Full Length Research Paper

Relation between Surfactant Protein-D level and cardiovascular complications in chronic Kidney disease

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Abstract

Chronic kidney disease (CKD) is a global public health problem that is estimated to affect many individuals worldwide. It is associated with a very high risk of premature cardiovascular mortality and morbidity. Surfactant protein D (SP-D) expression was observed originally in the lung but it has been found also in several extra pulmonary tissues, including the kidney. Circulating SP-D levels are strongly predictive of future risk of cardiovascular morbidity and mortality, independent of well established risk factors. The study aimed to evaluate the relation between serum SP-D and cardiovascular complications in CKD. The study was conducted on 90 participants, 60 patients with various degrees of CKD as well as 30 healthy volunteers as a control group. Patients were subdivided into 3 groups according to estimated glomerular filtration rate (eGFR); Group 1 included 20 patients with eGFR > 60 ml/min/1.73², Group 2 included 20 patients with eGFR < 60 ml/min/1.73², and Group 3 included 20 patients with eGFR < 15 ml/min/1.73². Serum SP-D levels were measured in all subjects using the quantitative sandwich enzyme immunoassay technique. As a marker of atherosclerosis, the carotid artery intima media thickness (CA IMT) was measured in all patients in addition to echocardiographic assessment of the cardiac dimensions and functions. The study showed a significant increase in the mean serum SP-D in CKD patients compared to that of the control group (6±1.36 ng/ ml vs.2.46±0.31, P=0.02) and also among groups 1, 2 and 3 CKD patients (2.38±0.34 vs. 5.63±1.84 vs. 9.98±3.51respectively, P<0.05). The study showed also a significant positive correlation between SP-D level and the diastolic blood pressure (DBP), the platelet count and smoking among CKD patients, while there was a significant negative correlation between SP-D level and serum albumin. There was no significant correlation between SP-D level and CA IMT and echo parameters among CKD patients. Serum SP-D is significantly elevated in patients with CKD. There was no significant correlation between SP-D and CA IMT as a marker of atherosclerosis and echocardiographic parameters of cardiac dimensions and functions.

Keywords: Surfactant Protein, Cardiovascular, Kidney disease.

INTRODUCTION

CKD is a global public health problem that is estimated to affect many individuals worldwide. Over the last two decades, several studies have reported a high prevalence of cardiovascular disease in patients with end –stage renal disease (ESRD). Cardiovascular pathology remains the leading cause of morbidity and mortality in those patients (Pateinakis and Papagianni, 2011).

Cardiovascular disease in CKD can be attributed to two distinct but overlapping pathological processes, namely atherosclerosis and arteriosclerosis. While atherosclerosis is primarily an intimal disease, patchy in distribution and occurring in medium-sized arteries, arteriosclerosis is a diffuse disease of the media which leads to increased arterial stiffness (Moody et al., 2013).

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The increase in cardiovascular risk is commonly attributed to co-existence of numerous traditional and non-traditional risk factors for the development of cardiovascular disease that frequently accompany reduced kidney function (Briasoulis and Bakris, 2013).

SP-D, a member of the collecting protein family, is produced by the alveolar type-II (AT-II) cells of the lungs. It is essential for the efficient exchange of gases and for maintaining the structural integrity of alveoli (Akella and Deshpande, 2013). It also plays an important role in innate host defense and regulation of inflammatory processes in the lung (Wright, 2005).

SP-D expression was observed originally in the lung, but it has been found also in several extra pulmonary tissues including the kidney (Stahlman et al., 2002). Serum SP-D was found to be significantly increased in patients with CKD compared to non–CKD patients (Xie et al., 2013).

SP-D is a potent modulator of inflammation according to in-vitro and in-vivo studies so, it is logical to speculate that SP-D may contribute to the innate immune mechanism in the pathogenesis of renal inflammatory diseases (Wright, 2005).

