Analysis of Coronary Artery Disease and Associated Risk Factors in Patients with Chronic Kidney Disease

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Abstract

Introduction: Cardiovascular diseases including coronary artery disease (CAD) are the leading cause of morbidity and mortality in chronic kidney disease (CKD) patients. The main factors responsible for this increased risk besides traditional risk factors (such as higher age, smoking, diabetes, and hypertension (HTN) are uremia related which includes inflammation, oxidative stress, malnutrition, endothelial dysfunction, coronary artery calcification, hyperhomocysteinemia, left ventricular hypertrophy, and bone mineral disorders.

Purpose: To find the occurrence of CAD in CKD and to study the clinical profile and various risk factors of CAD in this population.

Materials and Methods: This was a hospital-based cross-sectional study in which 100 CKD cases were recruited. CAD was diagnosed on the basis of history, electrocardiogram, 2D ECHO, and treadmill test findings, and accordingly, all CKD cases were subdivided into CAD and non-CAD group. Patients having acute renal failure, life-threatening infections, and age <20 years were excluded from the study.

Results: Out of 100 CKD cases, CAD was found in 35% patients. Mean age in CAD group was 52.40 years and non CAD group was 48.63 years (P > 0.05). Edema (76%), oliguria (74%), and dyspnea (70%) were most common symptoms among all CKD cases with no significant difference in both groups while chest pain (48.6% in CAD versus 4.6% in non-CAD group) was significant (P < 0.05). Among traditional risk factors, diabetes (45.7% vs. 24.6%), HTN (94.3% vs. 72.3%), tobacco chewing (68.6% vs. 47.7%), and smoking (57.1% vs. 30.8%) were significantly higher in CAD group (P < 0.05). Among non-traditional (uremia-related) risk factors, C-reactive protein (60% vs. 18.5%); ESR (mean 65 vs. 38.97 mm/h); creatine phosphokinase-MB (mean 65.743 vs. 32.162 IU); 24 h urine protein (mean 0.53 vs. 0.32 g/24 h), and diastolic blood pressure (DBP) (mean 97.26 vs. 92.09 mm Hg) were significantly higher in CAD group (P < 0.05).

Conclusion: CAD has high occurrence in CKD patients and timely detection of various risk factors in CKD patients, and their prompt treatment can delay the progression of cardiovascular complications.

Key words: Chronic kidney disease, Coronary artery disease, C-reactive protein, Diabetes, End-stage renal disease, Hypertension, Left ventricular hypertrophy, Treadmill test, Uremia

INTRODUCTION

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate (GFR). CKD is a major health problem worldwide. Approximately 20 million adults in the United States have CKD with or without decreased GFR.¹ In India, with its population >1 billion, the rising incidence of CKD is likely to pose major problems for both healthcare and the economy in future years.

The spectrum of cardiovascular diseases (CVD) not only involves obstructive coronary artery disease (CAD) but also involves other disease states such as chronic heart failure, sudden death, and arrhythmias.² The relationship between...
cardiovascular events and CKD has been repetitively shown by the epidemiological studies. Go et al. conducted a largest population-based study in more than 1.1 million adults and concluded that a decline in GFR was the main independent risk factor for CV events, secondary to peripheral artery disease, CAD, congestive heart failure, or stroke even after the elimination of confounding risk. In another study, it was found that age-adjusted CVD mortality is about 30 times higher in patients of end-stage renal disease as compared to general population.

Patients with CKD show a high prevalence of arteriosclerosis in addition to atherosclerosis in the pathogenesis of CAD. A wide variety of traditional and non-traditional CV risk factors are present in patients with CKD at all stages, but particularly in those receiving dialysis. Traditional risk factors are similar to those for the general population and comprise older age, male sex, hypertension (HTN), diabetes mellitus, dyslipidemia, cigarette smoking, physical inactivity, and a family history of premature CVD. A variety of non-traditional (uremia-related) CV risk factors, such as hyperhomocysteinemia, increased oxidative stress, malnutrition and inflammation, endothelial cell dysfunction, activation of the renin-angiotensin-aldosterone and the sympathetic nervous systems, vascular calcification due to bone mineral disorder, and anemia also facilitate CVD risks in CKD population.

