Introduction

Globally incidence of ESRD (end-stage renal disease) is rising [1]. One of the commonest etiologies for ESRD is diabetic nephropathy [2]. Therapy is directed towards prevention by improving glycemic control, blood pressure control and use of ACE (angiotensin-converting enzyme) inhibitors [3-5]. Clinically it starts from microalbuminuria to reduction in GFR (glomerular filtration rate) and an overt increase in urea/creatinine levels [6,7]. Various studies suggest that diabetic nephropathy occurs due to the accumulation of advanced glycosylated end products (AGEs), the activation of isoforms of protein C kinase, etc. Correlation of renal arterial flow resistance, GFR, and progression towards ESRD in DN is not well narrated in literature. Therefore, the main object of the study was to assess renal arterial flow resistance in patients with DN and to compare it with patients having non-evident diabetic nephropathy.

Methods

This is a case control study done in a retrospective manner in the central part of Rajasthan, India, based upon data collection of admitted patients. Arbitrarily, a record of 40 cases (all males) consisting of poorly controlled diabetic cases (Hba1C >10 %) without nephropathy (n=20, group A) was compared with records of diabetic cases with nephropathy (n=20, group B). Group B had been further subdivided according to CKD (chronic kidney disease) staging. Data were examined for vital parameters, Serum creatinine, e-GFR, R.I. (resistive index) in renal arterial Doppler, urine albumin.

Results: Group A and group B were characteristically the same. In group B 7 cases had CKD 1 (B1), 2 cases had CKD 2 (B2), 4 cases had CKD 3 (B3) and 7 cases had CKD 5 (B5) stage. In group B there was a progressive rise in R.I. index parallel to decline in GFR, rise in albuminuria from B1 to B5 stage (p<0.001). These parameters were normal in group A.

Conclusion: It is concluded that DN begins from an increase in resistance to flow in renal arteries primarily resulting from resistance in afferent arterioles due to the reduction in size. This reduction may be because of increased ACE/ basal sympathetic activity at the beginning. Later on, there is a further increase in resistance due to progressive deposition of AGE end products in afferent arterioles further reducing the size and hydrostatic pressure at the afferent arteriolar end, resulting in a progressive decrease in GFR. Simultaneously hypo-perfusion of kidney tissue activates the renin-angiotensin system further reduces flow and progresses the DN.

creatinine levels). Group B was further subdivided according to CKD (chronic kidney disease) staging [12], into subgroup B1, B2, B3, B4, B5 i.e. CKD 1, 2,3,4,5. All cases belong to the urban population of Ajmer city (a small sample of the population of one million). Only those cases were selected where a complete history and following investigation records were available, the permission was obtained from the hospital ethical committee.

**Data were examined for**

- Basal characteristics including age, sex, vital parameters like pulse rate, BP, temperature
- Serum Urea
- Serum creatinine [13]
- e- GFR – estimated GFR was calculated by CKD-EPI Creatinine Equation method [14]
- R.I. (resistive index) in renal arterial Doppler [15,16], (GE Voluson p 8 probe frequency C 2–5 MHz was used by the hospital)
- Urine albumin [17]
- Ultra Sonography [18]
- CKD Staging [19]
- Arterial Blood Gas analysis [20,21]
- Serum (sodium, potassium, calcium, lactic acid)
- Blood glucose [22]
- HBA1C [23],
- Fundus

**Results**

Group A and group B were characteristically the same. In group B 7 cases had CKD 1(B1), 2 cases had CKD 2(B2), 4 cases had CKD 3(B3) and 7 cases had CKD 5(B5) stage.

Group B (subgroup B1, B2, B3, B5) had an increase in R.I. index, albuminuria; reduction in serum albumin and e-GFR. These parameters were normal in group A. (Tables 1,2, Figures 1–5) (for R.I index, p<0.001 group 1 v/s subgroup B1, B2, B3, B5).

**Statistical analysis**

Statistical analysis was done with the help of SPSS 20.0 software by applying the appropriate test of significance. (Chi-square test).

