Relationship between serum uric acid, high sensitivity C-reactive protein (hs-CRP) Level and blood pressure in premenopausal and postmenopausal women

Aye Thiri Aung■, Sanda Kyaw♦, Than Oo■

Abstract

High serum levels of uric acid and high sensitivity C-reactive protein (hs-CRP) are major risk factors of cardiovascular diseases. Postmenopausal women are said to have increased risk of cardiovascular diseases compared with premenopausal women, due to loss of endogenous sex hormone production. The aim of the present study was to explore the relationship between serum uric acid, hs-CRP and blood pressure in premenopausal and postmenopausal women. Thirty-six premenopausal women (20 - 35 years) and 38 postmenopausal women (46 - 60 years) were recruited from University of Medicine 2, Yangon. The mean serum uric acid level was 4.5 ± 2.1 mg/dl in premenopausal women and 5.1 ± 1.0 mg/dL in postmenopausal women but the difference was not statistically significant ($P > 0.05$). However, the proportion of subjects with normal serum uric acid level was 83.3% (n = 30) in premenopausal group and 52.6% (n = 20) in postmenopausal group. Conversely, the proportion of subjects with higher than normal serum uric acid level was 16.7% (n = 6) in premenopausal group and 47.4% (n = 18) in postmenopausal group. The mean value of serum hs-CRP level, 1.9 ± 3.6 mg/dl, in premenopausal women was significantly lower than 3.6 ± 2.9 mg/dl observed in postmenopausal women ($P < 0.05$). Moreover, serum hs-CRP level was normal in 86.5% (n = 31) of premenopausal women and 55.3% (n = 21) of postmenopausal women. Serum hs-CRP level was high in13.5% (n = 5) of premenopausal women and 44.7% (n = 17) of postmenopausal women. However, there was no correlation between serum uric acid level and hs-CRP level in both premenopausal ($r = 0.06$, $P > 0.05$) and postmenopausal ($r = 0.01$, $P > 0.05$) women. There was a positive correlation between serum uric acid levels and both systolic blood pressure ($r = 0.36$, $P < 0.05$) and diastolic blood pressure ($r = 0.42$, $P < 0.01$) in premenopausal women only. Similarly, hs-CRP levels were found to be positively correlated with systolic blood pressure ($r = 0.64$, $P < 0.001$) as well as diastolic blood pressure ($r = 0.67$, $P < 0.001$) but only in postmenopausal women. It can be concluded that serum uric acid and hs-CRP are independent risk factors for cardiovascular dysfunction in premenopausal and postmenopausal women.

■ Lecturer, Department of Physiology, University of Medicine 2, Yangon

♦ Professor, Department of Physiology, University of Medicine 1, Yangon

■ Associate Professor (Retired), Department of Physiology, University of Medicine 2, Yangon

Introduction

Menopause is derived from Greek word “meno” (month) and “pauo” (to stop) and is applied to the permanent cessation of menstruation due to loss of ovarian follicular activity. The term “postmenopause” applies to the whole of a woman’s life after the menopause[1]. Epidemiological evidence suggested that premenopausal women are at lower risk of coronary heart disease (CHD) than men of comparable age, and this relative cardiovascular protection is lost following the menopause[2].

After menopause, serum uric acid values for women increase approximately to those of men[3]. Serum uric acid is increased in postmenopausal women due to changes in metabolism as a consequence of menopause and other age-related factors[4]. Some workers reported that hyperuricemia was not an independent risk factor for cardiovascular events[5]. However, there were several controversies about the nature of the relation between uric acid and cardiovascular events. It was exceedingly difficult to prove an independent role of uric acid because of the large number of risk factors involved in cardiovascular disease and their close relation to uric acid[6].

C reactive protein is also an independent risk factor for cardiovascular disease in healthy postmenopausal women[7]. CRP is an acute phase reactant and is synthesized primarily in hepatocytes and regulated by interleukin 6 (IL-6), interleukin 1 (IL-1), tumor necrotic factor alpha (TNF-α) and other cytokines. Serum CRP level is < 2 mg/L in populations without evidence of acute illness, and those with a level of > 3 mg/L have a high risk of future cardiovascular disease[8].

