Endothelial Dysfunction by Flow-Mediated Vasodilatation in Chronic Kidney Disease

Vaibhav Shukla¹, Rahul Dey², Ashok Chandra³, Ritu Karoli¹, Sachin Khanduri⁴

Abstract

Introduction: The last few years have seen a phenomenal increase in the prevalence of chronic kidney disease (CKD). Cardiovascular disease remains the most important cause of death in these patients. The present study was conducted to evaluate endothelial dysfunction in CKD patients as compared with controls.

Methods: Thirty-five patients of CKD and 32 age and sex-matched controls were included in the study. Flow-mediated vasodilatation was assessed in all individuals. Anthropometric measurements, haematological and biochemical assessment were also done.

Results: It was found that patients of CKD had significant endothelial dysfunction in comparison with controls as assessed by flow-mediated vasodilatation of brachial artery. It was also seen that late stages of CKD patients had significant endothelial dysfunction in comparison to early stages of CKD.

Conclusions: The present study concludes that chronic kidney disease patients have significant endothelial dysfunction and this is more pronounced in the later stages of the disease.

Editorial Viewpoint

• Endothelial dysfunction results in progression of CKD.
• Endothelial dysfunction was found to be more pronounced in the later stages of CKD in this study.

Introduction

The incidence and prevalence of chronic kidney disease (CKD) is increasing worldwide. Among selected population groups, the prevalence of early stages of CKD in India has been reported to be as high as 15.04% and 13.12% respectively using two different criteria for diagnosis.¹

Changing demographics, increasing affluence and sedentary lifestyles have led to the increasing prevalence of non-communicable lifestyle diseases like diabetes mellitus, obesity, hypertension (HTN), cardiovascular disease (CVD) and chronic kidney disease (CKD), even in developing countries like India. It is estimated that 80% of chronic disease deaths now occur in low-and middle – income countries.² CKD is important among this group as, apart from its own morbidity, mortality and high risk for progression to end-stage renal disease (ESRD), it has also been found to be an important risk factor for CVD.³⁴

Considering the relative importance of presence of endothelial dysfunction as a marker of complication and to see whether endothelial dysfunction has a relation with the severity of CKD and what other factors contribute to enhance the risk of endothelial dysfunction, the present study was planned. In present study an attempt has been made to study flow-mediated vasodilatation in brachial artery in patients of CKD as a marker of endothelial function and to compare endothelial function in early stage (stage 1 and 2) in comparison to late stage (stage 3 to 5) of CKD.

Materials and Methods

The study was done in the Department of Medicine, Era’s Lucknow Medical College and Hospital, Lucknow. Cases with chronic kidney disease attending as outdoor and indoor patients in the department were included in the study. An equal number of age and sex-matched controls were included. Conditions or diseases which were likely to affect the endothelial function like coronary artery disease, cerebrovascular disease, peripheral vascular disease, patients on statin therapy and chronic smokers were excluded from the study.

The total duration of study was 18 months. A total number of 67

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subjects (35 cases and 32 controls) were enrolled for the purpose of study. All consecutive cases of CKD who fulfilled the inclusion criteria were invited to participate in the study. An equal number of demographically matched normal healthy individuals were enrolled as controls. Informed consent was obtained from all the subjects willing to participate in the study.

At enrollment the demographic information was noted and anthropometric measurements were done. Haematological and biochemical assessment were also done. USG abdomen, ECG, chest skiagram, 2D-echocardiography were also done wherever it was required.

Measurement of flow-mediated vasodilatation (FMD) was done as follows: A longitudinal section of the brachial artery was analysed; (medial epicondyle was used as anatomical landmark for brachial artery). USG machine with high resolution (B) scan 7.5Hz linear accelerator was used to assess brachial artery diameter and its changes.

Flow-mediated vasodilatation (FMD), which reflects endothelium-dependent vasodilatation, was calculated as the percentage increase in diameter from baseline to the maximum value which is obtained after the cuff deflation using the following formula:

\[
FMD = \frac{d_2-d_1}{d_1} \times 100
\]

where \(d_2\) = Brachial artery diameter at 5 min post-deflation
\(d_1\) = baseline brachial artery diameter.

