ORIGINAL ARTICLE

Osteopontin in chronic obstructive pulmonary disease: Smokers and ex-smokers

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Received 16 October 2014; accepted 10 November 2014
Available online 8 December 2014

KEYWORDS
Osteopontin;
Smokers;
Ex-smokers;
COPD

Abstract Background: COPD is a widely distributed disease with high morbidity and mortality, associated with different pathologies. The link between osteopontin, smoking and COPD needs to be clarified.
Objectives: To study the osteopontin serum levels in smoker COPD patients and ex-smoker COPD patients.
Methods: Serum levels of osteopontin were measured in 38 male COPD patients divided into smoker and ex-smoker groups using human osteopontin ELISA kits.
Results: There was a significant difference between smokers and ex-smokers regarding their serum osteopontin levels. There was no significant difference in serum osteopontin level between COPD patients regarding severity in both groups. There was a significant difference in serum osteopontin level between the smokers group regarding their pack year index of smoking. There was no significant difference in serum osteopontin level between ex-smokers group regarding the duration of cessation.
Conclusion: Serum level of osteopontin is increased in COPD patients and decreases with cessation of smoking. It has no relation to disease severity.
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Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with some significant extra pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases [1].

Cigarette smoking is the major risk factor associated with the development of COPD: Heavy smokers are at greater risk of developing COPD than moderate smokers [2].
Osteopontin is a secreted phosphorylated glycoprotein expressed in mineralized tissues and damaged renal tissues; it is also expressed by immune cells during inflammation and enhances the proinflammatory T-helper 1 cell response and inhibits the T-helper 2 cell response [3].

Aim of the work

The aim of the current study was to study the osteopontin serum levels in smoker COPD patients and ex-smoker COPD patients.

Patients and methods

This work was carried out on 38 male patients with COPD diagnosed and classified according to GOLD 2010 [1], referred to chest hospital in Shebin El-Kom. The study also included ten healthy male controls; their ages were matched with the patients.

Subjects were divided into:

Group A: included 19 smoker patients with COPD and were subdivided into: 14 patients with moderate COPD and 5 patients with severe COPD.

Group B: included 19 ex-smoker patients with COPD and were subdivided into: 12 patients with moderate COPD and 7 patients with severe COPD.

Group C: included 10 healthy volunteers who had no symptoms or signs of any chest disease and had normal ventilatory function tests as a control group.

After having a written consent; each patient underwent:

1. Full history taking and clinical examination.
2. Chest X-ray.
3. Pulmonary function tests.

Morning spirometry was done and all patients had $\text{FEV}_1/\text{FVC}$ of less than 70% and post bronchodilator spirometry was performed after giving the patient a bronchodilator, such as an inhaled beta-agonist e.g. salbutamol 400 μg [4].

The following parameters were measured:

(a) Forced expiratory volume in the first second ($\text{FEV}_1$) pre and post bronchodilator.
(b) Forced vital capacity (FVC).
(c) $\text{FEV}_1$/FVC ratio.
(d) Peak expiratory flow rate (PEFR).

Patients were classified according to GOLD staging system (GOLD 2010) [1] into:

Stage I: mild COPD ($\text{FEV}_1/\text{FVC} < 70\%$; post bronchodilator $\text{FEV}_1 \geq 80\%$ predicted).
Stage II: moderate COPD ($\text{FEV}_1/\text{FVC} < 70\%$, $50\% \leq \text{post bronchodilator FEV}_1 \leq 80\%$ predicted).
Stage III: severe COPD ($\text{FEV}_1/\text{FVC} < 70\%$, $30\% \leq \text{post bronchodilator FEV}_1 \leq 50\%$ predicted).
Stage IV: very Severe COPD ($\text{FEV}_1/\text{FVC} < 70\%$, post bronchodilator $\text{FEV}_1 \leq 30\%$ predicted or post bronchodilator $\text{FEV}_1 \leq 50\%$ predicted plus chronic respiratory failure).

Serum osteopontin level was measured for all subjects using human osteopontin ELISA kit.