Circulating SP-D levels are strongly predictive of future risk of cardiovascular mortality, independent of well-established risk factors. These data implicate lung inflammation in the pathogenesis of heart and blood vessel disease and raise the possibility of using this protein as a biomarker to risk stratify cardiovascular disease patients above and beyond traditional risk factors such as serum cholesterol and C-reactive protein (Hill et al., 2011).

The study aimed to evaluate the relation between serum SP-D and cardiovascular complications in CKD patients.

**SUBJECTS AND METHODS**

The study included 90 participants, 60 patients with various degrees of CKD as well as 30 healthy volunteers as a control group. All patients were recruited to the study from the internal medicine department and outpatient clinic of Al-Zahraa University hospital in the period from January 2014 to October 2015.

**Inclusion criteria**

- Age >18 and ≤65 years.
- Patients with CKD due to any cause, of both sexes and of different stages (according to eGFR as calculated by MDRD formula (Woodhouse et al., 2006)).
- Patients with ESRD on chronic maintenance hemodialysis for at least three months.

**Exclusion criteria**

- Active malignancy
- Concurrent infection
- Acute and chronic liver diseases.
- Primary lung diseases e.g. bronchial asthma and interstitial pulmonary fibrosis.
- Antibiotics or immunosuppressive agents use.

CKD patients were further subdivided into 3 groups according to eGFR:

**Group 1**: included 20 patients with preserved kidney function and eGFR ≥ 60 ml/min/1.73² (stage 1 and 2 of Kidney Disease Outcomes Quality Initiative (KDOQI) classification of CKD (KDOQI, 2002))

**Group 2**: included 20 pre-dialysis CKD patients with sustained reduction (≥ 3 months) of eGFR ≤ 60 ml/min/1.73² (stage 3 and 4).

**Group 3**: included 20 patients with ESRD (stage 5) with eGFR < 15 ml/min/1.73², on chronic maintenance hemodialysis for at least 3 months.

Written informed consent was obtained from all participants before enrollment to the study.

All scheduled participants (patients and control group) were subjected to the following:

- Thorough medical history taking including the cause of CKD and the presence of comorbidities.
- Full clinical examination with special emphasize on measurement of blood pressure (BP) and estimation of body mass index (BMI). BP measurements were taken using sphygmomanometer as a mean of 3 measurements at different basal conditions. Body surface area (BSA) was calculated from Mosteller equation (Mosteller, 1987): BSA (m²) = √ (Height (cm) x weight (Kg)) / 3600 BMI was calculated using the equation BMI= weight (in Kg) divided by the square of the height (in meters).
- Laboratory investigation: Routine investigations as blood urea, serum creatinine, serum calcium, serum phosphorus, serum uric acid, serum albumin, lipid profile and C reactive protein (CRP) (positive or negative).

**Measurement of serum SP-D**

Whole blood was collected into vacutainer tubes. Serum was prepared by centrifugation for 10-15 minutes at 1500xg. The serum was clotted and stored at -80°C until analysed. Serum SP-D was measured using the quantitative colorimetric sandwich enzyme immunoassay technique. Antibody specific for SP-D has been pre-coated into a micro plate. Standards and samples were pipetted into the wells and any SP-D present was bound by the immobilized antibody. After removing any unbound substances, a biotin-conjugated antibody specific for SP-D was added to the wells. After washing, avidin conjugated Horse Radish Peroxidase (HRP) was added to the wells. Following a wash to remove any unbound avidin–enzyme reagent, a substrate solution was added to the wells and color developed in proportion to the amount of SP-D bound in the initial step. The color development was stopped and the
intensity of the color was measured. The detection range was 1.25 ng/ml – 80 ng/ml.

**Trans-thoracic Echocardiographic examination**

Conventional trans-thoracic echocardiographic examination was performed for all patients in left lateral position using Vivid -7 GE systems (GE Ultrasound; Horton Norway). All cases were examined by multi frequency (2.5 MHz) matrix probe M3S utilizing the standard views (Parasternal long axis, parasternal short axis, apical 4, 2 chamber and long axis views).