During the present decade, there are reports indicating close association between increased serum uric acid level and systemic inflammation, raised C-reactive protein (CRP), endothelial dysfunction, hypertension, and cardiovascular disease (CVD)[9]. Several studies have recently suggested that there is a direct correlation between levels of uric acid and CRP in patients with advanced renal dysfunction and hypertension[10].

The present study focused on blood pressure and its relationship with serum levels of uric acid and hs-CRP in premenopausal and postmenopausal women. The data on menopausal aged women could be beneficial for early detection and reduction of cardiovascular risks.

Materials and Methods

Subjects

Study population

Apparently healthy premenopausal women of age between 20 - 35 years and postmenopausal women of age between 46 - 60 years from the University of Medicine

2 (including students and staff) participated in this study. A written informed consent was obtained individually. History taking and clinical examination were carried out according to proforma. A total of 74 (36 premenopausal women and 38 postmenopausal women) participated in this study.

Methods

Determination of body mass index (BMI)

BMI was calculated with following formula[11]

$$\text{BMI (kg/m}^2\text{)} = \frac{\text{Weight in kilogram}}{(\text{Height in metre})^2}$$

Measurement of arterial blood pressure

Blood pressure was measured from upper arm by indirect method using mercury sphygmomanometer (ALPK2, Japan) and stethoscope (Littmann, USA)[12] taking standard precautions[13].

Determination of serum uric acid and serum hs-C reactive protein level

Serum uric acid level was measured by alkaline phosphotungstate method[14]. Serum hs-C reactive protein level was measured by enzyme-linked immunosorbent assay (DRG®, Hs-C reactive protein, EIA - 3954).

Cut-off value for high uric acid: > 5.7 mg/dl; (normal 2.4 - 5.7 mg/dl)[15]

Cut-off value for high hs-CRP: > 3 mg/L[16]

Experimental procedure

Experiments were done from 8:00 am to 10:00 am. After resting for 30 minutes, systolic and diastolic blood pressure of each subject was measured three times in sitting position, and the mean was recorded. Measurement of height (in meters) and weight (in kilograms) were carried out and BMI calculated. Blood sample (5 ml) was taken from cubital vein by using disposable syringe. Samples were collected into the test tubes without anticoagulant. The test tubes were capped and labeled. Serum was promptly separated and then stored at - 20^0 C for later analysis for uric acid and hs-CRP within 2 - 3 months.

Statistical Analysis

The computer based statistical package of statistical product and service solution (SPSS) version 16.0 was used for data handling and analysis. Results were expressed as mean ± SD. Unpaired 't' test was used to compare the means of the variables between

premenopausal and postmenopausal women, and Pearson's correlation coefficient was used to assess the relationship between serum uric acid, hs-C reactive protein and blood pressure. The level of significance was set at $P < 0.05$.

Results

Baseline characteristics of subjects are shown in Table - 1. A total of 74 subjects (36 premenopausal women and 38 postmenopausal women) participated in this study. It was noted that body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly higher in postmenopausal women than those in premenopausal women ($P < 0.001$). The mean serum uric acid level was 4.5 ± 2.1 mg/dl in premenopausal women and 5.1 ± 1.0 mg/dl in postmenopausal women but the difference was not statistically significant ($P > 0.05$). The mean serum hs-CRP level was significantly lower ($P < 0.05$) in premenopausal women (1.9 ± 3.6 mg/dl) compared with that in postmenopausal women (3.6 ± 2.9 mg/dl).