Results

Table 1 shows the distribution of the studied groups regarding GOLD stages of patients in each group (classified according to GOLD 2010), and there was:

From 19 smoker patients in group (A), 14 (73.7%) had moderate COPD, 5 (26.3%) had severe COPD. While from 19 ex-smoker patients in group (B), 12 (63.2%) had moderate COPD, 7 (36.8%) had severe COPD. There was a non significant difference between smokers and ex-smokers groups as regards the GOLD stage ($P$-value $> 0.05$).

Table 2 shows that the mean age of patients in group A was $55.89 \pm 8.17$ years. In group B; the mean age of patients was $54.73 \pm 6.37$ years. Lastly, in the control group (C); the mean age of patients was $53.40 \pm 9.45$ years. There were insignificant differences between the patients of both groups and between them and the control group as regards age ($P$-value $> 0.05$).

Table 3 shows a significant difference between group (A) and group (B) regarding their serum osteopontin level ($P$-value $< 0.01$). There was also a significant difference between group (A) and the control group (C) ($P$-value $< 0.01$). However, there was a non significant difference between group (B) and group (C) regarding their serum osteopontin level ($P$-value $> 0.05$).

Table 4 shows that there was no significant difference between moderate and severe COPD smokers as regards serum osteopontin level ($P$-value 0.853).

Table 5 shows the non significant difference between moderate and severe COPD ex-smokers as regards serum osteopontin level ($P$-value 0.673).

Table 6 shows that there was no significant difference in mean serum osteopontin level between ex-smokers group regarding their duration of cessation ($P$-value 0.514).

Discussion

COPD is an inflammatory disease caused mainly by smoking [5]. Osteopontin as a mediator of inflammation may be implicated in the pathogenesis of a variety of disease states including COPD and its complications [6].

This work was carried out on 38 patients with stable COPD diagnosed clinically and by spirometry and classified into two groups: Smokers (Group A) and Ex-smokers (Group B). In addition to 10 healthy non smoker subjects as a control group were included. Serum OPN was measured for all subjects.

In the present study, the results showed a significant difference ($P < 0.01$) between smokers and ex-smokers regarding their serum OPN level (higher in smokers), there was also a significant difference between group A and the control group ($P$-value $< 0.01$). There was a non significant difference between group B and the control group regarding their serum osteopontin level (Table 3). These results were matched with the results of the studies carried out by Bishop et al. [7] who
Table 1  Distribution of the studied groups according to their GOLD stage.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Smokers (A) (n = 19)</th>
<th>Ex-smokers (B) (n = 19)</th>
<th>$\chi^2$</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>%</td>
<td>No</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>14</td>
<td>73.7</td>
<td>12</td>
<td>63.2</td>
</tr>
<tr>
<td>Severe</td>
<td>5</td>
<td>26.3</td>
<td>7</td>
<td>36.8</td>
</tr>
</tbody>
</table>

Table 2  Distribution of the studied groups according to their age.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Smokers (Group A) (n = 19)</th>
<th>Ex-smokers (Group B) (n = 19)</th>
<th>Controls (Group C) (n = 10)</th>
<th>$F$ test</th>
<th>Post hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>55.89 ± 8.17</td>
<td>54.73 ± 6.37</td>
<td>53.40 ± 9.45</td>
<td>0.34</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.89 ± 8.17</td>
<td>54.73 ± 6.37</td>
<td>53.40 ± 9.45</td>
<td>0.34</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Table 3  Distribution of the studied groups according to their osteopontin level (pg/ml).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Smokers (Group A) (n = 19)</th>
<th>Ex-smokers (Group B) (n = 19)</th>
<th>Controls (Group C) (n = 10)</th>
<th>Kruskal–Wallis test</th>
<th>Post hoc value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>5453.40 ± 3508.54</td>
<td>1695.57 ± 587.59</td>
<td>1687.65 ± 1423.88</td>
<td>A versus B (&lt;0.01)</td>
<td>A versus C (&lt;0.01)</td>
</tr>
</tbody>
</table>

Table 4  Comparison of serum osteopontin levels (pg/ml) in different GOLD stages in group (A).