The presence of regional wall motion abnormalities was assessed in all standard views. Using 2-D echo guided M-mode; the following LV diameters were obtained:
- LV end diastolic diameter (EDD)
- LV end systolic diameter (ESD)
- LV ejection fraction (EF)
- LV fractional shortening (FS)
- Interventricular septal diameter (IVSD)
- LV posterior wall diameter (PWD)

**Carotid duplex:**

All ultra-sound examinations were performed using Vivid -7 GE systems (GE Ultrasound; Horton Norway) utilizing 10 MHz transducer. All patients were examined in the supine position with the neck extended and the head tilted slightly towards the opposite of the examined side. Both left and right common carotid arteries (CCAs) were depicted. The distal two centimeters of the CCAs were depicted in the longitudinal plane, with the diverging of the artery walls towards the carotid bifurcation as the distal limitation. The intima and media layers were visible in both the near and the far wall. The images were captured in the end diastolic phase (ECG assisted), when the artery had its smallest diameter. The image plane was most often an oblique sagittal plane, however, depending on the arteries tortuousness and depth, the image plane was shifted towards the coronal plane to better visualize the arteries parallel to the skin surface. The IMT was defined as the distance between the leading edge of the lumen- intima echo and the leading edge of media-adventitia echo (Gaarder and Seierstad, 2015). IMT values of more than 0.9 mm according to European Society of Cardiology was considered abnormal (Simova, 2015).

**Statistical methods**

IBM SPSS statistics (V.22.0, IBM Corp., USA, 2013) was used for data analysis. Numerical variable was expressed as mean and SD. The following statistical tests were used for analysis of data:
1- Student t test: to compare between two independent groups for parametric data.
2- Wilcoxon Rank-Sum test: to compare between two independent groups for non-parametric data.
3- Analysis of Variance (ANOVA): to test differences between two or more means.
4- Kruskal-Wallis test: to compare between more than two groups for non –parametric data.
5- Spearman’ s Rank correlation test: to study the possible association between each two variables among each group for non-parametric data.
6- Chi-square test: to study the association between each two variables or comparison between two independent groups as regard the categorized data.
7- Receiver operator characteristic (ROC) curve analysis: to determine the optimal cutoff value, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of SP-D between CKD patients and control group.

The probability of error < 0.05 was considered significant, while < 0.001 was considered highly significant.

**RESULTS**

**Demographic and clinical data**

- The study included 90 participants, 60 patients with various degrees of CKD and 30 healthy volunteers as a control group.
- The age of patients ranged from 23 to 65 years with the mean 54.85 ± 1.44 years while the age of the control group ranged from 25 to 65 years with the mean 44.4 ± 2.15 years.
- Patients included 34 males (56.7%) and 26 females (43.3%) while the control group included 15 males (50%) and 15 females (50%).
- 24 (40%) patients were hypertensive, 42 (70%) patients were diabetic, 13 (21.6%) patients were both diabetic and hypertensive, 7 (11.7%) patients with obstructive uropathy, 2 (3%) patients with atrophic kidneys and one patient (1.6%) with polycystic kidneys.
- 23 (38.3 %) CKD patients were smokers while only 6 (20%) of the control group were smokers.
- The mean BMI of CKD patients was 28.2 ± 0.40 while the mean BMI of the control group was 22.45± 0. 21, P < 0.001.
- The study showed high significantly increases in the mean systolic blood pressure (SBP) [142.8 ± 1.44 mmHg] and DBP [84.66± 0.99 mmHg] in CKD patients than that of the control group [118 ± 1.94 mmHg and 74.33 ± 1.03 mm Hg respectively], P < 0.001.

