Evaluation of Highly Sensitive C-Reactive Protein in Female Patients with Nodal Osteoarthritis

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ABSTRACT:
BACKGROUND:
Nodal Osteoarthritis is a subset of OA characterized by polyarticular interphalangeal and thumb base OA. Heberden’s and Bouchard’s nodes formation. C-reactive protein (CRP) is one of the first acute phase response proteins to be elevated in an inflammatory processes.

OBJECTIVE:
The aim of this study is to investigate whether the inflammatory processes have roles in the development of nodal osteoarthritis (NOA) in Iraqi female patients using serum highly sensitive C-reactive protein as an inflammatory marker.

SUBJECTS AND METHODS:
The study included eighty four females, divided into two main groups, sixty were patients with (NOA), and twenty-four represented the control group. Other subdivisions were applied according to body mass index and menopause status. Measurement of serum (hsCRP), was applied to all subjects included in this study, by ELISA sandwich method.

RESULTS:
Serum highly sensitive C-reactive protein (hsCRP) level was significantly higher (18.08±8.15) (P value < 0.05) in patients with NOA in comparison to control group (2.23±1.73).

CONCLUSION:
Highly significant elevated level of serum (hsCRP) observed in the NOA patients compared to control suggest that the inflammatory processes have roles in the development of NOA.

KEY WORDS: high sensitive C - reactive protein, nodal osteoarthritis.

INTRODUCTION:
Nodal osteoarthritis (NOA) a subset of OA, is characterized by polyarticular interphalangeal and thumb base OA. Heberden’s nodes are a classic sign of hand osteoarthritis, which is presented in the distal interphalangeal joint. Also in hand OA there is another nodes called Bouchard’s Nodes formation which is predominant in women has a clear genetic predisposition. OA can be localized on one, two, or more joints, but if it affects three or more joint groups, it is usually known as polyarticular or generalized that both systemic and local factors affect the likelihood of OA development in joint. The local biomechanical factors have a crucial influence on the final quality of articular cartilage. OA is synthesized mainly in liver and several extrahepatic cells like macrophages and adipocytes. It is one of the first acute phase response proteins to be elevated in an inflammatory processes and exhibiting the most dramatic increase in concentration.

Risk Factors:
Risk factors for NOA include:
1. Female sex:
2. Increasing age older than 40 years:
3. Menopausal:
4. Family history of hand OA:
5. Obesity:
6. High bone density:
7. Increased forearm muscle strength:
8. Joint laxity:
9. Previous hand injury, hand usage related to occupation or recreation:

The classical symptoms of hand OA include:
- Joint pain, morning stiffness, (duration < ½ hour) and loss of motor function.
Clinical signs of the disease include: Crepitus, joint effusion and Heberden's and Bouchard's nodes. Women had more incident disease than men in almost all hand joints. The joints most frequently affected are the same in both sexes: the distal interphalangeal, followed by the base of the thumb, proximal interphalangeal, and metacarpophalangeal joints.

Criteria for the diagnosis of OA should be clearly stated. Patients should fulfill validated criteria for the classification of OA such as those published by the American College of Rheumatology.

Clinical criteria:
1. Hand pain, aching, or stiffness for most days of prior month.
2. Hard tissue enlargement of >2 of 10 selected hand joints.
3. Fewer than 3 swollen MCP joints.
4. Hard tissue enlargement of 2 or more DIP joints.
5. Deformity of 2 or more of 10 selected hand joints.

OA present if items 1, 2, 3, 4 or items 1, 2, 3, 5 are present. It has sensitivity 92% and specificity 98%.

Ten selected hand joints include bilateral 2nd and 3rd DIP joints, 2nd and 3rd PIP joints and first CMC joints.

Pathophysiology of CRP:
Among the changes observed during the acute-phase response to an inflammatory stimulus is an dramatic increase in hepatic synthesis of a number of plasma proteins, collectively known as acute-phase proteins. C-reactive protein is a major human acute-phase protein whose concentration may increase >1000-fold in severe inflammatory states. In particular, the synthesis of CRP is upregulated, principally in hepatocytes, under the control of cytokines originating at the site of pathology.

The determination of CRP is more sensitive, evaluating a quick response by a direct measurement. It reflects the extension of the inflammatory process or clinical activity. C-reactive protein (CRP), a stable pentameric protein, which has a half-life of 19 hr, is not subject to diurnal variation, and can serve as a marker of wellness and a candidate for future direct access testing for people monitoring their health after adopting a healthier lifestyle. The CRP level may be influenced more by lifestyle than by genetics. Along with the erythrocyte sedimentation rate (ESR), CRP is probably the most popular laboratory marker of activity in joint diseases, the rise in CRP is one of the main hallmarks of inflammatory arthropathies, where as in OA, which is commonly classified as a “non-inflammatory” arthropathy, CRP has until now been considered useless. However, serum CRP determination has recently been proposed in OA of the hip and knee, as a marker of disease severity.

In NOA, the recent availability of a new highly sensitive method for CRP (hsCRP) determination could probably improve the value of disease severity.

