Introduction

Sulfur mustard (SM) is an alkylating agent that was used extensively as a chemical warfare during World War I and the Iraq–Iran War. Eyes, skin, and in particular, respiratory system are three primary target organs affected by mustard gas. Injuries in these organs may persist for 20 years after exposure.\(^1\) The reported late respiratory complications of SM include chronic bronchitis, bronchiectasis and fibrosis. Bronchiolitis obliterans has also been reported as the main late complication of SM exposure.\(^2\) SM and its derivatives are known to react with cysteine residues in proteins, as well as with histidine, glutamic acid and aspartic acid. It has been shown that albumin is effectively alkylated by SM and that the Cys\(^{34}\) residue is an important site for alkylation.\(^3\) In the case of SM toxicity, inactivation and depletion of the antioxidant enzymes results in oxidative stress and activation of the immune system in the lungs. It is not clear whether oxidative stress is a direct effect of mustard gas toxicity or a consequence of the inflammation.\(^4\) In any case, the oxidant/antioxidant imbalance may cause a variety

**Original Article**

Serum albumin and paraoxonase activity in Iranian veterans 20 years after sulfur mustard exposure

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Abstract

Sulfur mustard, a chemical warfare agent, has short- and long-term effects on various organs including respiratory system. Its late toxic effects on biological macromolecules among exposed veterans have not been well studied. We performed a study to determine paraoxonase-1 (PON1) activity and phenotype distribution as well as its correlation with albumin level in 289 male veterans with severe pulmonary complications who had exposure to sulfur mustard 20 years ago and in 66 age and ethnic matched healthy male subjects as controls. Serum albumin levels were lower in the veterans compared to controls (\(P < 0.001\)). Mean basal PON1 activity was 91.61 ± 44.80 U/mL in the veteran group versus 110.27 ± 50.23 U/mL in controls (\(P = 0.005\)). Arylesterase activity was not significantly different between the two groups. Paraoxonase to arylesterase activity ratio was significantly lower in the veterans as compared to controls (\(P = 0.005\)), mainly indicative of decreased PON1 activity rather than enzyme level. Significant reduction was found in serum albumin and PON1 activity with disease severity. Moreover, decreased high active BB (high activity) phenotype and increased intermediate active AB (moderate activity) phenotype were found in the veterans. This condition may lead to long-term accumulation of reactive oxygen metabolites resulting in a pro-oxidation milieu, which in turn can lead to increased peroxide levels and decreased antioxidant PON1 activity. In conclusion, lower serum PON1 activity and albumin might contribute to morbidity and occurrence of other complications such as atherosclerosis and rapid aging in the veterans suffering from late toxic effects of sulfur mustard.

**Keywords:** Sulfur mustard, pulmonary complications, paraoxonase, albumin, oxidative stress
of respiratory diseases such as bronchiolitis obliterans, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis and asthma.\(^{(6)}\)

Paraoxonase-1 (PON1, E.C.3.1.8.1) is a 44 kDa Ca\(^{2+}\)-dependent glycoprotein. It is synthesized mainly in the liver and circulates on the surface of high-density lipoprotein (HDL). It is a multifunctional antioxidant enzyme which hydrolyzes a variety of organic compounds including organophosphates, aryesters, lactones and specific oxidized lipids. Oxidative stress, by increasing lipid and protein oxidation or decreasing vitamins and antioxidant enzymes, has also negative effects on the PON1 expression and activity; therefore, dietary antioxidants would preserve PON1 activity.\(^{(6)}\) PON1 possesses peroxidase-like activity, which confers a protective effect against lipoprotein oxidation and homocysteine thiolactonase activity involved in its antiatherogenic properties.\(^{(7)}\)