**Results**

There were 21 males and 14 females among cases and 19 males and 13 females among controls. The age of patients ranged from 18-70 years. The mean age of patients was 36.71±16.75 years. Majority of patients were in the range of 21-40 years. Majority of patients (18) were stage V CKD patients (51.4%). A total of 2 (5.7%) patients were Stage III, 3 (8.6%) were stage I, 4 (11.4%) were stage II and 8 (22.9%) patients were in stage IV.

A comparison of the brachial artery diameter between cases and controls at baseline and after the procedure revealed that both absolute as well as percentage changes in brachial artery diameter size in centimeters were significantly lower in cases as compared to controls (p<0.001) (Table 1).

For subsequent analysis the cases were divided into two groups according to stage of kidney disease (Table 2). Stage 1 and 2 were taken in group 1 and stages 4 and 5 were taken in group 2. A comparison of brachial artery diameters between the two groups was done. A significant difference between two groups was observed both for absolute and percentage change in brachial artery diameter after the procedure. It was observed that both the parameters were significantly lower in Group 2 as compared to Group 1 (p<0.001) (Table 3).

If we consider subgroup analysis, among diabetics both absolute as well as percentage change in brachial artery diameter was significantly lower in diabetic group as compared to non-diabetic group (p<0.05).

If we take body-weight into consideration, both absolute as well as percentage changes in brachial artery diameter were significantly higher in those with body-weight >70 kg as compared to those with body-weight <70 kg, however it was not statistically significant.

A comparison of hypertensive patients with non-hypertensive individuals revealed that percentage change and absolute change in brachial artery diameter were lower in hypertensive as compared to normotensives but

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### Table 1: Comparison of FMD in cases and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cases (n=35)</th>
<th>Controls (n=32)</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td>t</td>
</tr>
<tr>
<td>Change in diameter in cm</td>
<td>0.028±0.028</td>
<td>0.076±0.013</td>
<td>-8.888</td>
</tr>
<tr>
<td>% change</td>
<td>20.400±7.675</td>
<td>4.000±2.190</td>
<td>-10.202</td>
</tr>
</tbody>
</table>

### Table 2: Comparison of biochemical parameters in two groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n=7)</th>
<th>Group 2 (n=26)</th>
<th>Significance of difference (Mann-Whitney U test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td>z</td>
</tr>
<tr>
<td>Blood urea (mg/dl)</td>
<td>58.29±7.86</td>
<td>137.87±53.20</td>
<td>3.678</td>
</tr>
<tr>
<td>S. creatinine (mg/dl)</td>
<td>1.31±0.09</td>
<td>8.48±5.37</td>
<td>4.009</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>79.77±10.27</td>
<td>11.28±5.53</td>
<td>4.008</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>136.29±3.30</td>
<td>136.35±4.19</td>
<td>0.133</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.43±0.43</td>
<td>5.05±1.23</td>
<td>1.502</td>
</tr>
<tr>
<td>Calcium (mEq/L)</td>
<td>8.14±0.45</td>
<td>7.38±0.42</td>
<td>3.373</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dl)</td>
<td>136.29±39.54</td>
<td>110.38±34.06</td>
<td>2.645</td>
</tr>
<tr>
<td>PP blood sugar (mg/dl)</td>
<td>188.43±85.32</td>
<td>143.35±41.12</td>
<td>2.356</td>
</tr>
<tr>
<td>S. cholesterol (mg/dl)</td>
<td>220.71±44.97</td>
<td>208.85±53.85</td>
<td>0.397</td>
</tr>
<tr>
<td>S. Triglyceride (mg/dl)</td>
<td>170.14±72.94</td>
<td>175.96±75.17</td>
<td>0.199</td>
</tr>
<tr>
<td>S. LDL (mg/dl)</td>
<td>51.37±14.08</td>
<td>46.84±17.27</td>
<td>0.927</td>
</tr>
<tr>
<td>S. HDL (mg/dl)</td>
<td>130.49±50.21</td>
<td>129.48±49.58</td>
<td>0.022</td>
</tr>
<tr>
<td>S. VLDL (mg/dl)</td>
<td>38.80±20.94</td>
<td>39.88±18.71</td>
<td>0.265</td>
</tr>
</tbody>
</table>

### Table 3: Comparison of FMD in two groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n=7)</th>
<th>Group 2 (n=26)</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td>z</td>
</tr>
<tr>
<td>Change in diameter in cm</td>
<td>0.06±0.030</td>
<td>0.015±0.011</td>
<td>7.246</td>
</tr>
<tr>
<td>% change</td>
<td>20.400±7.675</td>
<td>4.000±2.190</td>
<td>-10.202</td>
</tr>
</tbody>
</table>
the difference was not significant statistically (p>0.05).