**Discussion**

Diabetic nephropathy (DN) is one of the commonest causes of end-stage renal disease (ESRD). Optimal therapy includes prevention by improving glycemic control, blood pressure control, use of ACE inhibitors and ARBs (angiotensin receptor blockers). Before the onset of overt proteinuria, there are multiple renal functional changes including renal hyperfiltration, hyperperfusion and increased permeability to macromolecules.

About pathogenesis, previous studies have demonstrated, that diabetic nephropathy occurs as a result of the complex interaction of metabolic (Glucose, AGE, polyols) and hemodynamic factors (RAS, Endothelin) in renal microcirculation. There is an accumulation of advanced glycosylated end products (AGEs), the activation of isoforms of protein C kinase and activation of aldose reductase pathway, increased activity of the renin–angiotensin activity also plays an important role in the progression of the disease. Other factors including excess accumulation of extracellular protein, podocyte abnormality, albuminuria, and oxidative stress have also been implicated in DN [24–28]. Endothelial dysfunction is closely associated with the development of DN [29].

Clinically it starts from microalbuminuria to reduction in GFR and an overt increase in urea and creatinine levels. A few studies have suggested that complications of diabetic nephropathy are related to atherosclerosis of intrarenal and extrarenal arteries. This study focuses upon measurement of intrarenal arterial flow resistance, (indirectly suggestive of afferent arteriolar flow) in different stages of CKD and to compare it with patients having poor glycemic control with non-evident nephropathy and to find possible mechanism (steps) towards progression to ESRD, and to look for some therapy aspect related to pathology.

Assessment of flow in intra-renal arteries was done with Renal Arterial Doppler [15,16].

The study was done in a case control, retrospective manner through data collection in Mittal hospital and research center, Pushkar Road Ajmer, Rajasthan, India. Hospital record of 40 cases (20 diabetic cases without nephropathy (control, group A) and 20 diabetic cases with the nephropathy (study group, group B) admitted between July 2016 and July 2018 was observed. We divide the discussion into four parts-

1) Findings of the study

1a) Diabetic cases not having nephropathy (Group A)

In long–standing diabetic cases (>5 years); HbATC > 10 %, the cases were not associated with albuminuria; R.I. index was normal (<0.7) (Figure 1); e-GFR normal (Table 2).

1b) Diabetic cases having nephropathy (Group B).

1bA) In CKD stage 1(Subgroup B1), there was albuminuria (+), borderline (0.7–0.8) increase in R.I. index, e–GFR normal–91 ml/min/1.73 m² (Figures 2,3). These cases didn’t show an evident effect on reduction in GFR (urea/creatinine normal).

**Table 1:** Vital parameters of Group 1 and Group 2.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Age/Years (mean)</th>
<th>Sex</th>
<th>BMI (kg/m²) mean</th>
<th>Pulse rate,mean</th>
<th>Respiratory rate,mean</th>
<th>Blood Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1(n=20)</td>
<td>56 Male</td>
<td>24.6</td>
<td>80</td>
<td>14</td>
<td>148/90</td>
<td></td>
</tr>
<tr>
<td>Group 2A(n=20)</td>
<td>59 Male</td>
<td>24.8</td>
<td>82</td>
<td>14</td>
<td>152/90</td>
<td></td>
</tr>
</tbody>
</table>

instead previous studies suggest that glycosuria may increase GFR [30] (p<0.001).

**tbB**) CKD stage 2 (subgroup B2), albuminuria was +2, R.I. index was >.8 (high), e-GFR reduced - 66 ml/min/1.73 m² (p<0.001).

**tbC**) CKD stage 3b (subgroup B3), albuminuria was +2, R.I. index was 0.9 (high) e-GFR reduced - 34 ml/min/1.73 m² (Figure 4) (p<0.001).

**tbD**) In CKD stage 5, (subgroup B5) albuminuria was +4 and there was marked increase in R.I. index 1.1, e-GFR markedly reduced - 6 ml/min/1.73 m² (Figure 5) (Table 2)(p<0.001).