PON1 varies in its hydrolyzing capacity due to several polymorphisms in the coding and non-coding regions of its gene.\(^{(5)}\) The capacity of PON1 alloenzymes to protect LDL from oxidation is the inverse of that of paraoxon hydrolytic activity.\(^{(9)}\) Several studies have revealed the relationship between PON1 and pulmonary diseases,\(^{(10)}\) the presence or extent of coronary artery diseases (CAD) and cardiovascular diseases.\(^{(11)}\) An epidemiologic study has shown that, in middle-aged men, low paraoxynase activity is an independent risk factor for coronary events.\(^{(12)}\) It is also proposed that hypoalbuminemia may be a causal risk factor for lung injury\(^{(13)}\) and atherosclerosis.\(^{(14)}\) Furthermore, conditions with high oxidative stress such as coronary heart disease, dyslipidemias (low-HDL syndrome, hypertriglyceridemia), inflammatory processes, diabetes mellitus and certain neuropathies result in decreased PON1 activity.\(^{(15)}\) Low serum PON1 activity was reported independent of genotype in diseases associated with accelerated atherogenesis such as type 2 diabetes mellitus, hypercholesterolemia, iron-deficiency anemia and renal failure.\(^{(11,16)}\) Furthermore, exposure to environmental chemicals such as organophosphate pesticide and nerve gas also result in PON1 inhibition.\(^{(17)}\) A decreased capacity to detoxify nerve gas due to low serum PON1 activity was reported to be contributed to the development of Gulf War Syndrome.\(^{(14)}\)

The possible role of oxidative stress in the pathogenesis of SM toxicity in conjunction with the antioxidant role of PON1 is the rational for investigating PON1 activity and phenotype distribution in pulmonary incapacitated veterans with history of SM exposure. To our knowledge, there has been no comprehensive study on the PON1 activity and phenotype distribution in this regard. It can also be speculated that PON1 activity could help to further identification of subjects with an elevated risk of other diseases such as atherosclerosis.

### Materials and methods

The study was performed on 289 SM-exposed male veterans with clinically significant pulmonary complications and 66 healthy male from victims’ family members with the same age as controls. An informed consent was obtained from all subjects before measurements. Patients’ history of hypercholesterolemia, hypertension, diabetes, and current smoking habits was obtained from their medical records. Baseline data were collected by trained research assistants during face-to-face interviews. Pulmonary function test was performed in all participants according to the American Thoracic Society Criteria using spirometry device (Chest 801 Spirometry).

#### Blood samples

A venous blood sample after overnight fasting was obtained from all participants. The blood samples were collected in tubes with K\(_2\)EDTA. The samples were centrifuged, aliquoted and immediately frozen at −70°C for later assessment. Serum was used for the determination of biochemical parameters.

#### Biochemical analyses

Serum levels of glucose, urea, creatinine, uric acid, total protein, triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL)-cholesterol, and HDL-cholesterol were measured by available assay kits (Pars Azmoon-Co, Tehran, Iran). Serum albumin level was measured colorimetrically (Pars Azmoon-Co, Tehran, Iran), serum lipoprotein(a) (LP(a)), apoA-I and apoB levels were determined using commercial assay kits (Alpha Laboratories, Eastleigh, UK) on an ELISA reader (Biotek Power wave XS2, USA).

#### Assay of paraoxonase activity

PON1 baseline activity (without NaCl) and salt-stimulated activity (with 1 mol/L NaCl) were assayed according to absorbance at 405 nm for 5 min following the formation of p-nitrophenol. The assay buffer contained 0.125 mol/L Tris-HCl, 1.25 mmol/L CaCl\(_2\), and 1 mol/L NaCl (pH 8.5). For each set of assays, 6 mmol/L of paraoxon (O,O-diethyl- O-p-nitrophenylphosphate; Sigma Chemical Co., USA) substrate solution was freshly prepared from a stock solution of 120 mmol/L paraoxon in acetone diluted with 0.125 mmol/L Tris-HCl. Paraoxon stock solution was handled very cautiously with protective measures. The assay tube contained 790 µL of Tris buffer, 10 µL of serum and 200 µL of 6 mmol/L paraoxon. The reaction was initiated at 37°C with adding the substrate solution; absorbance was continuously monitored at 405 nm. The PON1 unit was defined as the enzyme quantity that disintegrates 1 µmol of paraoxon substrate per min. \([\text{PON1 activity with 1 mol/L NaCl} – (\text{basal PON1 activity})/\text{basal PON1 activity}] \times 100.\]