<table>
<thead>
<tr>
<th>Smokers</th>
<th>Moderate</th>
<th>Severe</th>
<th>Mann–Whitney</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>5856.0 ± 3625.6</td>
<td>4326.20 ± 3243.09</td>
<td>0.18</td>
<td>0.853 (NS)</td>
</tr>
</tbody>
</table>

Table 5  Comparison of serum Osteopontin levels (pg/ml) in different GOLD stages in group (B).

<table>
<thead>
<tr>
<th>Ex-smokers</th>
<th>Moderate</th>
<th>Severe</th>
<th>Mann–Whitney</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>1718.0 ± 654.28</td>
<td>1657.20 ± 498.26</td>
<td>0.42</td>
<td>0.673 (NS)</td>
</tr>
</tbody>
</table>

Table 6  Comparison of serum osteopontin level (pg/ml) in ex-smokers according to the duration of cessation of smoking.

<table>
<thead>
<tr>
<th>Ex-smokers</th>
<th>Duration of cessation (Y)</th>
<th>Mann–Whitney</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>&lt; 3</td>
<td>≥ 3</td>
<td></td>
</tr>
<tr>
<td>Serum osteopontin (pg/ml)</td>
<td>1802.20 ± 752.73</td>
<td>1577.10 ± 330.75</td>
<td>0.65</td>
</tr>
</tbody>
</table>
found that cigarette smoking caused a concentration-dependent increase in osteopontin levels in cultured human endothelial cells and this effect was significantly reduced in the presence of antioxidants, suggesting a role for oxidants in the expression of osteopontin. Serum osteopontin levels were lowered in human subjects whose oxidative stress/inflammatory burden had likely been lowered by smoking cessation [7]. Hillas et al. [8] found that osteopontin levels were significantly higher in COPD smokers compared to non-smokers, and both non-smoking and smoking controls.

Berania et al. [9] showed that total white blood cell count (as a marker of inflammation) was significantly higher in active smokers than in those who had never smoked and ex-smokers. There was no significant difference between moderate and severe COPD smokers as regards serum osteopontin level (Table 4). Also there was no significant difference between moderate and severe COPD ex-smokers as regards serum osteopontin level (Table 5). These results were in concordance with the results of the study carried out by Zhao et al. [10] in which there was no significant association between OPN concentration and disease severity.

Ma et al. [11] studied serum osteopontin levels in patients with stable chronic obstructive pulmonary disease and exacerbations. Osteopontin was higher in patients with acute exacerbation than with stable COPD and in healthy control subjects. Lee et al. [12] studied plasma osteopontin levels in COPD patients classified into stable, frequent exacerbators and infrequent exacerbators, the results showed that patients with COPD exacerbations had increased plasma OPN levels compared with those with stable COPD and healthy controls. Also frequent exacerbators had higher plasma osteopontin levels compared with infrequent exacerbators. Accordingly, the presence of exacerbation and frequency of exacerbations are important factors in elevating serum osteopontin levels in patients with chronic obstructive pulmonary disease not the stage of the disease.

In the current study, there was no significant difference in mean serum osteopontin level between ex-smokers group regarding their duration of cessation; OPN levels were compared in ex-smokers who quit smoking for less than three years with ex-smokers who quit smoking for three years or more and found no significant difference between both groups (Table VI). These results can be explained by the results of Bishop et al. [7] study which showed that in smokers who quit smoking for 5 days, serum osteopontin levels were significantly lowered compared to those measured prior to smoking cessation. Accordingly we can predict that after less than six months of smoking cessation, serum osteopontin level reaches a steady level which will not be affected by longer duration of smoking cessation.

Conclusion

From the present study we concluded that the serum level of osteopontin is increased in smoker COPD patients. Osteopontin can be used as a new marker of inflammation caused by smoking in COPD patients. OPN levels in COPD patients have no relation to GOLD stage and it decreases with cessation of smoking.

Conflict of interest

The authors declare that there is no conflict of interest.

References