The diagnosis of CAD and ACS in CKD population is a challenging task. The typical symptoms of CAD may not be seen in CKD patients as well as various diagnostic modalities are not very much predictive such as: (1) classic triad of ischemic symptoms, elevated cardiac biomarkers, and electrocardiogram (ECG) changes is frequently absent in CKD patients, (2) left ventricular hypertrophy (LVH) with a strain pattern may mask diagnostic ST depression and (3) creatine kinase-MB isoform and cardiac troponin may be elevated in the absence of true myocardial necrosis because of myocardial apoptosis or small vessel disease. Exercise electrocardiography is limited by lack of specificity of ST segment response and by inability of many CKD patients to exercise to a diagnostic workload. The risk of contrast agent-induced nephrotoxicity also limits the use of computerized tomography coronary angiography and perfusion MRI.

This study was undertaken to analyze CKD patients for the occurrence of CAD and for the assessment of clinical profile of CAD and various traditional and non-traditional (uremia related) risk factors so that correlation of risk factors with the occurrence of CAD can be studied.

**MATERIALS AND METHODS**

This study was a hospital-based cross-sectional study where 100 CKD cases including both male and female patients, irrespective of etiology, were recruited. A person was considered CKD if his/her illness was of more than 3 months duration and had abnormal USG findings and reduced creatinine clearance pointing to CKD.

Patients were categorized into five stages of CKD based on National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines and GFR was estimated GFR using the 4-variable modification of diet in renal diseases formula.

The following patients were excluded from the study: Patients not willing to be a part of the study, all cases of acute renal failure, and patients having any kind of life-threatening infections.

All these patients were clinically evaluated for cardiac involvement and the following investigations were done: Complete hemogram, ESR, lipid profile, renal function test, liver function test, serum electrolytes, blood glucose level, C-reactive protein (CRP) level, creatine phosphokinase-MB (CPK-MB) level, 24 h urine protein using standard techniques in the clinical laboratory.

A standard 12-lead ECG (using Magic R model) was done and any changes suggestive of ischemic heart diseases (IHD) such as QS pattern or ST and T changes in various chest leads were recorded.

2D and color Doppler echocardiography (using Philips HD-7 XE model) was done in all patients and abnormalities were classified as LVH if left ventricular wall thickness more than 12 mm and regional wall motion abnormality (RWMA) if any segmental area of thinning and decreased or absent contractility was observed in the absence of non-ischemic cause.

Patients were subjected to treadmill exercise testing (using Schiller CS-200 model) according to standard Bruce protocol and horizontal or downsloping ST depression ≥ 1 mm measured 80 m after the J point, and ST elevation ≥ 1 mm measured 40 m after the J point, were regarded as positive results.

Diagnosis of CAD was made using the following criteria:

1. **CAD-ACS (STEMI/NSTEMI/unstable angina):**
   - Symptoms of ischemia along with detection of a rise and/or fall of cardiac biomarker values with at least one value above the upper reference limit was considered as acute MI.
   - Symptoms of ischemia along with one of the following in the absence of raised cardiac biomarkers:
• New or presumed new significant ST-segment–T-wave (ST-T) changes or new left bundle branch block.
• Development of pathological Q waves in the ECG.
• Imaging evidence of new loss of viable myocardium or new RWMA.

2. Evidence of prior myocardial infarction (any one of the following)
   • Pathological Q waves with or without symptoms in the absence of non-ischemic causes.
   • Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause.

3. Treadmill test (TMT) positive for inducible ischemia irrespective of history of anginal chest pain.
4. Documented history of coronary angioplasty or CABG or significant coronary artery stenosis (>50%) on coronary angiography.

Based on the presence or absence of CAD among all patients, they were categorized into two major groups, i.e., CAD and non-CAD group for further analysis.