#### Assay of arylesterase (AE) activity

AE activity was measured with phenylacetate substrate as previously described.\(^{(19)}\) AE activity was manipulated with salt. The assay tube contained 748 µL of 0.1 mol/L Tris-HCl (pH 8.5), 1 mmol/L CaCl\(_2\), 125 µL of 12 mmol/L
phenylacetate and 2 µL of serum. The absorbance was continuously monitored at 270 nm at 37°C. The units were expressed as milimoles of phenylacetate hydrolyzed per minute.

Distribution of PON1 phenotypes
PON1 phenotype was determined using double substrate method in each participant as follows: salt-stimulated paraoxonase activity was divided by the arylesterase activity. Based on this ratio, samples were divided into three phenotypes: ratios of 0.3–1.2 as AA (low activity); 1.21–3.25 as AB (moderate activity) and 3.26–6.7 as BB (high activity).

Statistical analysis
Statistical analyses were conducted using SPSS 18.0 software (SPSS Inc., Chicago, IL, USA). Data are expressed as mean ± standard deviation. Normality of the sample distribution of each continuous variable was tested with the Kolmogorov–Smirnov test. Differences of continuous variables were evaluated by the Student’s-t or Mann–Whitney U-tests, based on the shape of the distribution curves.

Results
The basic values of biochemical serum parameters of the two study groups are shown in Table 1. There were no significant differences between the two groups in terms of blood glucose, uric acid, cholesterol (LDL and HDL), triglyceride and creatinine levels. However, a significantly higher serum urea level and lower serum albumin level and albumin to globulin ratio were found in the SM-exposed veterans as compared to controls.

Table 2 summarizes paraoxonase activities in the study groups. Serum basal and salt-stimulated PON1 activities were significantly lower in the veterans compared with the controls. Mean basal PON1 activity was 110.27 ± 50.23 (range 44.3–289.9) U/mL in controls and 91.61 ± 44.80 (range 28.6–253.9) U/mL in non-diabetic veterans (P = 0.005). Mean activity of PON1 in the presence of 1 M NaCl (salt-stimulated paraoxonase activity) was 257.25 ± 175.81 (range 60.02–605.3) U/mL in controls vs. 191.70 ± 124.02 (range 40.17–585.87) U/mL in non-diabetic SM-exposed veterans (P = 0.001). These features reveal up to a ten-fold variation in enzymatic activities within the study groups. Arylesterase activity, indicative of PON1 level, was not significantly reduced in non-diabetic veterans as compared to controls.

Standardizing the PON1 activity based on serum levels of HDL-cholesterol (PON1/HDL) or apoA-I (PON1/apoA-I) revealed that the standardized enzyme activity (PON1/HDL) was also significantly lower (P = 0.006) in veterans comparing to controls (Table 3). However, there was no significant difference between veterans and controls in term of PON1/apoA-I ratio. Furthermore, positive but not significant correlation was found between serum PON1 activity and HDL-cholesterol level in veterans (r = 0.006, P = 0.929). Arylesterase activity was not significantly different between the two groups (Table 2). PON1 arylesterase activity was also standardized based on HDL-cholesterol level (Arylesterase/HDL) and ApoA-I (Arylesterase/apoA-I), but no significant differences were found between the study groups (Table 3). There were no significant differences in term of TC/HDL-cholesterol and apoB/apoA-I ratios between the two study groups.

The ratio of salt-stimulated paraoxonase to arylesterase activity showed a trimodal PON1 frequency distribution in both SM-exposed subjects and controls (Table 4). The relative PON1 phenotype distribution appeared to be significantly different between controls and veterans.
Veterans were grouped based on disease severity in order to verify the roles of PON1 activity and albumin levels on pulmonary complications (Table 7). Arylesterase activity was not significantly different between controls and any of patient groups. However, albumin levels and paraoxonase activity were significantly lower in veterans with severe pulmonary diseases as compared to controls and a gradual decrease in paraoxonase activity and albumin levels was found with increasing disease severity.