**Laboratory investigations**

**Blood indices**

The study showed high significantly decreased mean RBCs count and hemoglobin content of the CKD
patients(3.81 ± 0.07 M/UL and 10.54 ± 0.32 gm/dl respectively) compared to control group(4.14 ±0.06 M/UL and 12.15 ± 0.13 gm/dl respectively) (P<0.001), while there was high significantly increased mean total leukocytic count of CKD patients(10.29± 0.53x1000/UL)compared to that of the control group (6.02 ± 0.18 x1000/UL) (P< 0.001), also there was significantly higher mean platelet count of CKD patients (252.68 ± 12.35x 1000/UL) compared to that of the control group (213.1± 9.64x 1000/UL) (P<0.05).

Renal profile

The study showed high significantly increase of the mean serum creatinine, blood urea, serum phosphorus, and serum uric acid of CKD patients (3.55 ± 0.37 mg/dl, 112.1 ± 8.53 mg/dl, 4.91 ± 0.17 mg/dl, and 7.54 ± 0.24 mg/dl respectively) compared to that of the control group (0.85 ± 0.03 mg/dl, 18.3± 0.75 mg/dl, 3.43 ± 0.09 mg/dl, and 4.03 ± 0.08 mg/dl respectively) (P< 0.001), while there was high significantly decrease of the mean serum calcium of CKD patients (8.54 ±0.12 mg/dl) compared to that of the control group (9.05± 0.083 mg/dl) (P < 0.001).

Hepatic profile

The study showed high significantly increase of the mean serum alanine transferase (ALT) and serum aspartate transaminase (AST) of CKD patients (28.83 ± 2.56, and 29.5 ± 3.16 mg/dl respectively) compared to that of the control group (12.1 ± 0.80, and 17.83 ±1.37 mg/dl respectively) (P<0.001). While the mean serum albumin of CKD patients (3.29 ± 0.07 gm/dl) was high significantly decreased compared to that of the control group (4.48 ± 0.083 gm/dl) (P<0.001).

Lipid profile

The mean total cholesterol of the CKD patients was in normal range(172.47 ± 6.91 mg/dl) and it was not significantly different from that of the control group (1.64.8 ±2.99 mg/dl). Also the mean serum triglycerides of the CKD patients was in normal range (146.15± 9.56 mg/dl) but it was significantly higher than that of the control group (85.9 ±3.43 mg/dl)(P< 0.001).

Plasma SP-D

The mean plasma SP-D of the CKD patients was significantly increased compared to that of the control group (Table 1).

**Correlation between SP-D and age, BMI, and blood pressure among CKD patients**

The study showed positive correlation between SP-D and DBP but there was no significant correlation between SP-D and age, BMI, or SBP(table 2), figure (1).

**Correlation between SP-D and blood indices of CKD patients**

The study showed high significantly positive correlation between the mean SP-D and the mean platelet count of CKD patients but there was no significant correlation with other blood indices. (Table 3)

**Correlation between SP-D and kidney and liver functions of CKD patients**

The study revealed significant negative correlation between the mean SP-D and the mean serum albumin in CKD patients, however there was no significant correlation between SP-D and other renal and hepatic profile as shown in table (4).

**Correlation between SP-D and lipid profile in CKD patients**

There was no significant correlation between the mean SP-D and the mean total cholesterol and the mean serum triglycerides of CKD patients as shown in table (5).

**Correlation between SP-D and CIMT**

The study showed that the range of right IMT values among CKD patients varied from 0.11mm to 1.3 mm and the mean was 0.86 ± 0.047 mm, while the left IMT values ranged from 0.13 mm to 1.5 mm and the mean was 0.89 ± 0.046 mm.

There was no significant correlation between the mean SP-D and the mean CIMT OF CKD patients as shown in table (6).

**Correlation between SP-D and echocardiographic parameters**

The study showed no significant correlation between the mean SP-D and the mean echocardiographic parameters among CKD patients as shown in table (7).