SUBJECTS AND METHOD:
Sixty female patients with NOA and twenty-four healthy control women matched for age, and BMI have been studied. The patients studied in this case-control study have been randomly selected from patients attended Rheumatology and Rehabilitation Out-Patient Clinic, Medical City, Baghdad Teaching Hospital during the period from 1st of April to 1st October 2010.

The sixty female patients with NOA have been diagnosed clinically according to American Committee of Rheumatology clinical criteria, and the diagnosis was confirmed radiologically. Some of laboratory tests have been done for each patient to exclude other possible causes of arthritis. These tests were: serum RF and serum uric acid. All patients are clinically examined to exclude other co-excited diseases starting from history, clinical examination and other laboratory tests included general urine examination and fasting blood sugar. The control group included apparently healthy age and weight matched women. Excluding information regarding infections was collected by the pre-tested questionnaire that designed to obtain information from both patient and control groups.

BMI calculated according to the following equation: BMI = weight (kg)/ square height (m²). The national institutes of health (NIH) classify subjects according to their BMI as:

- Normal: 18.5 - 24.9 kg/m².
- Overweight: 25 - 29.9 kg/m².
- Class I obesity: 30 - 34.9 kg/m².
- Class II obesity: 35 - 39.9 kg/m².
- Class III obesity: >40 kg/m².

In order to evaluate the relation of highly sensitive C-reactive protein level with NOA, patient and control groups have been subdivided as follows:

1-Patients group:
It represents sixty female patients with NOA mean (±SD) age (50.3±14.3) year subdivided according to BMI into overweight /obese group and normal group.

A- Thirty three female patients with BMI of ≥ 25 kg/m² were overweight and obese group.
B- Twenty seven female patients with BMI of (18.5-25) kg/m² were included in the normal weight group. Also patients group was subdivided again according to menopausal status into:
   a- Twenty eight premenopausal patients
   b- Nine women with BMI (18.5-25) kg/m² were normal group.

Also control group was subdivided again according to menopausal status into:
   a- Eleven premenopausal.
   b- Thirteen postmenopausal women.

2- Control group:
Include twenty-four women of mean age (49.5 ±12.4) year old subdivided according to BMI into:
   A- Fifteen women with BMI≥ 25 kg/m² were overweight and obese group.
   B- Nine women with BMI (18.5-25) kg/m² were normal group.

RESULT:
Number and percentage of studied groups and subgroups. The main groups were patients and the control, while the subgroups include overweight/obese and normal; the premenopausal and postmenopausal status.

Table 1 : Statistical analysis of both the patients and control groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Premenopause</th>
<th>Postmenopause</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>28 (46.6%)</td>
<td>32 (53.4%)</td>
<td>-</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>29.5±2.7</td>
<td>32.5±3.8</td>
<td>N.S</td>
</tr>
<tr>
<td>hsCRP (mg/l)</td>
<td>17.1±8.05</td>
<td>19.0±8.27</td>
<td>N.S</td>
</tr>
<tr>
<td>ESR (mm/3/hr)</td>
<td>23.5±6.4</td>
<td>24.7±7.6</td>
<td>N.S</td>
</tr>
<tr>
<td>WBC (×10⁹/liter)</td>
<td>6.3±0.87</td>
<td>6.5±0.21</td>
<td>N.S</td>
</tr>
<tr>
<td>PCV (%)</td>
<td>0.38±0.23</td>
<td>0.38±0.22</td>
<td>N.S</td>
</tr>
</tbody>
</table>

Table 2: Statistical data of patients and control groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Overweight &amp; obese</th>
<th>Normal weight</th>
<th>Premenopause</th>
<th>Postmenopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (71.4%)</td>
<td>Number</td>
<td>33</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Percentage</td>
<td>55</td>
<td>45</td>
<td>46.6</td>
</tr>
<tr>
<td>Controls (28.6%)</td>
<td>Number</td>
<td>15</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Percentage</td>
<td>62.5</td>
<td>37.5</td>
<td>45.9</td>
</tr>
<tr>
<td>Total 84 (100%)</td>
<td>Number</td>
<td>48</td>
<td>36</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Percentage</td>
<td>57.2</td>
<td>42.8</td>
<td>46.4</td>
</tr>
</tbody>
</table>

Results expressed as mean ±SD.
N.S : not statistically significant.

The study showed that the mean(±SD) of serum hsCRP level was significantly higher in the patients group compared with the controls group (P.value<0.05). The other parameters age, BMI, ESR, WBC, and PCV showed no significant difference (P.value>0.05).
C-REACTIVE PROTEIN IN PATIENTS WITH NODAL OSTEOARTHRITIS-FEMALE

Table 3: Statistical data of patients subgroup, according to BMI.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients</th>
<th>Control</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>60 (71.4%)</td>
<td>24 (28.6%)</td>
<td>-</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.3±14.3</td>
<td>49.5±12.4</td>
<td>N.S</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>31.0±3.05</td>
<td>30.4±3.36</td>
<td>N.S</td>
</tr>
<tr>
<td>hsCRP (mg/l)</td>
<td>18.0±8.15</td>
<td>2.23±1.73</td>
<td>0.001</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>24.10±5.4</td>
<td>20.78±5.98</td>
<td>NS</td>
</tr>
<tr>
<td>WBC (×10⁹/liter)</td>
<td>6.42±1.05</td>
<td>6.4±1.31</td>
<td>N.S</td>
</tr>
<tr>
<td>PCV (%)</td>
<td>0.38±0.02</td>
<td>0.38±0.06</td>
<td>N.S</td>
</tr>
</tbody>
</table>

Results expressed as mean ±SD. N.S : not statistically significant.