Veterans were also divided into two groups based on serum albumin levels (data not shown). Paraoxonase activity in veterans with albumin levels <4.75 mg/dL was significantly lower than in those with higher albumin levels. Veterans with low albumin levels (<4.75) had also low total protein levels. No significant difference was found between the two groups of veterans in terms of arylerase activity.

**Discussion**

Oxidative stress seems to be involved in SM toxicity and may contribute to the pathogenesis of various diseases and injuries. Based on the impact of oxidative stress in respiratory and heart diseases and the lack of studies on the role of antioxidants, including albumin and PON1, in the population suffering of late toxic effects of SM, we evaluated serum levels of albumin and PON1 activity in these individuals. In a recent study, cardiac symptoms and signs in mustard gas exposed patients were evaluated by physical examination. The prevalence of chest pain was higher in veterans than in controls, but no difference was reported in term of cardiac signs. Several authors strongly emphasized on the importance of serum PON1 concentrations and activities in relation with COPD and ischemic stroke susceptibility. Accordingly, it is expected that the lower PON1 activity 

**Table 2. PON1 activities in SM-exposed patients and controls.**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (n = 66)</th>
<th>Exposed (n = 250)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraoxonase (U/mL)</td>
<td>110.27 ± 50.23</td>
<td>92.18 ± 45.05</td>
<td>0.005</td>
</tr>
<tr>
<td>Arylesterase (kU/L)</td>
<td>117.71 ± 23.01</td>
<td>108.42 ± 29.83</td>
<td>0.182</td>
</tr>
<tr>
<td>Salt-stimulated paraoxonase (U/mL)</td>
<td>257.25 ± 175.81</td>
<td>191.70 ± 124.02</td>
<td>0.001</td>
</tr>
<tr>
<td>Percentage of activation by 1 M NaCl</td>
<td>118.94 ± 98.21</td>
<td>99.23 ± 65.02</td>
<td>0.052</td>
</tr>
<tr>
<td>Paraoxonase/arylesterase activity</td>
<td>2.19 ± 1.37</td>
<td>1.77 ± 0.99</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.
Serum albumin and paraoxonase activity in chemical veterans

Serum basal and especially salt-stimulated paraoxonase activities were significantly lower in SM-exposed veterans; however, arylesterase activity, an index of enzyme concentrations, was not significantly reduced in this group. The higher differences in paraoxonase activity between veterans and controls in the presence of salt may be partly due to the presence of enzymes with low activity and/or inactivated enzymes in the veterans.

In vitro experiments showed that high levels of urea, creatinine and uric acid did not affect PON1 activity. Therefore, the significant increased urea level in our series may have not affected the paraoxonase activity and the observed reduced activity seemed to be due to other factors.

Can Demirdogen et al. reported that the paraoxonase/arylesterase activity ratio may be a protective factor for ischemic stroke. In our study, this ratio was significantly lower in veterans comparing to controls, indicative of reduced PON1 activity rather than enzyme level. Both Paraoxonase and arylesterase activities were lower in subjects with significant CAD, lung cancer, active pulmonary tuberculosis, sepsis, β-thalassemia minor and active Helicobacter pylori infections. Other studies on patients with chronic liver impairment as well as in HIV-infected subjects have shown decreased PON1 activity despite the increased PON1 concentration. In this study however, the paraoxonase activity and concentration were not similar to those in the aforementioned studies.

HDLC and LDL-C levels were not significantly different between veterans and controls. However, paraoxonase/HDL-C and paraoxonase/LDL-C ratios were significantly decreased in veterans as compared to controls. It has also been shown that HDL-C level, the carrier of PON1, is significantly low in majority of studies as is the concentration of PON1, but in our study neither HDL-C nor arylesterase activity were found to be different in the study groups. This finding reveals

Table 5. Serum PON1 activity in the AA, AB and BB phenotypes of SM-exposed patients and controls.

