Endothelial and Some Cytokine Inflammatory Markers as Risk Factors of Hypertension in Postmenopausal Women

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Abstract: Objective: The aim of this study was to evaluate the role of endothelial marker (sICAM-1) and some cytokines inflammatory markers (hs-CRP, IL-6, IL-1 β) as risk factors of development of hypertension in postmenopausal women. **Study Design:** This case controlled study included three hundred postmenopausal women. All participants are classified into two main groups; group-1, included postmenopausal women with hypertension (Hypertensive group; n = 160), group 2, included postmenopausal women without hypertension (Control group; n = 140). Patients with peripheral vascular disorders, renal diseases, psychological disorders, past history of hypertension or use of antihypertensive drugs before menopause were excluded from this study. Full history taken, general and physical examinations were done for all postmenopausal women. Blood samples were obtained from each participant and collected into anticoagulated tubes. Blood samples were spun for 10 minutes, and then all plasma samples were aliquoted within 15 minutes after centrifugation and frozen at – 70°C until time of assay. We measured three inflammatory markers, including (hs-CRP, IL-6, IL-1β) and one endothelial marker, soluble intercellular adhesion molecule-1 (sICAM-1) using ELIZA technique. **Results:** There was no statistically significant difference between hypertensive group and control group regarding age (61.4 year vs 59.8 year, with p-value = 0.24), body mass index (26.3 kg/m2 vs 25.9 kg/m2, with p-value = 0.32), waist circumferences (81.4 cm vs 80.3 cm, with p-value = 0.26), physical activity (18.2 hour vs 17.6 hour, with p-value = 0.35) or smoking percentage (8.3% vs 7.85%, with p-value = 0.63). However, there was statistically significant difference regarding hs CRP, between both groups (2.3 mg/L vs 1.5 mg/L, with p-value < 0.001). Also there was statistically significant difference regarding IL-6 between both groups (1.8 ng/L vs 1.2 ng l with p-value < 0.005), however, there was no statistically significant difference between hypertensive and control groups regarding IL-1β (0.4 ng/L vs 0.36 ng/L, with p-value = 0.38). This study has also shown that there was statistically significant difference regarding the endothelial marker, soluble intercellular adhesion molecule-1(sICAM-1) between both groups (287.8 ng/L vs 236.5 ng/L, with p-value < 0.01). **Conclusion:** In conclusion, high sensitivity-C reactive protein (hs-CRP), interleukin-6 (IL-6), and soluble intercellular adhesion molecule-1 (s ICAM-1) are considered as risk factors for the development of hypertension in postmenopausal women. Interleukin-1β carries no risk factor for the development of hypertension in the postmenopausal women. Postmenopausal period per-se seems to be precipitating or predisposing factors for initiation of endothelial activation and pro- inflammation that produce such cytokines which play important role in the development of hypertension in the postmenopausal women.

1.Introduction:

Hypertension is considered the most common chronic disease affecting more than 20% of the adult population [1]. Biochemical markers like some inflammatory markers as high-sensitivity-CRP (hs-CRP), interleukin-6 (IL-6), interleukin 1-beta (IL-1β), and endothelial marker like soluble intercellular adhesion molecule-1 (sICAM-1) as risk factors of developing hypertension are less studied parameters. Both endothelial activation and chronic inflammation are pathophysiologic processes potentially implicated in the development of hypertension [20]. It has been shown that inflammatory markers attenuate the synthesis of nitric oxide (NO) in endothelial cells [14 & 16] and stimulate progressive endothelial dysfunction [5 & 15]. A number of cross-sectional studies have demonstrated high circulating levels of inflammatory markers among human subjects with increased blood pressures [2, 3, 11 & 14]. Meanwhile, only a few prospective studies have examined baseline plasma inflammatory markers typically including CRP with subsequent risk of hypertension among initially normotensive persons [7, 9, 10, & 19]. From the endocrine point of view, menopause is considered a deficiency state and estrogen therapy regarded as restoring the pre-menopausal endocrine milieu. The term post menopause defines the phase after the final menstrual period, and the median age at the menopause currently around 51 years [21]. It has been suggested that, age at menopause may be a biological marker of

ageing, and later menopausal age being associated with longevity. There are a number of factors which increase the likelihood of endothelial dysfunction in the postmenopausal women. Age related vascular changes coupled with the effect of estrogen withdrawal predispose to changes in endothelial biology [8]. The aim of this study was to evaluate the role of endothelial marker (sICAM-1) and some cytokines inflammatory markers (hs-CRP, IL-6, IL-1 β) as risk factors of development of hypertension in postmenopausal women.

