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Elevated High-Sensitivity C-Reactive Protein And Interleukin-6 Plasma As Risk Factors For Symptomatic Lumbar Osteoarthritis In Postmenopausal Women

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Abstract

AIM: To determine whether elevated high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and erythrocyte sedimentation rate (ESR), as risk factors of symptomatic lumbar osteoarthritis (OA) in estrogen deficiency postmenopausal women.

METHODS: A case-control study was conducted between January and June 2017. The inclusion criteria include post-menopausal women with estrogen deficiency with low back pain. Exclusion criteria were: patients with a history of undergoing bilateral oophorectomy, taking hormonal replacement therapy or corticosteroid, malignancies, and lumbosacral spine trauma. The blood examinations were taken to measure IL-6 level by ELISA, hs-CRP level by spectrophotometry and ESR by modified Westergren method.

RESULTS: A group of 44 pairs of subjects were divided equally into case and control groups showed that in estrogen deficiency postmenopausal women, an increased level of hs-CRP increased the risk for symptomatic lumbar OA (OR = 2.83, CI95% = 1.065-8.776, p = 0.034). Also, a high level of IL-6 increased the risk of symptomatic lumbar OA (OR = 2.7, CI95% = 0.991-8.320, p = 0.033). No such significant findings were found for an increased ESR level.

CONCLUSION: Elevated level of plasma hs-CRP and IL-6 were concluded as risk factors for symptomatic lumbar OA in post-menopausal women.

Introduction

Low back pain (LBP) is often as a chief complaint of the degenerative spine lesion. The prevalence of osteoarthritis at the age of 50 years both in men and women is relatively similar and increasing in women of over 50 years old. Numerous causes have been proposed, including estrogen alterations that frequently arise in post menopausal women in post-menopausal age [1], [2].

Lumbar osteoarthritis (OA) is a cartilage degeneration involving the narrowing of the intervertebral discs, lumbar vertebral osteophyte, and osteoarthritis of the facet joints [2], [3], [4]. Some suspected causes of lumbar OA include hormonal changes in post menopausal women, including changes in the hormone estrogen, mechanical stress caused by weight gain and ageing process, and inflammatory process.

Chronic inflammation that occurs in lumbar OA involved the role of cytokines, like interleukin 6 (IL-6), IL-10 and IL-1ra [5]. According to another study, IL-6 level and IL-6/IL-10 ratio were predictive as the risk of lumbar OA [2]. An increased level of inflammatory mediators will cause a systemic

inflammatory reaction. It is now believed that patients with LBP have increased levels of hs-CRP and ESR [6] [7]. C-reactive protein is well established as a systemic marker for inflammation and tissue injury [7]. Commonly, can be detected within 6-8 hours after the injury. Meanwhile, ESR is well-known as a non-specific marker of inflammation.

Currently, limited studies have been reported regarding hsCRP and ESR levels in LBP patients, especially in hormonal-related OA [6] [7] [8] [9]. The association between increased hsCRP and low back pain is controversial.

The goal of this study is to elucidate elevated hs-CRP, IL-6, and ESR, as risk factors for symptomatic lumbar OA in estrogen deficiency postmenopausal women.

Patients and Methods

This was a case-control study that conducted between January and June 2017 at Sanglah Hospital. The ethical clearance was certified by the Committee of Ethical Research of Udayana University/Sanglah Hospital. All patients have signed an informed consent paper to be included in this study.

The total subjects were 88 patients, distributed equally into two groups. The case group consists of 44 post-menopausal women with symptomatic lumbar OA and estrogen deficiency. Subjects whose history of bilateral oophorectomy, taking hormonal replacement therapy or corticosteroid, malignancies, lumbosacral spine trauma, or other large joint arthritis, were excluded from the study. The control group consists of equally 44 postmenopausal women, with asymptomatic lumbar OA. They were matched individually by body mass index (BMI) and age to the case group.

Plasma IL-6, hs-CRP, and ESR were analysed using enzyme-linked immunosorbent assay (ELISA), spectrophotometry, and modified Westergren method, respectively. The descriptive analysis described subjects characteristics. McNemar's chi-square was used for bivariate analysis. The odds ratio was used for risk estimation. The correlation between hs-CRP and IL-6 was analysed using Pearson's Correlation test.

Results

The total number of subjects in this study was 88. They were paired and distributed equally to the case and control groups. The median age of the subjects was 58 years old. Subject characteristics are shown in Table 1.