**Relation between SP-D and smoking**

The study showed that the mean SP-D of the 23
Table 1. Comparison between the mean SP-D in CKD patients and the control group

<table>
<thead>
<tr>
<th>Data</th>
<th>Control group</th>
<th>CKD patients</th>
<th>P value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP-D (ng/ml) (mean± SD)</td>
<td>N=30</td>
<td>N=60</td>
<td>0.02</td>
<td>S</td>
</tr>
<tr>
<td>Range</td>
<td>(0.53-7.73)</td>
<td>(0.36-64.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Correlation between SP-D and age, BMI, and blood pressure of CKD patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>R</th>
<th>P</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.159</td>
<td>0.226</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>0.197</td>
<td>0.132</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>0.256</td>
<td>0.064</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>0.283</td>
<td>0.029</td>
<td>S</td>
</tr>
</tbody>
</table>

Figure 1. Significant correlation between SP-D and DBP in CKD patients

Table 3. Correlation between SPD and blood indices of CKD patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>SP-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>P</td>
</tr>
<tr>
<td>RBC (M/UL)</td>
<td>-0.136</td>
</tr>
<tr>
<td>HB % (gm/dl)</td>
<td>-0.202</td>
</tr>
<tr>
<td>WBC (x 1000/UL)</td>
<td>0.255</td>
</tr>
<tr>
<td>PLT (x 1000/UL)</td>
<td>0.491</td>
</tr>
</tbody>
</table>

Table 4. Correlation between SP-D and kidney, liver functions of CKD patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>SP-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (mg/dl)</td>
<td>R</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>0.204</td>
</tr>
<tr>
<td>MDRD (ml/min/1.73m²)</td>
<td>0.161</td>
</tr>
<tr>
<td>CA (mg/dl)</td>
<td>0.008</td>
</tr>
<tr>
<td>PO4 (mg/dl)</td>
<td>0.195</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>0.117</td>
</tr>
<tr>
<td>Albumin (gm/dl)</td>
<td>-0.316</td>
</tr>
<tr>
<td>ALT (mg/dl)</td>
<td>-0.035</td>
</tr>
<tr>
<td>AST (mg/dl)</td>
<td>-0.014</td>
</tr>
</tbody>
</table>
smokers of CKD patients was high significantly increased compared to that of the 37 non-smokers as shown in table (8).

Comparison between the 3 groups of CKD patients as regard demographic and clinical data

There were significant differences in the mean age, DBP, SBP, and number of smokers of the 3 studied groups of CKD patients, while there was no significant difference as regard BMI. (Table 9)

Comparison between the 3 groups of CKD patients regarding the level of SP-D

The study showed significant increase of the mean SP-D in the 3 groups of CKD patients (P< 0.05) (Table 10)

Comparison between the 3 groups of CKD patients regarding CIMT

The study showed no significant difference between the 3 groups regarding CIMT, P > 0.05 (Table 11).

Comparison between the 3 groups of CKD patients regarding echocardiographic parameters

The study showed no significant difference between the 3 groups of CKD patients as regard the mean echocardiographic parameters except the mean EF of group 2 which was significantly decreased than that of group 3 (Table 12). Concentric LV hypertrophy (LVH) was detected in 23 patients (38.3%) of CKD patients. They were distributed as follow:

- Group 1: 7 patients (35%)
- Group 2: 7 patients (35%)
- Group 3: 9 patients (45%)

Relation between CRP and SP-D

CRP was positive in 30 CKD patients and was negative in the other 30 CKD patients. The mean SP-D in CRP positive patients (6.34± 1.67 ng/ml) was higher than that of CRP negative patients (5.5 ± 2.1 ng/ml) however; this increase did not reach statistically significant difference ( P =0.785)

Cutoff point, sensitivity, specificity, PPV, and NPV of SP-D

ROC curve was used to determine the optimal cutoff value, sensitivity, specificity, PPV, and NPV of SP-D in CKD patients (Table 13, Figure 2).