2.Subjects and Methods:

This case controlled study was conducted at department of Obstetrics and Gynecology, El-Minia Maternity and Children University Hospital, in the period from August 2010 to November 2011. Two hundreds and eighty postmenopausal women were included in this study. All participants are classified into two main groups; group-1, included postmenopausal women with hypertension (Hypertensive group; n = 160), group 2, included postmenopausal women without hypertension (Control group; n = 140). Patients with peripheral vascular disorders, renal diseases, psychological disorders, past history of hypertension or use of antihypertensive drugs before menopause were excluded from this study. Patient was considered as hypertensive if his systolic blood pressure was ≥ 140 mmHg, and diastolic blood pressure was ≥ 90 mmHg. Blood pressure was measured at baseline visit using standard protocols with each participant sitting for 5 minutes before measurement. The mean of 2 readings of blood pressure obtained 30 minutes apart was used for accurate measurement. A signed informed consent was taken from each participant in this study. Full history taken, general and physical examinations were done for all postmenopausal women. Blood samples were obtained from each participant and collected into anticoagulated tubes. Blood samples were spun for 10 minutes, and then all plasma samples were aliquoted within 15 minutes after centrifugation and frozen at − 70oC until time of assay. We measured three inflammatory markers,

including (hs-CRP, IL-6, IL-1β) and one endothelial marker, soluble intercellular adhesion molecule-1 (sICAM-1) using ELIZA technique.

Statistical Analysis:

Student t-test was used to determine the significance. Values were expressed, as mean ± SD. Data was analyzed by SPSS "version 13.0" software (Statistical Package for the Social Sciences). Independent sample t-test was used to compare between studied groups. P-value < 0.05 was considered significant.

3.Results:

This study included 300 postmenopausal women classified into two main groups; group-1, included postmenopausal women with hypertension (Hypertensive group; n = 160), group 2, included postmenopausal women without hypertension (Control group; n = 140). There was no statistically significant difference between hypertensive group and control group regarding age (61.4 ± 5.2 year vs 59.8 ± 6.5 year, with p-value = 0.24), body mass index (BMI) (26.3 kg/m^2 vs 25.9 kg/m^2, with p-value = 0.32), waist circumferences (81.4 ± 12.7 cm vs 80.3 ± 14.3 cm, with p-value = 0.26), physical activity (18.2 ± 3.6 hours vs 17.6 ± 3.9 hours, with p-value = 0.35) or smoking percentage (8.3% vs 7.85%, with p-value = 0.63) as shown in table 1. However, there was statistically significant difference regarding hs CRP, between both groups (2.3 ± 0.8 mg/L vs 1.5 ± 0.6 mg/L, with p-value < 0.001). Also there was statistically significant difference regarding IL-6 between both groups (1.8 ± 0.4 ng/L vs 1.2 ± 0.5 ng/L with p-value < 0.005), however, there was no statistically significant difference between hypertensive and control groups regarding IL-1β (0.4 ng/L vs 0.36 ng/L, with p-value = 0.38) as shown in table 2. This study has also shown that there was statistically significant difference regarding the endothelial marker, soluble intercellular adhesion molecule-1(sICAM-1) between both groups (287.8 ± 67.5 ng/L vs 236.5 ± 48.2 ng/L, with p-value < 0.01) as shown in table 2.

Table 1: Patient's characteristics in both hypertensive and control groups.

Parameters	Hypertensive group (N = 160)	Control group (N = 140)	p-value
Age (mean ± SD, years)	61.4 ± 5.2	59.8 ± 6.5	0.24
BMI (kg/m^2)	26.3	25.9	0.32
Waist circumference (mean ± SD, cm)	81.4 ± 12.7	80.3 ± 14.3	0.26
Physical activity (mean ± SD, hours/week)	18.2 ± 3.6	17.6 ± 3.9	0.35
Smoking %	8.3	7.8	0.63

BMI = Body Mass index

There is no significant difference in different parameters between both groups. *→ means significant

Table 2: The mean ± SD of the different inflammatory (hs-CRP, IL-6, IL-1β) and endothelial (sICAM-1) markers in both groups.