Table - 1. Baseline characteristics of premenopausal and postmenopausal women in the study

Parameter	Premenopausal Women Mean ± SD (n = 36)	Postmenopausal Women Mean ± SD (n = 38)	P value
Weight (kg)	51.98 ± 6.66	57.10 ± 4.72	**P < 0.05**
Height (cm)	155.18 ± 4.34	154.60 ± 3.34	**NS: P > 0.05**
BMI (kg/m^2)	21.61 ± 2.6	23.89 ± 2.07	**P < 0.001**
SBP (mmHg)	119.44 ± 10.93	140.26 ± 15.15	**P < 0.001**
DBP (mmHg)	77.5 ± 6.03	85.26 ± 7.25	**P < 0.001**
Serum uric acid (mg/dl)	4.5 ± 2.1	5.1 ± 1.0	**NS: P > 0.05**
Serum hs-CRP (mg/dl)	1.9 ± 3.6	3.6 ± 2.9	**P < 0.05**

Out of 74 women, the number of those with normal serum uric acid level was 83.3% (n = 30) in premenopausal women and 52.6% (n = 20) in postmenopausal women, while the number of those with high serum uric acid level was 16.7% (n = 6) in premenopausal women and 47.4% (n = 18) in postmenopausal women. Moreover, out of 74 women, those with normal serum hs-CRP level was 86.5% (n = 31) in premenopausal group and 55.3% (n = 21) in postmenopausal group while those with high serum hs-CRP level was 13.5% (n = 5) in premenopausal group and 44.7% (n = 17) in postmenopausal group (Figure - 1).

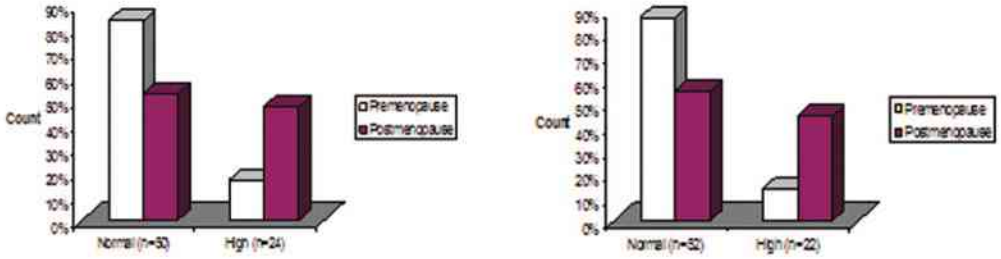

Figure - 1. The prevalence of increased serum uric acid (left panel) and hs-CRP level (right panel) in premenopausal and postmenopausal women

However, there was no correlation between serum uric acid and hs-CRP level in both premenopausal ($r = 0.06$, $P > 0.05$) and postmenopausal ($r = 0.01$, $P > 0.05$) women (Data not shown).

A positive correlation between serum uric acid and both SBP ($r = 0.36$, $P < 0.05$) and DBP ($r = 0.42$, $P < 0.01$) was observed only in premenopausal women (Figure - 2). In contrast, a positive correlation between hs-CRP level and SBP ($r = 0.64$, $P < 0.001$) and DBP ($r = 0.67$, $P < 0.001$) was observed only in postmenopausal women (Figure - 3).

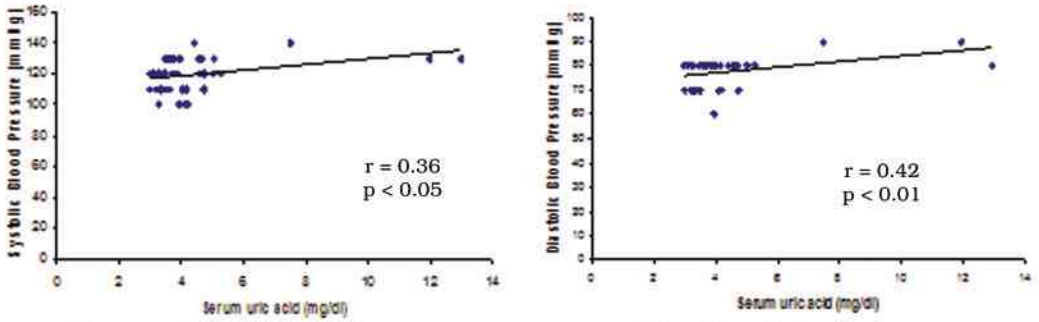

Figure - 2. Correlation between serum uric acid level and blood pressure in premenopausal women (n = 36)