DISCUSSION

CKD is a worldwide public health problem and is a
### Table 8. Relation between SP-D and smoking among CKD patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Smokers (N=23)</th>
<th>Non-smokers (N=37)</th>
<th>P value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SP-D (ng/ml)</td>
<td>11.84 ± 2.36</td>
<td>2.10 ± 0.35</td>
<td>0.002</td>
<td>HS</td>
</tr>
</tbody>
</table>

### Table 9. Comparison between groups 1, 2, and 3 regarding demographic and clinical data

<table>
<thead>
<tr>
<th>Variance (Mean ±SE)</th>
<th>Group 1 (N=20)</th>
<th>Group 2 (N=20)</th>
<th>Group 3 (N=20)</th>
<th>P value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.5 ± 2.72</td>
<td>59.1 ± 1.17</td>
<td>55.54 ± 2.91</td>
<td>0.013</td>
<td>S</td>
</tr>
<tr>
<td>Male sex n (%)</td>
<td>16 (80%)</td>
<td>10 (50%)</td>
<td>8 (40%)</td>
<td>0.029</td>
<td>S</td>
</tr>
<tr>
<td>Smokers' n (%)</td>
<td>3 (15%)</td>
<td>8 (40%)</td>
<td>12 (60%)</td>
<td>0.001</td>
<td>HS</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>27.41 ± 0.93</td>
<td>29.21 ± 1.59</td>
<td>27.98 ± 0.49</td>
<td>0.20</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>136.5 ± 2.08</td>
<td>145 ± 2.35</td>
<td>147 ± 2.52</td>
<td>0.005</td>
<td>HS</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>81.6 ± 1.66</td>
<td>86.5 ± 1.66</td>
<td>87 ± 1.79</td>
<td>0.03</td>
<td>S</td>
</tr>
</tbody>
</table>

### Table 10. SP-D level in group 1, 2 and 3 CKD patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean SP-D (ng/ml)</th>
<th>Range</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.38 ± 0.34</td>
<td>0.36-7.8</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>5.63 ± 1.84</td>
<td>1.2-35.1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>9.98 ± 3.51</td>
<td>1.26-64.3</td>
<td></td>
</tr>
</tbody>
</table>

### Table 11. CIMT in group 1, 2, and 3 CKD patients

<table>
<thead>
<tr>
<th>Data (Mean ± SE)</th>
<th>Group 1 (N=20)</th>
<th>Group 2 (N=20)</th>
<th>Group 3 (N=20)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right CIMT (mm)</td>
<td>0.88 ± 0.05</td>
<td>0.90 ± 0.04</td>
<td>0.82 ± 0.053</td>
<td>NS</td>
</tr>
<tr>
<td>Left CIMT (mm)</td>
<td>0.91 ± 0.05</td>
<td>0.92 ± 0.035</td>
<td>0.84 ± 0.053</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 12. Comparison between the 3 groups of CKD patients regarding Echocardiographic parameters

<table>
<thead>
<tr>
<th>Data (mean ±SE)</th>
<th>Group 1 (N=20)</th>
<th>Group 2 (N=20)</th>
<th>Group 3 (N=20)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF (%)</td>
<td>56.8 ± 2</td>
<td>55.6 ± 3</td>
<td>57 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>EDD (cm)</td>
<td>5.34 ± 0.12</td>
<td>5.39 ± 0.15</td>
<td>5.06 ± 0.13</td>
<td>NS</td>
</tr>
<tr>
<td>ESD (cm)</td>
<td>3.81 ± 0.19</td>
<td>3.88 ± 0.21</td>
<td>3.67 ± 0.16</td>
<td>NS</td>
</tr>
<tr>
<td>IVSD (cm)</td>
<td>0.98 ± 0.04</td>
<td>0.94 ± 0.05</td>
<td>1.11 ± 0.07</td>
<td>NS</td>
</tr>
<tr>
<td>LV PWD (cm)</td>
<td>0.99 ± 0.05</td>
<td>0.94 ± 0.05</td>
<td>1.07 ± 0.06</td>
<td>NS</td>
</tr>
<tr>
<td>FS (%)</td>
<td>31.5 ± 1.71</td>
<td>29.8 ± 1.69</td>
<td>31.7 ± 1.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 13. Cutoff point, sensitivity, specificity, PPV, NPV, and AUC of SP-D in CKD patients