	Hypertensive group (N = 160)	Control group (N = 140)	*p* -value
hs-CRP (mg/L)	2.3 ± 0.8	1.5 ± 0.6	< 0.001*
IL-6 (ng/l)	1.8 ± 0.4	1.2 ± 0.5	< 0.005*
IL-1β (ng/L)	0.4	0.36	0.38
sICAM-1 (ng/L)	287.8 ± 67.5	236.5 ± 48.2	< 0.01*

- * → means significant
- hs-CRP = high sensitivity C- reactive protein
- IL-6 = Interleukin-6
- IL-1β = Interleukin- 1β
- sICAM-1 = Soluble intercellular adhesion molecule -1

There is statistically significant difference between both groups regarding hs-CRP, IL-6, sICAM-1, however there is no significant difference regarding IL-1β between both groups.

4.Discussion:

This study has shown that there is a positive association between plasma concentrations of high sensitivity-C- reactive protein (hs-CRP), inteleukin-6 (IL-6), and soluble intercellular adhesion molecule-1 (sICAM-1) and presence of hypertension in postmenopausal women. However, there was no such association between interleukin-1β and hypertension in the same women. Our results are in accordance with recent study [18], in some aspect regarding the association between hs-CRP, IL-6 and presence of hypertension in the postmenopausal women, but in contrast with other aspect of there is no association between sICAM-1 and hypertension contradicted our results that have shown there is positive association between sICAM-1 and hypertension in postmenopausal women. This difference might be attributed to non-adjustment and non cross matching regarding BMI and waist circumferences between the two studies. It has been reported that systemic inflammation and endothelial activation are involved in the development of hypertension [20]. Meanwhile, experimental studies have shown that CRP, the most extensively studied inflammatory marker, may stimulate endothelial activation by decreasing the expression and activity of nitric oxide synthase [14 & 16], facilitating release of endothelin-1 [6] and reducing endothelial cell survival and differentiation. It has been documented that, in case of endothelium activation and subsequent endothelium dysfunction, endothelium-dependent vasorelaxation is impaired, and vascular tone compromised, ultimately leading to increases in blood pressure. On the surface of activated endothelial cells, the expression of cell adhesion molecules such as ICAm-1 and vascular adhesion molecule-1 (VCAM-1) is markedly increased which is accompanied by release of the soluble forms into the circulation. The adhesion molecules mediate attraction and migration of immune cells, which would further exacerbate vascular inflammation and endothelial injury. Our study extends previous cross-sectional and case control studies of endothelial markers with hypertension [23]. Inflammatory cytokines may also promote the development of hypertension through endothelium-dependent mechanisms [17]. The prospective association between CRP and incident hypertension was examined in a few studies, in some of them [19] but not all [7] studies, a positive association remained significant after controlling for body mass index. In our study both hs-CRP and IL-6 have positive associations with the development of hypertension in postmenopausal women, and this results were in contrast with what have been reported before that no significant association was found particularly after adjustment of body mass index. Obesity considered well known predictor factor for the development of hypertension and may confound the association between inflammation and hypertension. Meanwhile, inflammation and obesity share common pathways leading to hypertension, such as up-regulation of the rennin-angiotensin system [6 & 17], and disturbance of insulin actions [22]. Furthermore, adipose tissues have been characterized as dynamic endocrine organs that produce inflammatory cytokines [12], which make it more difficult to distinguish the independent effect of inflammation and obesity on hypertension. Our study has revealed that, the association between hs-CRP, IL-6, and sICAM-1 and hypertension in postmenopausal women was not related to obesity, since both groups were matched and there was no significant differences between hypertensive and control groups regarding BMI and waist circumference, the situation that considered postmenopausal period per se might be considered as a precipitating or predisposing factor for the initiation of endothelial damage and pro- inflammation that produce such cytokines which play important role in the development of hypertension in the

postmenopausal women. However, more researches are needed to support our hypothesis of such association. In conclusion, high sensitivity-C reactive protein (hs-CRP), interleukin-6 (IL-6), and soluble intercellular adhesion molecule-1 (s ICAM-1) are considered as risk factors for the development of hypertension in postmenopausal women. Interleukin-1β carries no risk factor for the development of hypertension in the postmenopausal women. Postmenopausal period per-se seems to be precipitating or predisposing factors for initiation of endothelial activation and pro- inflammation that produce such cytokines which play important role in the development of hypertension in the postmenopausal women.

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