We used the cut-off point of IL-6 was 2.264 pg/L and hs-CRP level of 5.00 mg/L. The odds ratio (OR) was 2.7 (95% CI = 0.991-8.320, p = 0.033); 2.83 (95% CI = 1.065-8.776, p = 0.034) respectively, as shown in Table 2.

Table 1: Subject characteristic of each study group

Characteristic	Case group	Control group
Age (years), median (IQR[1])	58 (54-61)	58 (53-60)
Duration of menopause (years), median (IQR)	7 (4-10)	8 (3-10)
Blood estrogen level (pg/mL), median (IQR)	12.7 (9.00-20.87)	14.16 (9.51-19.23)
BMI (kg/m^2), median (IQR)	25.92 (23.27-28.06)	25.28 (22.86-27.37)
IL-6 (pg/L), mean ± SD[2]	76.358 ± 152.798	6.966 ± 12.244
hs-CRP (mg/L), mean ± SD	5.795 ± 4.137	3.568 ± 3.303
ESR (mm/hour), mean ± SD	13.831 ± 14.798	16.730 ± 12.517

[1]Interquartile range; [2]Standard deviation.

Discussion

Osteoarthritis is a complicated process of joint degeneration. Inflammation maybe plays a critical role as interleukin upregulation, which arises following the ageing of the immune system or obesity [10].

Table 2: McNemar's test for IL-6, hs-CRP, and ESR in symptomatic lumbar osteoarthritis

Variables	OR[1]	p	95% CI
IL-6 (pg/L)	2.7	0.033	0.991-8.320
hs-CRP (mg/L)	2.8	0.034	1.065-8.776
ESR (mm/hour)	0.5	0.179	0.538-0.181

[1]McNemar's test, p < 0.05 as significant.

Despite being a degeneration process, inflammation also plays a role in OA. The inflammatory development that happens in lumbar osteoarthritis involves the role of proinflammatory cytokines, or anti-inflammatory cytokines [2], [4].

In this study, IL-6 was found to be statistically significant with (OR = 2.7; p = 0.033). Both Weber et al., and Valdes also reported that IL-6 was higher in LBP patients [11], [12]. Both IL-1 and IL-10 were also reported to correlate with the risk of osteoarthritis [11], [12]. Chingford reported that circulating IL-6 was related to OA development in women.[13] Postmenopausal female with knee osteoarthritis also showed higher IL-6 levels (p < 0.001) as compared to healthy female subjects [14], [17].

Ershler et al. also found an increase of IL-6 in postmenopausal patients [18], [19]. In postmenopausal patients, as the estrogen levels decline, the osteoclast formation increased and leading to bone resorption. The cartilage regulation also affected by estrogen levels because the isomer of the estrogen receptor (ER-α) is expressed in joint and growth plate cartilage in humans and other

species [1], [20].

We also found that hs-CRP levels significantly acted as a risk factor (OR = 9.0, p = 0.011) similar to reports by Rannou et al., [21]. Reports suggested that hs-CRP was elevated in the acute phase of inflammation [21], [22], [23]. Gebhardt found that hs-CRP level was not associated with either somatic function or pain level in LBP patients [24].

Both ESR and hs-CRP tests are used to detect inflammation. In inflammation, fibrinogen will enter the blood and cause raise the ESR [25]. The hs-CRP is synthesised in the liver and is often called an acute-phase protein [25]. The elevated hs-CRP level is also linked with the manifestation of synovial inflammatory infiltrates, and it is also correlated with proportions of T-cells in the synovial membrane. These findings were independent of the stage of OA disease [25]. Stümer reporteda correlation between pain scale and hs-CRP in patients with acute sciatic pain, where a higher hs-CRP level was associated with a higher pain level [26].

Kim found that IL-6 levels were elevated in postmenopausal women who healthy, nonobese, and elderly. The IL-6 may be a better marker of constant mild inflammatory activity [27]. In this study, as the age and BMI were controlled and adjusted, the hs-CRP and IL-6 level in symptomatic lumbar osteoarthritis in postmenopausal women were significantly elevated.

Mild systemic inflammation may have a more significant role in symptomatic lumbar OA rather than radiographic findings [28]. Symptomatic lumbar OA was a degenerative spine disorder in which the inflammation also plays a role in the symptom manifestation. In this study, the ESR was not significant statistically as a risk factor (OR = 0.53, p = 0.179). This possibly caused by the fact that ESR is less specific for inflammation marker compared than hs-CRP.

In conclusion, a high level of plasma IL-6 and hs-CRP are risk factors for symptomatic lumbar OA in estrogen deficiency postmenopausal women, indicating the role of the inflammation process in this lumbar OA.

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