Statistical Analysis
Data were analyzed using SPSS for Windows version 20.0 (trial version) and Microsoft Office Word and Microsoft Office Excel were used to generate tables and graphs. Chi-square/Fisher’s exact test was used for categorical variables and continuous variables were analyzed using independent t-test when the data were normally distributed otherwise non-parametric test (Mann–Whitney U-test) was applied. A P < 0.05 was considered statistically significant.

RESULTS
Out of 100 patients, there were 58% males and 42% females with overall M:F ratio of 1.38:1 and mean age of all CKD patients was 49.95 years, ranging from 22 to 80 years. Maximum number of patients in both CAD and non-CAD group belonged to age group of 50-59 years (28.6% vs. 26.2%).

CAD was found in 35 out of 100 patients; thus, there was 35% occurrence of CAD in CKD patients. Majority of the CAD patients belonged to Stage IV (25.7%) and Stage V (71.4%) CKD and similar trend was seen in non-CAD group.

Among all CKD cases, edema (76%) was the most common presenting complaint followed by oliguria (74%), dyspnea (70%), and chest pain (20%). Other symptoms observed were nausea, vomiting, generalized body ache, and decreased appetite (Table 1).

In our study, diabetes (32%), HTN (80%), tobacco usage (55%), smoking (40%), positive CRP (33%), severe anemia (61%), and low HDL (58%) were most commonly associated risk factors among all CKD patients.

Among traditional risk factors, diabetes, HTN, tobacco chewing, smoking, and chronic alcoholism were significantly higher (P < 0.05) in CAD group as compared to non-CAD group (Table 2a and b).

Among non-traditional (uremia-related) risk factors, CRP, ESR, CPK-MB, 24 h urine protein, and DBP were significantly higher in CAD group (P < 0.05) and other risk factors such as severe anemia (<8 g/dl) and low HDL (<40 mg/dl); they were higher in CAD group as compared to non-CAD group, but they were not statistically significant (P > 0.05) (Table 2a and b).

Basic clinical and biochemical characteristics of patients belonging to CAD and non-CAD group were compared (Table 3).

Among ECG changes, LVH was the most common finding which was present in 41% of CKD patients followed by ST-T changes in various chest leads (Figure 1). On echocardiography, LVH and RWMA were the most common findings observed among all CKD patients (Figure 2).

Exercise ECG testing using TMT was done on 20 out of 100 CKD patients and TMT was found positive for inducible ischemia in 25% of patients, negative in 65% of patients, and inconclusive in 10% of patients (Figure 3).

DISCUSSION
Historically, Richard Bright in 1836 observed that patients with advanced uremia had high mortality rates and massive
left ventricular enlargement at autopsy, and Lindner in 1974 postulated that accelerated atherosclerosis was the major driver of heart disease in most dialysis patients.\(^6\)

Patients with CKD are at increased risk for CVD for several reasons: (1) CKD is associated with increased prevalence of traditional and non-traditional cardiovascular risk factors, (2) CKD is an independent risk factor for CVD, (3) many CVD risk factors are also risk factors for progression of CKD, and (4) the presence of CVD may be a risk factor for CKD. This interrelationship between cardiovascular and CKD, with each contributing to the pathogenesis of the other, leads to a cycle of cardiovascular and kidney disease progression.\(^7\)

In our study, we found 35% occurrence of CAD in CKD patients. Our findings were consistent with Levin.\(^8\) (2003) where they found that at least 35% of CKD patients

### Table 1: Distribution on basis of presenting symptoms

<table>
<thead>
<tr>
<th>Presenting symptoms</th>
<th>CAD group n=35 (%)</th>
<th>Non CAD group n=65 (%)</th>
<th>Total n=100 (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>25 (71.4)</td>
<td>51 (78.5)</td>
<td>76 (76)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Oliguria</td>
<td>23 (65.7)</td>
<td>51 (78.5)</td>
<td>74 (74)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>24 (68.6)</td>
<td>46 (70.8)</td>
<td>70 (70)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Chest pain</td>
<td>17 (48.6)</td>
<td>3 (4.6)</td>
<td>20 (20)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CAD: Coronary artery disease