<table>
<thead>
<tr>
<th>Cutoff</th>
<th>Sens.</th>
<th>Spec.</th>
<th>PPV</th>
<th>NPV</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=0.87</td>
<td>69.41</td>
<td>66.67</td>
<td>98.33</td>
<td>7.14</td>
<td>0.601</td>
</tr>
</tbody>
</table>
common condition in which there is a loss of kidney function over time. CKD is associated with an increased risk of cardiovascular disease and chronic renal failure. It is the ninth leading cause of death in the United States (Pateinakis and Papagianni, 2011).

SP-D is produced mainly in the lung but it has been found also in other tissues including the kidney. It is a potent modulator of inflammation and has been emerged as a predictor of future cardiovascular disease (Wright, 2005; Hill et al., 2011).

We aimed in this work to study the relation between serum SP-D and cardiovascular complications in CKD patients.

The study included 90 participants, 60 patients with various degrees of CKD as well as 30 healthy volunteers as a control group. The mean age of patients in our study was 54.85 ± 1.44 years. Hypertension was found in 24(40%) patients while, 42(70%) patients were diabetic and 13(21.6%) patients were both diabetic and hypertensive.

These results are concordant with the results of Zahran 2011, who focused on demographic data among 514 patients with ESRD on regular hemodialysis in Menofia governorate during the year 2011 and reported that the mean age of patients was 52.03: 14.67 years and the main known causes of ESRD were hypertension (34.8%), and diabetic nephropathy (16.6%), also Hassan Ahmed et al. 2015 in their study on hemodialysis units in Kafer El-Shakh governorate during the year 2012, reported that the mean age of patients was 51.34 ± 13.5 years and the main known causes of ESRD were hypertension (34%) and diabetic nephropathy (14%) whereas unknown causes represented 25.3% of the cases. Increasing the mean age of ESRD patients reflects the improvement of health care, however; it still away from developed countries as the mean age in the United States was 61.1 (Collins et al., 2012) and in the united kingdom was 69.9 years (Stenkamp et al., 2011).

The study showed that the mean level of SP-D in CKD patients was significantly increased compared to that of the control group. Also, it was significantly increased among the 3 groups of CKD patients. This result is consistent with the results of Xie et al. (2013) who reported also a significant increase of serum SP-D in patients with CKD when compared to non-CKD patients. They reported also that serum SP-D levels were positively correlated with eGFR.

The study revealed also that the mean level of SP-D in CKD smoker patients was significantly higher than non-smokers. This result was also reported by Sorensen et al., (2016) who found that SP-D was significantly higher in current smokers than in previous smokers or never smokers (P<0.001). Similar result was noted by Xie et al., (2013) who reported that CKD patients had higher levels of SP-D if they were smokers.

In this study, the mean serum albumin was highly significantly decreased compared to that of the control group. This result is consistent with the result of Lecker.

Figure 2. ROC curve showing the cutoff point for SP-D level was <=0.87ng/ml discriminating between CKD patients and control group at which the sensitivity of the SP-D was 96.41%, the specificity was 66.67%, PPV was 98.33%, NPV was 7.14% and area under ROC was 0.601.
et al. (2006). They reported that reduction in the glomerular filtration rate does not itself, predispose to hypoalbuminemia. Conditions that often accompany CKD profoundly influence albumin synthesis as chronic metabolic acidosis and inflammation from concurrent illness. The study showed also a significant correlation between the mean SP-D and the mean serum albumin in CKD patients. A similar result was noted by Zaky et al., (2014). They reported that serum SP-D was negatively correlated to serum albumin in patients with stable chronic obstructive pulmonary disease.