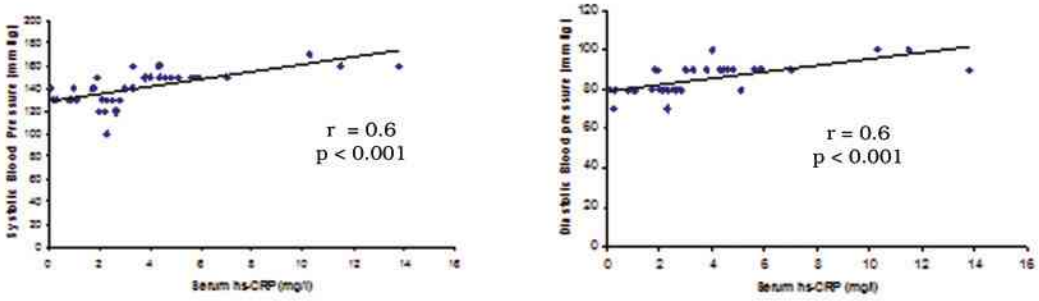

Figure - 3. Correlation between serum hs-CRP level and blood pressure in postmenopausal women (n = 38)

Discussion

In the present study, postmenopausal women had higher BMI compared with that of premenopausal women. The relationship between BMI and menopause may be due to the metabolic alterations as a result of menopause which causes significant changes in body fat distribution[17]. In the present study, both SBP and DBP were increased in postmenopausal women. Menopause is an age-related phenomenon and hypertension is an age-related disease associated with renal dysfunction, increased peripheral resistance, endothelial dysfunction and obesity[18]. Moreover, the menopause transition is marked by changes in hormonal balance, including a rapid decline of endogenous estradiol level. Estrogens decrease cholesterol level and prevent atherosclerosis[19]. Hence atherosclerotic changes might play a role in the rise in BP observed in postmenopausal women.

In 1998, Wingrove *et al* [20] reported that serum uric acid level of 50 premenopausal women and 88 postmenopausal women were 201 ± 6.25 μmol/l and 220 ± 5.9 μmol/l respectively suggesting a significant difference between premenopausal and post-menopausal women. However, in the present study, mean serum uric level was not significantly different between premenopausal women and postmenopausal women. However, the proportion of women with high uric acid level was 16.7% (n = 6/74) in premenopausal group and 47.4% (n = 18/74) in postmenopausal group. Our results suggest that menopausal status could be associated with high serum uric acid level, and this again may be due to rapid decline in endogenous estradiol level since oestrogen has been shown to induce renal uric acid excretion[21]. Ishizaka *et al* in 2005 reported that serum uric acid concentrations were positively correlated with blood pressure and total and regional adiposity[22]. However, the present study found a positive correlation between serum uric acid concentration and both SBP ($r = 0.36$, $P < 0.05$) and DBP ($r = 0.42$, $P < 0.01$) only in premenopausal women but not in postmenopausal women ($r = 0.11$, $P > 0.05$).

From a study on 1274 premenopausal women and 447 postmenopausal women, Hyun Koh *et al* (2008) reported serum hs-CRP level of 0.01 ± 0.29 mg/L in premenopausal women and 0.20 ± 0.65 mg/L in postmenopausal women suggesting that postmenopausal women had significantly higher hs-CRP level compared with that of premenopausal women[23]. The findings of the present study are consistent with those of Hyun Koh *et al* (2008). Increased BMI in postmenopausal women might be a contributory factor.

In the present study, it was found that there was significant positive correlation between hs-CRP and both SBP and DBP in postmenopausal women ($r = 0.6$, $P < 0.001$) but not in premenopausal women. One of the plausible explanations might be increased body mass index as obesity is associated with increased plasma levels of proinflammatory cytokines, including interleukin-6 and tissue necrotic factor α, which increase circulating CRP levels[24]. CRP has been shown to cause hypertension by initiating and propagating

atherosclerosis and increasing the tissue damage[25], by causing endothelial dysfunction by elaborating cytokines[26] and by decreasing endothelial nitric oxide (NO) expression[27].

In the present study, there was no significant positive correlation between serum uric acid and hs-CRP levels in premenopausal and postmenopausal women (data not shown). Therefore, it can be concluded that serum uric acid and hs-CRP are independent risk factors for cardiovascular dysfunction in premenopausal and postmenopausal women.

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