---

**Table 2: R.I. index, e-GFR and statistical significance.**

<table>
<thead>
<tr>
<th>Group A(n=20) (male)</th>
<th>Mean Serum Creatinine (in mg/dl)</th>
<th>Mean e-GFR ml/min/1.73m²</th>
<th>Mean R.I. index</th>
<th>P-value Group A v/s Subgroups of Group B</th>
<th>Urine Albumin</th>
<th>USG (Kidneys)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B(n=20) (male)</td>
<td>0.7</td>
<td>122</td>
<td>0.60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgroup B1(n=7) (male)</td>
<td>0.9</td>
<td>91</td>
<td>0.80</td>
<td>P&lt;0.001</td>
<td>1</td>
<td>Size normal, increased cortical echogenicity</td>
</tr>
<tr>
<td>Subgroup B2 (n=2) (male)</td>
<td>1.2</td>
<td>66</td>
<td>0.86</td>
<td>P&lt;0.001</td>
<td>2</td>
<td>Size normal, increased cortical echogenicity</td>
</tr>
<tr>
<td>Subgroup B3 (n=4) (male)</td>
<td>2.1</td>
<td>34</td>
<td>0.90</td>
<td>P&lt;0.001</td>
<td>2</td>
<td>Size small, increased cortical echogenicity</td>
</tr>
<tr>
<td>Subgroup B4 (n=0)</td>
<td>10.2</td>
<td>6</td>
<td>1.10</td>
<td>P&lt;0.001</td>
<td>4</td>
<td>Reduced cortico-medullary differentiation, size small</td>
</tr>
</tbody>
</table>

---

**Figure 1:** Normal R.I. index.

**Figure 2:** Border line high R.I. index.

**Figure 4:** High R.I. index.

**Figure 5:** Very high R.I. index.
2) Possible correlation between R.I. index and GFR.

2a) Normal R.I. index is associated with normal GFR (group 1).

2b) Increase in R.I. index (resistance to flow) is associated with decrease in GFR. This decrease is a progressive i.e. reduction in GFR from CKD stage 1 to CKD stage 5; parallel to a progressive rise in R.I. index, urea, creatinine levels. Findings suggest that the R.I. index is inversely related to GFR. GFR=1/R.I. index (CKD 2, 3, 5) (except stage 1 where damage to endothelium is evident from albuminuria but GFR is normal or may be high because of glycosuria) [31,32].

2c) Normal R.I. index in patients with a long-standing disease without nephropathy suggests that no resistance to flow is associated with normal kidney functions.

2d) Increase in R.I. index starts at the earliest i.e. at albuminuria without an increase in urea/creatinine values (Table 2).

3) Determinants of the GFR in physiology and its correlation with the current study-  

3a) The GFR is determined by (a) the sum of the hydrostatic and colloid osmotic forces across the glomerular membrane, which gives the net filtration pressure, and (b) the glomerular capillary filtration coefficient, Kf. The GFR equals the product of Kf and the net filtration pressure:

\[ \text{GFR} = K_f \times \text{Net filtration pressure} \]

The net filtration pressure represents the sum of the hydrostatic and colloid osmotic forces that either favor or oppose filtration across the glomerular capillaries. These forces includes (A) hydrostatic pressure inside the glomerular capillaries depends upon pressure at afferent arteriolar end (glomerular hydrostatic pressure PG), which promotes filtration (B) the hydrostatic pressure in Bowman’s capsule (PB) outside the capillaries, which opposes filtration; (C) the colloid osmotic pressure of the glomerular capillary plasma proteins (πG), which opposes filtration; and (D) the colloid osmotic pressure of the proteins in Bowman’s capsule (πB), which promotes filtration. The GFR is expressed as: [33-37].

\[ \text{GFR} = K_f \times (P_G - P_B - \pi G + \pi B) \]

---

Bernoulli’s principle says that a rise (fall) in pressure in a flowing fluid must always be accompanied by a decrease (increase) in speed, and conversely, is an increase (decrease) in the speed of the fluid results in a decrease (increase) in the pressure [34]. Reduction in afferent arteriolar diameter is associated with increased speed and hence a reduction in hydrostatic pressure at the afferent arteriolar end.

4) Possible mechanism of reduction in GFR (Co-relation between observed findings and facts in physiology).