### Table 2a: Distribution on basis of traditional and uremia related risk factors

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>CAD group n=35 (%)</th>
<th>Non CAD group n=65 (%)</th>
<th>Total n=100 (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>16 (45.7)</td>
<td>16 (24.6)</td>
<td>32 (32)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HTN</td>
<td>33 (94.2)</td>
<td>47 (72.3)</td>
<td>80 (80)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Tobacco</td>
<td>24 (68.6)</td>
<td>31 (47.7)</td>
<td>55 (55)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Smoking</td>
<td>20 (57.1)</td>
<td>20 (30.8)</td>
<td>40 (40)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Chronic alcoholism</td>
<td>10 (28.6)</td>
<td>8 (12.3)</td>
<td>18 (18)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CRP</td>
<td>21 (60.0)</td>
<td>12 (18.5)</td>
<td>33 (33)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CAD: Coronary artery disease, HTN: Hypertension, CRP: C-reactive protein

### Table 2b: Distribution on basis of traditional and uremia related risk factors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean±SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR</td>
<td>65.00±23.823</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPKMB</td>
<td>65.74±35.975</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24 h urine protein</td>
<td>0.52±0.395</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HDL</td>
<td>37.34±10.009</td>
<td>0.079</td>
</tr>
<tr>
<td>eGFR</td>
<td>11.98±7.542</td>
<td>0.490</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>7.51±1.697</td>
<td>0.645</td>
</tr>
<tr>
<td>SBP</td>
<td>161.20±23.95</td>
<td>0.080</td>
</tr>
<tr>
<td>DBP</td>
<td>97.26±12.75</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

CAD: coronary artery disease, SD: Standard deviation, eGFR: Estimated glomerular filtration rate, DBP: Diastolic blood pressure, SBP: Systolic blood pressure

### Table 3: Distribution on basis of clinical and biochemical parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean±SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>52.4±11.64</td>
<td>0.186</td>
</tr>
<tr>
<td>BMI</td>
<td>23.48±3.13</td>
<td>0.164</td>
</tr>
<tr>
<td>TLC</td>
<td>9614.2±4178.03</td>
<td>0.067</td>
</tr>
<tr>
<td>FBS</td>
<td>120.17±49.99</td>
<td>0.067</td>
</tr>
<tr>
<td>PPBS</td>
<td>162.6±66.2</td>
<td>0.070</td>
</tr>
<tr>
<td>UREA</td>
<td>163.5±83.9</td>
<td>0.207</td>
</tr>
<tr>
<td>CREAT</td>
<td>6.6±3.8</td>
<td>0.659</td>
</tr>
<tr>
<td>Na</td>
<td>133.54±4.4</td>
<td>0.940</td>
</tr>
<tr>
<td>K</td>
<td>5.3±0.6</td>
<td>0.477</td>
</tr>
<tr>
<td>Ca</td>
<td>8.6±0.9</td>
<td>0.828</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>3.3±0.6</td>
<td>0.804</td>
</tr>
</tbody>
</table>

CAD: Coronary artery disease, BMI: Body mass index, SD: Standard deviation
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had evidence of ischemic event (myocardial infarction or angina) and Foley et al. (1998) where prevalence of CAD was approximately 40% among patients undergoing hemodialysis or peritoneal dialysis. Goldsmith and Covic (2001) concluded that angiographically confirmed prevalence of significant (>50%) stenosis in the epicardial coronary arteries vary from 24% prevalence in a young, non-diabetic hemodialysis population undergoing evaluation for renal transplantation to 85% in long-standing diabetic dialysis patients over 45 years. Nikparvar et al. (2015) in their study on hemodialysis patients using dipyridamole myocardial perfusion imaging to detect undiagnosed IHD found that 21.7% of the study population had IHD.