<table>
<thead>
<tr>
<th>Activities</th>
<th>Control</th>
<th>Exposed</th>
<th>Control</th>
<th>Exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA (n = 25)</td>
<td>AB (n = 29)</td>
<td>BB (n = 12)</td>
<td>AA (n = 97)</td>
<td>AB (n = 155)</td>
</tr>
<tr>
<td>Arylesterase (kU/L)</td>
<td>103.11 ± 21.65</td>
<td>121.12 ± 22.34^a</td>
<td>117.88 ± 20.38</td>
<td>107.29 ± 24.99</td>
</tr>
<tr>
<td>Paraoxonase (U/mL)</td>
<td>64.91 ± 15.17</td>
<td>130.00 ± 36.89^a</td>
<td>157.05 ± 53.41^b,c</td>
<td>56.74 ± 14.82^d</td>
</tr>
<tr>
<td>Salt-stimulated paraoxonase (U/mL)</td>
<td>95.71 ± 24.81</td>
<td>285.10 ± 85.44^a</td>
<td>526.51 ± 149.30^b,c</td>
<td>86.90 ± 25.36</td>
</tr>
</tbody>
</table>

Significant compared with AA (*P < 0.01, ^aP < 0.001, ANOVA tukey post hoc); Significant compared with AB (*P < 0.001, ANOVA tukey post hoc); Comparison between exposed and control (*P < 0.01, independent t-test).

Table 6. Correlation between arylesterase and paraoxonase activity.

<table>
<thead>
<tr>
<th>Arylesterase level</th>
<th>n</th>
<th>Control Mean ± SD Median</th>
<th>P value</th>
<th>Exposed Mean ± SD Median</th>
<th>P value</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;91.7</td>
<td>11</td>
<td>61.11 ± 18.69 54.48</td>
<td>&gt;0.001</td>
<td>69.73 ± 25.96 63.71</td>
<td>0.293</td>
<td>----</td>
</tr>
<tr>
<td>91.7–107</td>
<td>17</td>
<td>88.26 ± 32.90 79.87</td>
<td>&gt;0.001</td>
<td>88.69 ± 38.67 84.03</td>
<td>0.967</td>
<td>----</td>
</tr>
<tr>
<td>107–125.2</td>
<td>18</td>
<td>117.37 ± 40.00 118.66</td>
<td>&lt;0.001</td>
<td>91.29 ± 37.96 87.72</td>
<td>&lt;0.001</td>
<td>0.013</td>
</tr>
<tr>
<td>&gt;125.2</td>
<td>20</td>
<td>149.61 ± 50.94 142.20</td>
<td>&gt;0.001</td>
<td>120.64 ± 57.82 115.19</td>
<td>&lt;0.001</td>
<td>0.048</td>
</tr>
</tbody>
</table>

Figure 1. Pearson correlation between (A) Arylesterase and salt-stimulated paraoxonase activity in controls (n = 66, r = 0.499, P < 0.001) and veterans (n = 271, r = 0.431, P < 0.001). (B) Albumin and paraoxonase activity in controls (n = 63, r = 0.254, P = 0.045) and veterans (n = 243, r = 0.135, P = 0.035).
that low paraoxonase activity in veterans is independent of the serum levels of PON1, HDL-C and LDL-C. It has been reported that decreased PON1 activity could be secondary to enzyme inactivation due to increased oxidative stress or accompanying an acute phase response that inhibits hepatic synthesis of PON1.\(^{(27)}\) The latter mechanism was not the case in our study because arylesterase activity, indicative of enzyme level and/or its synthesis, was not significantly different between the two groups. Therefore, factors reducing oxidative stress are potentially capable of improving PON1 activity.