Hypoalbuminemia is strongly associated with mortality and CVD in hemodialysis patients. Albumin is probably still the most commonly used nutritional marker in hemodialysis patients. However, its value has been questioned because a low albumin level may reflect not only poor nutrition, but also reflect the presence of an inflammatory reaction. The prevalence of chronic inflammation is high in dialysis patients and it is associated with an increased mortality risk, yet the origin of chronic inflammation in dialysis patients remains unclear (Selim et al., 2007).

The study showed no significant correlation between the mean SP-D and age, sex or BMI of CKD patients. Similar result was also reported by Sorensen et al., 2016.

The study showed no significant correlation between the mean SP-D and CIMT of CKD patients. This result was discordant to the result of Hu et al. (2016) who reported that the serum SP-D level was positively correlated with CIMT in patients on regular hemodialysis and as CIMT is a well-established surrogate marker of subclinical atherosclerosis, they suggested that the SP-D may be a novel marker of atherosclerosis in patients on hemodialysis.

Hill et al. (2011) reported that circulating SP-D is a good predictor of cardiovascular morbidity and mortality and adds prognostic information of well-established risk factors such as age, sex, and plasma lipids and is a promising biomarker to link lung inflammation/injury to CVD.

In consistent with our result, Sorensen et al. (2016) did not support a relationship between subclinical atherosclerosis and SP-D. They had studied genetic proteins and a nominal association was found between coding SP-D gene (SFTPD) variants and subclinical atherosclerosis and showed that the association is dependent on tobacco smoking and independent of SP-D levels. They did not find a significant relationship between SP-D and IMT or the presence of protruding plaques in the right carotid artery. They recommended that this potential relationship should ideally be investigated in advanced atherosclerosis rather than in subclinical atherosclerosis. However, they observed a nominal significant association between tested (SFTPD) single nucleotide polymorphism (rs3088308 and rs721917) and the presence of plaques or IMT in the carotid artery, leading to the conclusion that SFTPD variations may influence disease development and that this relationship is markedly dependent on effects of tobacco smoking.

The mechanism of SP-D in the modulation of atherosclerosis is still not known. It is suggested that SP-D may dampen the inflammatory signaling from vascular smooth muscle cells as well as from infiltrating macrophages. However, both pro-and anti-inflammatory effects of SP-D are recognized (Barrow et al., 2015).

The study showed no significant correlation between the mean SP-D and the mean echocardiographic parameters of LV dimensions and functions among all CKD patients and there was no significant difference between the 3 groups that represented the different grades of severity of CKD as regard these parameters. Many studies have evaluated LV functions in CKD patients. Debnath et al. (2014) reported that CKD patients had a higher prevalence of LVH and higher prevalence of systolic dysfunction which was more pronounced in CKD stage 4-5. However, in our study, we used conventional echocardiography to assess LV functions in CKD patients and we did not apply the more advanced techniques as tissue Doppler imaging and speckle tracking echocardiography which were proved to be more sensitive in early detection of LV dysfunction in different loading conditions.

Some limitation of our study includes the small sample size which comes from a single centre. This might affect the statistical significance of variables included in the study.

CONCLUSION

Serum SP-D is significantly increased in CKD patients compared to healthy control group and it is significantly higher in in advanced grades of CKD compared to less advanced grades. There was no significant correlation between SP-D level and cardiovascular complications in CKD patients as early atherosclerosis detected by CIMT or early cardiac changes detected by echocardiography.

RECOMMENDATION

Further studies on a wide scale and larger sample size and longer duration are needed to investigate the relationship between advanced atherosclerosis and SP-D in CKD patients.

REFERENCES