Discussion

Endothelial dysfunction resulting in disintegration of vascular structure and function is a key element in the progression of chronic kidney disease (CKD). Cardiovascular disease is the main cause of death in patients with chronic kidney disease and its incidence and severity increases in direct proportion with kidney function decline. This relationship seems to be bidirectional, leading to a vicious circle. Keeping this relationship in mind, the present study was carried out.

It was observed that cases (subjects with chronic kidney disease) had FMD values significantly lower as compared to that in controls, thereby indicating a higher order of endothelial dysfunction. Similar results were obtained by Recio-Mayoral et al5 who observed that CKD patients had reduced FMD values as compared to controls. Similar findings were found by Yilmaz et al6 Ghiadoni et al7 Migliacci et al.8 However Wilson et al9 did not find a difference in FMD of cases and controls in a group of subjects aged between 6-20 years. The variability in our results and that of Wilson et al9 could be attributed to difference in profile of patients.

Comparison of FMD values between early and late stages of CKD showed the mean values in lower stages to be significantly higher as compared to that in higher stages of CKD. If we look back into the case-control comparison, we can find that the FMD values in lower stages of CKD were near to the values obtained for controls, thus indicating that lower stages have little effect on endothelial function. The findings in the present study are in consonance with the observations made by Recio–Mayoral et al5 who observed that FMD values in CKD patients decrease with increasing severity of disease. In their study too, they found that compared with predialysis patients, the FMD levels were significantly lower among patients with hemodialysis subjects. Ghiadoni et al7 too found that reduced endothelium-dependent dilatation in the CKD patients is related to renal disease severity and held increased oxidative stress to be partially responsible for it. Although the present study also reports a similar relationship yet whether oxidative stress was responsible for it or not was beyond the scope of present study.

A number of studies have shown a mutual association between severity of kidney disease, diabetes, hypertension and metabolic syndrome components and their impact on endothelial dysfunction.1615 In the present study too, an attempt was made to understand the impact of diabetes, hypertension and body-weight on brachial artery diameter. It was observed that non-diabetics had significantly higher FMD values as compared to diabetics. However those with heavier body-weight had higher FMD values as compared to those with lower body-weight. Mean FMD of patients with hypertension was lower as compared to that of patients without hypertension although this was not statistically significant. The reason for an unexpected response for body-weight and a non-significant impact of hypertension as observed in the present study could be explained on the basis of highly distorted proportion of patients with heavier body-weight as compared to those with lighter body-weight and presence of only three normotensives as compared to 32 hypertensives.

Although direct impact of hypertension on FMD could not be illustrated in the present study owing to fewer number of normotensive cases in present study, yet the fact that early stage patients had lower blood pressure levels and higher FMD values tries to explain this relationship indirectly. As most of the cases in the present study were hypertensive, it was difficult to illustrate this relationship, however, the FMD pattern in different stages of CKD explains the impact of blood pressure levels i.e. severity of hypertension. Unfortunately, owing to limitations of design, adequate number of normotensive patients with CKD could not be enrolled in the present study to illustrate this relationship more vividly. However, the co-existence of hypertension and CKD itself are able to explain this relationship.1416 But whether hypertension is an independent predictor of endothelial dysfunction remains unexplained in this study.

Though in the absence of a large sample size and within the limitations of the study, endothelial function of patients with chronic kidney disease was found to be significantly reduced as compared to that of healthy controls while endothelial function of patients with higher stages of CKD was found to be significantly impaired as compared to that of lower stages of CKD. It is a fact that patients with CKD are far more likely to die from cardiovascular disease than progress to end-stage renal disease requiring dialysis or transplantation (Keith et al)17 and the present study tries to explore the reason for this increased cardiovascular risk among patients of CKD which is difficult to be explained by traditional risk factors.18

In conclusion, the findings in the present study show an implication of chronic kidney disease in causation of endothelial dysfunction. We require a large scale study to see whether these findings hold true with a large sample size. Future studies could also be directed at seeing whether differential interventions in early CKD can stop or delay
the progression of endothelial dysfunction.

References