In this study, patients with CAD had edema (71.4%), dyspnea (68.6%), and oliguria (65.7%) as more common symptoms as compared to chest pain which was present in only 48.6% of the patients. Sosnov et al. (2006) observed that patients with kidney disease were less likely to report chest pain (odds ratio 0.57) or arm pain (odds ratio 0.52) while more likely to report shortness of breath (odds ratio 1.35) in comparison to patients without kidney disease in the setting of acute myocardial infarction (Table 1).

In our study, diabetes (32%), HTN (80%), tobacco usage (55%), smoking (40%), positive CRP (33%), severe anemia (61%), and low HDL (58% patients) were most common risk factors in all CKD patients. Sharma et al. (2005) found HTN (91%), diabetes (39%), and smoking (14%) as common risk factors in renal transplant candidates and Ix et al. (2003) found HTN (75%), diabetes (26%), smoking (14%), and high CRP (> 0.38 mg/dl) (29%) as risk factors in CKD patients. These findings were consistent with our study.

Comparison of Risk Factors among CAD Group versus Non-CAD Group

Among traditional risk factors, diabetes (45.7% vs. 24.6%), HTN (94.2% vs. 72.3%), tobacco chewing (68.6% vs. 47.7%), smoking (57.1% vs. 30.8%), and chronic alcoholism (28.6% vs. 12.3%), and among non-traditional (uremia-related) risk factors, CRP (60% vs. 18.5%), ESR (mean 65 ± 23.82 vs. mean 38.97 ± 18.27), CPK-MB (mean 65.743 ± 35.975 vs. mean 32.162 ± 14.418), 24 h urine protein (mean 0.525 ± 0.395 vs. mean 0.323 ± 0.381), and DBP (mean 97.26 ± 12.75 vs. mean 92.09 ± 9.69) were significantly higher (P < 0.05) in CAD group as compared to non-CAD group. Nikparvar et al. (2015) also found HTN and diabetes to be significantly higher (P < 0.05) in IHD group of hemodialysis patients as compared to non-IHD group and Ohtake et al. (2003) found diabetes to be significantly associated (P < 0.05) in CKD patients having coronary artery stenosis (≥ 70% on angiography).

In our study, LVH (60%) was the most common 2D ECHO finding among all CKD patients and RWMA in the form of decreased or absent contractility was observed in 32% of the patients. Laddha et al. (2014) found LVH in 74.3% patients, pericardial effusion in 14% patients, and RWMA in 13% of patients having CKD, and Shivendra et al. (2014) in their study on ESRD patients found LVH in 48% patients, pericardial effusion in 17% patients, and RWMA in 8.5% patients (Figure 2).

In our study, out of 100 CKD cases, exercise ECG testing using TMT was done on 20 CKD patients and TMT was found positive for inducible ischemia in 25% of patients which was consistent with studies of Sharma et al. (2005) where exercise test result was positive in 17% patients and Ix et al. (2003) where inducible ischemia was found in 42% of chronic renal insufficiency patients (Figure 3).

CONCLUSION

CKD is a major health problem worldwide, and there is highly increased risk of development of cardiovascular...
abnormalities during CKD due to the collective influence of both traditional risk factors and uremia-related non-traditional risk factors, which contribute significantly to the morbidity and mortality of these patients. LVH was the predominant finding on both ECG and echocardiography and it can be a major contributory factor in the development and progression of various cardiovascular disorders in CKD patients. Echocardiography is a cost-effective and non-invasive diagnostic test which can detect early changes in the cardiac parameters. Thus, timely detection and identification of various comorbidities in CKD patients and their prompt treatment along with close vital monitoring and periodic routine follow-up can delay the appearance and progression of cardiovascular complications including CAD which, in turn, can lead to better quality of life.

**Limitations**

1. Follow-up was not done in our study which would have given a better idea about progression of renal dysfunction and its effect on cardiovascular morbidity and mortality.

2. Lack of availability of various diagnostic modalities including dobutamine stress echocardiography, thallium perfusion scans, and coronary angiography at our institute.

**REFERENCES**


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