PON1 attached to HDL may block inflammatory responses by preventing the oxidation of LDL.\(^{(27)}\) Decreased PON1 activity during an acute phase reaction is related to decreased apoA-I and missed contact of PON1 with HDL. In this condition, HDL failed to protect LDL from oxidation.\(^{(27)}\) The failure of HDL to protect LDL from oxidation has been shown in patients with coronary atherosclerosis as a result of low PON1 activity despite relatively normal HDL levels.\(^{(34)}\)

It is investigated whether changes in apoA-I level were responsible for decreased PON1 activity and found that the PON1/apoA-I ratio was not different in veterans and controls. This result indicates that low apoA-I levels may also play a role in lower paraoxonase activity in veterans. Modification of apoA-I by reactive oxygen species under systemic inflammation might be a possible cause in the lack of apoA-I ability to play its normal function.\(^{(35)}\) However, we did not find any relationship between plasma HDL-C level and PON1 activity. It seemed that inflammation did not proportionately reduce the HDL-C and apoA-I levels and PON1 activity despite the fact that apoA-I and PON1 were both bound to HDL particles.\(^{(36)}\)

Using two-substrate analysis to determine the PON1 phenotypes, we found different PON1 phenotypes distribution in the control and patient groups. Three phenotypes were postulated for PON1 based on the enzyme activity: low (AA), intermediate (AB), and high (BB). The A and B isoforms are characterized by a low and high paraoxonase activity respectively. PON1 phenotype distribution in the control group was the same as PON1 phenotypes in healthy Iranian population.\(^{(19)}\) In accordance with previous study,\(^{(19)}\) the BB phenotype was associated with increased serum TGs levels in controls. Considering the discrepancy between different studies on PON1 polymorphisms and serum lipid levels,\(^{(37,38)}\) further studies are required to clarify the actual influence of PON1 phenotypes on lipid profile.

Variability of PON1 status would impact the metabolism of many drugs and environmental toxic agents such as pesticides and various war gases. The capacity of paraoxonase to hydrolyze lipid peroxides and some toxins such as soman and sarin was reported to be the inverse of paraoxon hydrolytic activity.\(^{(39)}\) The B polymorphism was demonstrated as an independent cardiovascular risk factor and constitutes a better predictor of vascular disease than PON1 gene polymorphisms.\(^{(40)}\) It has been reported that PON1 polymorphisms and low PON1 activity might be considered as an independent risk factor for COPD.\(^{(41)}\) However, there is no comprehensive study regarding the relation of PON1 phenotype distribution with various pulmonary diseases. In our study, the intermediate activity (AB) phenotype was more frequent in the SM-exposed veterans than in controls. Therefore, it can be claimed that the high activity (BB) phenotype may also be inactivated due to the metabolic condition in veterans’ body. This difference in PON1 activity phenotypes could be ascribed to the observed complications in veterans.\(^{(42)}\)

In this study, a significant decrease was found in serum albumin level and albumin to globulin ratio in the SM-exposed veterans. Albumin is the most abundant protein in the plasma and is known as an extracellular antioxidant, because it binds redox active metals and limits the production of metal-catalyzed free radicals.
Decreased total thiol levels have been attributed to a decrease in serum albumin levels and increased oxidative stress in the elderly. PON1 is also inactivated due to the interaction of its free sulfhydryl group (Cys) with oxidized lipids. Direct correlation between serum albumin and PON1 activity was found in our study which is indicative of the possible role of albumin in paraoxonase protection. However, lower correlation of albumin with paraoxonase activity with disease severity was observed. Therefore, albumin level can serve as a simple prognostic biomarker for heart failure in SM-intoxicated veterans.

Conclusions

The possible long-term increase in reactive oxygen metabolites in SM-exposed veterans may result in a pro-oxidation environment in their body, which in turn can lead to increase in peroxide levels and decrease in antioxidant PON1 activity and albumin level. However, further assessment on other factors such as trace element and other antioxidant is required to verify our conclusion and to provide more information regarding the factors causing a decreased PON1 activity. In conclusion, it is predicted that PON1 activity and albumin level will be varied with the progress of pulmonary complications in SM-intoxicated veterans. We also speculate that SM-exposed veterans have increased susceptibility to cardiovascular disease and rapid aging.

Acknowledgements

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Declaration of interest

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