Normally, the main determinant of GFR is hydrostatic pressure (60 mmHg) at afferent arteriole/afferent end of the capillary. In our finding, there is a progressive increase in resistance (R.I. index) to flow at the afferent arteriolar end associated with a reduction in hydrostatic pressure, parallel to a decrease in e-GFR (Figures 6,7). This increase in the RI index is due to a decrease in afferent arteriolar diameter due to persistently increased ACE activity/ increased basal sympathetic discharge in the beginning and deposition of AGE end products/arteriosclerosis [38-40] material in afferent arteriole in late stages. Reduction in afferent arteriolar flow compromises all the functions of the kidney simultaneously as whole renal tissue is supplied by the afferent arteriolar flow. Normal blood supply of glomerulus including glomerular basement membrane (GBM) is through afferent arteriole. Even subtle hypo-perfusion/reduction in afferent arteriolar flow at the beginning of nephropathy may affect functions of GBM i.e. albuminuria which up to some extent responds to ACE...
Flow Chart 1

Normal afferent arteriolar flow
↓
Normal R.I. Index
↓
Normal Renal functions
↓
Increased ACE activity / increased basal sympathetic discharge
↓
ACE inhibition / Beta blocker

Increased R.I. Index
↓
Decreased afferent arteriolar flow
↓
Subtle hypo perfusion of kidney tissue
↓
Early GBM damage
↓
Micro albuminuria
↓
Increased RAAS activity / AGE deposition
↓
ACE inhibition / AGE removal

Increased R.I. Index
↓
Decreased afferent arteriolar flow
↓
Mild decrease in GFR – early CKD
↓
Mild hypo perfusion of kidney tissue
↓
Increased RAAS activity / Increased AGE deposition
↓
Further Increase in R.I. Index/ further decrease in afferent arteriolar flow
↓
Further decrease in GFR – progression of CKD
↓
Global renal Hypo perfusion – (Loss of cortico – medullary differentiation)
↓
Marked decrease in GFR
↓
Marked increase in RAAS activity
↓
ESRD

κ - Site for action in DN

Evidence of diffuse hypo-perfusion is also suggested by perfusion scan. Previous MRI scans have suggested the hypo-perfusion of kidneys in DN [33,34]. Which in turn activates RAAS (renin-angiotensinaldosterone system) worsens the perfusion of kidneys in DN [33,34]. Which in turn activates perfusion scan. Previous MRI scans have suggested the hypo-perfusion of kidneys in DN [33,34]. Which in turn activates RAAS (renin-angiotensinaldosterone system) worsens the perfusion of kidneys in DN [33,34]. Which in turn activates perfusion scan. Previous MRI scans have suggested the hypo-perfusion of kidneys in DN [33,34]. Which in turn activates RAAS (renin-angiotensinaldosterone system) worsens the perfusion of kidneys in DN [33,34]. Which in turn activates perfusion scan. Previous MRI scans have suggested the hypo-perfusion of kidneys in DN [33,34]. Which in turn activates RAAS (renin-angiotensinaldosterone system) worsens the perfusion of kidneys in DN [33,34].

Conclusion

It is concluded that DN begins from an increase in resistance to flow in renal/intrarenal arteries primarily resulting from resistance in afferent arterioles due to a reduction in size [31,32]. This is depicted by progressive increase in RI index parallel to reduction in GFR. Activation of RAAS further leads to progression towards ESRD.

Suggestions

Besides available methods for treatment of DN, all attempts must be done to try to reduce resistance/improvement in flow in renal vasculature to improve GFR by using ACE inhibitors/ARBs/Beta blockers. A strong strategy to inhibit AGE by strict blood glucose control and for AGE removal from afferent arterioles either by diet or drugs which seems to be the key step in preventing/treating DN.

References


Discover a bigger Impact and Visibility of your article publication with Peeretechz Publications

**Highlights**

- Signatory publisher of ORCID
- Signatory Publisher of DORA (San Francisco Declaration on Research Assessment)
- Articles archived in worlds’ renowned service providers such as Portico, CNKI, AGRIS, TDNet, Base (Bielefeld University Library), CrossRef, Scilit, J-Gate etc.
- Journals indexed in ICMJE, SHERPA/RoMEO, Google Scholar etc.
- OAI-PMH (Open Archives Initiative Protocol for Metadata Harvesting)
- Dedicated Editorial Board for every journal
- Peeretechz journals wishes everlasting success in your every endeavours.

Copyright: © 2019 Saxena T, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.