0.029           | <0.001          | 0.055           | <0.001          | <0.001          |
| GPx*(U/L)  | 91.8 (82.4-99.4) | 78.2 (69.7-86.7) | 71.3 (58.6-78.1) | 61.1 (56.1-67.9) | 0.001           | <0.001          | <0.001          | 0.066           | <0.001          | 0.025           |
| GST*(U/ml) | 0.76 (0.59-0.79) | 0.59 (0.46-0.69) | 0.31 (0.14-0.50) | 0.28 (0.14-0.61) | 0.023           | <0.001          | <0.001          | <0.001          | 0.009           | 0.733           |

Values are median (interquartile range)
p value <0.05 are statistically significant

*CAT one enzyme unit = µmole of H₂O₂ decomposed
*SOD one enzyme unit = enzyme amount that gives 50% inhibition of NBT reduction
*GPx one enzyme unit = µg of glutathione utilized
*GST one enzyme unit = µmole of CDNB conjugated

Group 1 - normotensive postmenopausal women as control
Group 2 - hypertensive postmenopausal women
Group 3 - hypertensive postmenopausal women with diabetes
Group 4 - hypertensive postmenopausal women with renal insufficiency

\[ r_s = 0.386 \]
\[ p = 0.004 \]
\[ n = 75 \]
Discussion

A study conducted on Sprague-Dawley rats revealed reduced levels of circulating estradiol to be associated with diabetes mellitus. They emphasised the fact that estradiol supplementation might reduce the risk of diabetic renal complications [20]. Another study on Sprague-Dawley rats confirmed that estradiol protect from renal disease progression through attenuation of renal superoxide production [21]. Hormone therapy augmented plasma catalase activity, thereby suggesting beneficial antioxidant activity in postmenopausal women [22].

Several studies have proved the renoprotective effects of estrogen and its deficiency to be involved in the onset and progression of chronic kidney diseases [23, 24]. Oophorectomy aggravates renal injury and cause hypertension in laboratory animals. Estrogen inhibits components of the renin-angiotensin-aldosterone system (RAAS), including angiotensin type 1 receptor expression and reduces angiotensin-converting enzyme activity, thereby confer renal protection. The loss of endogenous estrogen leads to impaired renal sodium handling, oxidative stress and hypertension, due to reduced nitric oxide bioavailability and increased angiotensin II activity [25].

The antioxidant defense system comprises of a spectrum of enzymatic and non-enzymatic antioxidants that interact with each other to protect cells against oxidative injury [26]. CAT, GPx and GST activities were significantly decreased in hypertensive postmenopausal women (group-2) compared to normotensive postmenopausal women (group-1). Reduced CAT, GPx and GST activities were also observed in erythrocytes of hypertensives compared to normotensives [27].

In the present study, CAT, SOD, GPx and GST were significantly decreased in hypertensive postmenopausal women with diabetes (group-3) compared to normotensive postmenopausal women (group-1). Similar results were reported in diabetic patients [28].

Type 2 diabetes mellitus patients exhibited reduced CAT activities, whereas SOD activity was significantly increased as compared to healthy controls. This confirms the fact that diabetic state is associated with elevated cell oxidative stress [29]. A significant increase in extracellular-superoxide dismutase and a significant decrease in catalase activity were observed in diabetic postmenopausal women compared to non-diabetic postmenopausal women [30]. The present study reports are in partial agreement with these statements.

Enzymatic antioxidant activities were significantly decreased in hypertensive postmenopausal women with renal insufficiency (group-4) compared to normotensive postmenopausal women (group-1). In peritoneal dialysis and hemodialysis patients GPx activity was significantly reduced compared to those of the controls [31]. A drastic reduction in plasma GPx activity was observed in hemodialysis patients compared to patients with renal impairment. This emphasises the fact that renal disease progression goes hand in hand with decline in GPx activity [32]. In contrast to the present study, CAT increased significantly in chronic kidney disease subjects compared to controls [33].

Plasma and RBC GPx activities were reported to be significantly higher in postmenopausal women compared to premenopausal women. Elevated oxidative stress owing to estrogen deficit associated with menopause is an important modulator of GPx activity in postmenopausal women [34]. CAT, GPx and SOD activities were drastically depleted during prepubertal and menopausal state [35]. In the present study, enzymatic antioxidant activities were reduced in experimental groups and this can be attributed to elevated oxidative stress associated with menopause.

The antioxidant effects of estradiol can be attributed to the aromatic hydroxylation at either the C2 or C4 position of 17β-estradiol during its metabolism yielding 2-hydroxyestradiol and 4-hydroxyestradiol, having antioxidant activities [36]. Estrogen modulates prooxidant and antioxidant enzyme expression and activity, including NADPH oxidase and superoxide dismutase thereby inhibiting production of ROS in invitro and animal models. It is postulated that increased ROS production in the postmenopausal estrogen-deficient state is a contributing factor for progression to hypertension and vasoconstriction [37].

A significant positive correlation between E2 and GPx was observed in the menstrual cycle of healthy eumenorrheic women. Whereas, CAT and SOD did not exhibit significant correlation with plasma E2 levels in the study group [38]. There was an inverse correlation between estradiol and SOD in male stroke patients.

Estradiol did not show significant correlation with CAT and GPx in male and female stroke patients and control group [39]. There was a significant positive correlation between estradiol level and SOD activity in the blood samples of women with endometrial polyps [40].
A significantly higher estradiol level and GPx activity were observed in premenopausal women than the postmenopausal group. SOD activity did not differ between the two groups. Serum estradiol levels revealed a significant positive correlation with GPx activity, suggesting that the antioxidant action of estradiol to be attributed not only to its chemical structure also to its influence on cellular antioxidant enzyme defense system [41].

**Conclusion**

Reduced levels of estradiol and enzymatic antioxidant activities in hypertensive postmenopausal women with co-morbidities, suggests a possible relation between estradiol levels and co-morbid conditions.

Reduced enzymatic antioxidant activities can be attributed to elevated oxidative stress associated with menopause. The significant positive correlations exhibited by estradiol with catalase, superoxide dismutase and glutathione peroxidase activities emphasise the antioxidant activities of estradiol.

As women attain postmenopausal stage, there is a decline in the antioxidant effects of estradiol on oxidative stress. This condition seems to be fuelled and aggravated by the onset and progression of co-morbidities in postmenopausal women.

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