2- Statistical analysis of patients group.

Although the study showed significant difference among the patients subgroup according the body mass index, there was no significant difference in the serum highly sensitive C-reactive protein values in such subgroup. (P >0.05)(Table 3).

Table 4: Statistical data of the patients subgroup according to the menopausal status.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overweight &amp; Obese</th>
<th>Normal weight</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>33 (55%)</td>
<td>27 (45%)</td>
<td>-</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>37.5±6.5</td>
<td>24.5±0.5</td>
<td>0.001</td>
</tr>
<tr>
<td>hsCRP (mg/l)</td>
<td>18.4±8.02</td>
<td>17.6±8.46</td>
<td>N.S</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>25.5±6.2</td>
<td>23.7±4.6</td>
<td>N.S</td>
</tr>
<tr>
<td>WBC (×10⁹/liter)</td>
<td>6.4±1.02</td>
<td>6.3±1.09</td>
<td>N.S</td>
</tr>
<tr>
<td>PCV (%)</td>
<td>0.38±0.02</td>
<td>0.38±0.02</td>
<td>N.S</td>
</tr>
</tbody>
</table>

Results expressed as mean ±SD. N.S : not statistically significant.

DISCUSSION:

Highly sensitive C-reactive protein:

Most of the traditional methods for CRP, which are not highly sensitive, can only detect a value of >6 mg/L, whereas this acute phase protein may be found in the blood at concentration of 0.00035 mg/L[8]. Thus, even in the presence of a 100-fold increase of CRP, the CRP variation may be undetectable by methods which are not highly sensitive. Previously one of the reasons for this discrepancy in CRP results may be due to the use of non-sensitive methods for the evaluation of CRP[9]. In the present study the mean±SD age of patients group was (50.3±14.3) year and the mean±SD BMI was (31.05 kg/m²±3.05). The mean age was (60.5 years) and BMI was (31.03 kg/m²) in (Botha-scheepers and Riyazi,2009) study[10] , in other study like (Dahaghin and Bierma-Zeinstra;2007) the mean age was( 66 years) and the BMI was (26.3 kg/m²)[11].

In this present study (46.6%) of patients group was premenopause and (53.4%) was post menopause. In( Botha-scheepers and Riyazi, 2009) study (86.7%) was postmenopausal[10] and in (Bijsterbosch and Bemmel;2011) study (90%) of the cases was postmenopausal[12].

In this study the mean (±SD) hsCRP of the patients group (18.8 mg/l ±8.15) was significantly higher than the mean (±SD) serum hsCRP of controls group (2.23mg/l±1.28mg/l) .(p value <0.05), but there was no significant relationship in other laboratory parameters (ESR ,WBC and PCV) in patients groups compared with control group. In
pathological CRP is derived from articular, mainly synovial tissue. According to this hypothesis, a recent study (Loose et al., 2003) found in patients with OA the median hsCRP concentrations is 3 times higher than in age matched control (15). In a study by Chen et al. (2008), the serum concentration of CRP derived from hepatic production and that inflammatory cytokines, in particular interleukin (IL-6), are mainly responsible for its synthesis. In turn it has been demonstrated that, even at lower levels than in inflammatory arthropathies, the principal proinflammatory cytokines such as IL1b, IL6, IL8, and tumour necrosis factor are increased in the synovial fluid of OA (17).

Thus, it seems logical that most of the circulating IL6 which can stimulate synthesis of CRP is derived from articular, mainly synovial tissue. Obviously because in OA of the hands the tissues producing cytokines are relatively small in comparison with OA of large joints, it may be that serum levels of CRP in NOA better reflect disease activity when more joints are affected by the inflammatory phase. Another interpretation of the differences between the NOA and the control group, is that patients with NOA have serum levels of CRP constitutionally higher than those control group. With the higher serum levels of soluble receptors of IL2, markers of lymphocyte activation, found in NOA in comparison with control group (18). Recently (Stern et al., 2003) have reported an association between HOA and nucleotide polymorphisms in a Caucasoid population, further supporting a potential role for inflammation in the pathogenesis of this subtype of NOA (19). These hypotheses imply that NOA is a subset of OA with peculiar characteristics and predispositions and an inflammatory phase and not the normal OA course.

CONCLUSION:
The increase of serum hsCRP in NOA confirms the presence of inflammatory activity in this form of arthropathy and the possibility that a severe local injury as in OA also has a systemic component and the inflammatory cytokines responsible for synthesis of hepatic CRP is derived from articular, mainly synovial tissue. The higher levels of serum hsCRP seen in the early stages of NOA reflects that the NOA is an inflammatory condition rather than normal ageing process.

REFERENCES:


