Prevalence of Non-Diabetic Renal Disease in Type 2 Diabetic Patients in a Diabetes Centre in Southern India

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Abstract

- Objective: The aim of study is to determine the prevalence of non-diabetic renal disease among South Indian type 2 diabetic subjects based on renal biopsy.
- Methods: Three thousand five hundred and ninety subjects with complete records were included for the study. One hundred and forty subjects who had proteinuria but no evidence of retinopathy undertook a 24-hour proteinuric estimation. Of these 140 subjects, 28 subjects had proteinuria > 1000 mg/day and were subjected to renal imaging. Seven subjects were excluded due to renal calculi, cysts or contracted kidneys. Of the remaining 21 diabetic subjects, one subject was excluded as he had a mild diabetic retinopathy on fundus fluorescein angiography. Of the 20 subjects included 18 participated in the renal biopsy study (response rate - 90%). Renal pathology of these subjects were studied.
- Results: Of the 18 renal biopsies, two were excluded due to different reasons. Out of 16 patients, eight (50%) had pathological changes suggestive of diabetic etiology, five (33.3%) had classical membranous nephropathy, one (6.2%) had tubulo-interstitial disease and two (12.5%) were categorized as others with minimal changes. The subjects with non-diabetic renal disease had significantly higher creatinine clearance (p = 0.024), serum cholesterol (p = 0.036), triglyceride levels (p = 0.045) and LDL cholesterol (p = 0.048) compared to subjects with diabetic nephropathy.
- Conclusion: This study suggests that even in subjects clinically suspected to have non-diabetic renal disease many may turn out to have diabetic nephropathy on renal biopsy. (J Assoc Physicians India 2002;50:1135-1139)

Introduction

Diabetic nephropathy remains a major cause of morbidity and mortality in diabetes mellitus.1 About 20-40% of patients with type 2 diabetes mellitus develop diabetic renal disease and eventually progress to end stage renal failure.2 A recent study from our group in a consecutive series of 1848 type 2 diabetic patients attending our centre showed that 9.4% had diabetes related proteinuria (defined as proteinuria plus retinopathy). In addition, 3.8% had evidence of proteinuria without retinopathy.3 Although the absence of diabetic retinopathy suggests a non-diabetic etiology for the proteinuria in the latter patients but it still does not rule out diabetes as the cause for the proteinuria. Renal biopsy is the only method of differentiating non-diabetic renal disease from diabetic glomerulosclerosis.4,5 In this paper, we attempt to identify the etiology of non-diabetic proteinuria in a series of type 2 diabetic patients seen at a diabetes centre in Southern India.

Material and Methods

The study group comprised of 4488 consecutive type 2 diabetic patients attending the MV Diabetes Specialities Center, Chennai during the period 1st July 1998 to 1st December 2000. Type 2 diabetes was diagnosed based on the WHO study group report on diabetes.6 Of the 4488 patients, 898 subjects with incomplete records, proteinuria not tested twice, retinal examination not done, presence of urinary tract infection or heart failure were excluded. There was no significant differences in the age, sex distribution, plasma glucose or glycosylated haemoglobin (HbA1c) levels between these 898 patients and the 3950 patients included in the study.

Urinary protein was measured on a random spot urine sample by sulfosalicylic acid technique. Creatinine was measured using Jaffe’s method (CV = 5.7%). Proteinuria was calculated based on protein : creatinine ratio as previously described.7

A complete ocular examination was done which in-
cluded visual acuity assessment, intraocular pressure measurement and a detailed fundus examination. For retinal assessment both direct and indirect ophthalmoscopy was done by retinal specialists. If the retina was normal as assessed by fundus examination and if proteinuria (≤ 1000 mg/day) was present then fundus flourescein angiography (FFA) was performed. This was done to confirm the absence of diabetic retinopathy and these patients then underwent renal biopsy to assess the cause of proteinuria. Only those patients with proteinuria measurements made on at least two consecutive visits were included. Patients with persistent proteinuria (i.e. ≤ 500 mg/day of proteinuria) in the presence of any diabetic retinopathy were classified as "diabetic proteinuria". Patients with proteinuria ≤ 500 mg/day but who had no evidence of retinopathy were considered as "proteinuria probably due to non-diabetic etiology". Figure 1 shows a flow chart for the selection of patients in the study.

Patient selection for renal biopsy studies

The 20 patients without retinopathy were requested to participate in renal biopsy study. 90% (n=18) participated in the study after signing an informed consent form. All 18 individuals had sterile urine cultures and normal bleeding, clotting and prothrombin times.

Definition of Renal Pathology

Diabetic Glomerulopathy: was diagnosed if any of following features were present:

i. Nodular glomerulosclerosis: Classical Kimmelstein and Wilson lesion with globular mesangial nodules.

ii. Diffuse glomerulosclerosis: Uniform widening or thickening of the mesangial region.

iii. Fibrin cap

iv. Capsular drop

Membranous Nephropathy: Presence of diffuse thickening of the glomerular basement membrane capillary wall and immunofluorescent study revealing deposition of IgG and C3.

Minimal Change Nephropathy: Glomeruli of normal structure with mild mesangial hypercellularity were diagnostic of minimal change nephropathy.

Tubulo-interstitial Disease

This included inflammatory infiltrates involving the interstitial space between the tubules with normal glomerular structure.

Results

As outlined above, 18 patients ultimately underwent the renal biopsy procedure. One patient had haematuria post biopsy for a day, presumably because of damage to one of the renal blood vessels. This however settled down after a day. The biopsies were uneventful in the other 17 patients. Two patients were excluded as one had insufficient tissue sample and in the other, immunofluorescence could not be performed.

Table 1 shows the histopathological findings of renal biopsies done in the 16 patients in whom good quality biopsies were obtained. Immunofluorescence revealed IgM and C3 deposits in diabetic glomerulopathy while IgG and C3 deposits were seen in membranous nephropathy.

Table 2 shows the clinical and biochemical differences between the patients with "diabetic" and "non-diabetic" nephropathy.

There was no significant difference in the age, fasting or postprandial plasma glucose or glycosylated haemoglobin levels between two groups.
Table 1: Histopathological findings in the 16 type 2 diabetic patients who underwent renal biopsy

<table>
<thead>
<tr>
<th>Lesions</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic glomerulosclerosis</td>
<td>4 (25%)</td>
</tr>
<tr>
<td>Diabetic glomerulosclerosis and tubulo interstitial disease</td>
<td>4 (25%)</td>
</tr>
<tr>
<td>Membranous Nephropathy</td>
<td>5 (33.3%)</td>
</tr>
<tr>
<td>Tubulo Interstitial Disease</td>
<td>1 (6.2%)</td>
</tr>
<tr>
<td>Others e.g. minimal change glomerulosclerosis</td>
<td>2 (12.5%)</td>
</tr>
</tbody>
</table>

There was no significant difference in the male/female ratio or the prevalence of hypertension between the two groups. However, the duration of diabetes was longer in group A (diabetic nephropathy) compared to Group B, though it was not statistically significant (p = 0.064) probably due to small numbers. Creatinine clearance (p = 0.024), serum cholesterol (p = 0.036), triglycerides (p = 0.045) and LDL cholesterol (p=0.048) levels were higher among the subjects with non-diabetic nephropathy compared to the patients with diabetic nephropathy.

Discussion

Diabetic nephropathy is diagnosed clinically based on long duration of diabetes, presence of retinopathy and proteinuria. Nodular glomerulosclerosis is a characteristic feature of diabetic nephropathy and these patients progressively deteriorate with increasing azotemia and finally result in end-stage renal disease (ESRD). Various studies have suggested that diabetic patients could also suffer from renal disease of non-diabetic origin. The presence of "non-diabetic renal disease" should be suspected under the following situations.

i. Proteinuria in the absence of diabetic retinopathy.

ii. Short duration between the diagnosis of diabetes mellitus and onset of nephropathy (< 5 years).

iii. Renal failure in the absence of, or insignificant,
proteinuria.

iv. Urinary sediments or hæmaturia.

Studies from the UK have shown that among migrant Asian Indians, the prevalence of both diabetic and non-diabetic renal disease is higher in Indians compared with Europeans. Our earlier studies have reported on the prevalence of proteinuria and microalbuminuria in consecutive series of type 2 diabetic patients.

In the present study, 50% of the renal biopsies performed on type 2 diabetes particularly suspected clinically to have non-diabetic renal disease actually had evidence of diabetic nephropathy. These results are similar to that reported by Christensen et al, who reported diabetic glomerulopathy in 69% of patients with suspected non-diabetic renal disease. An earlier study by Olsen et al on 33 biopsies showed that only four of these 33 patients actually had evidence of a non-diabetic nephropathy. In the remaining 29 patients, typical diffuse (n=9) or nodular (n=20) diabetic lesions were found. While, John et al reported that 21.5% had proliferative glomerulonephritis, of the 80 type 2 diabetic subjects studied. These studies suggest that even among patients suspected to have a non-diabetic renal disease, at least 50% be usually due to diabetes.

We found that the duration of diabetes was longer in the group with diabetic nephropathy and this suggests that the shorter the duration of diabetes the greater would be the chances of a non-diabetic etiology. A study of Korean subjects also identified a short duration of diabetes to be strongly associated with non-diabetic renal disease.

We also noted that the actual protein excretion was also greater in non-diabetic nephropathy group. The creatinine clearance was lower in the diabetic nephropathy group and this was statistically significant. This suggests (but does not prove) that the clinical course and progression in diabetic nephropathy is more rapid than non-diabetic renal disease. Christensen et al compared the clinical course and progression of renal function, in biopsy proven diabetic glomerulosclerosis (DG) with non-diabetic glomerulopathies (NDG). Glomerular filtration rate was determined at least once a year and albuminuria, arterial blood pressure and HbA1c were determined every 3-6 months. The patients were followed for a median of 7.7 years and in the DG group, GFR was more rapid i.e. decreased from 82-38 ml/min. In our study, there was no significant difference in the prevalence of hypertension among subjects with diabetic nephropathy and non-diabetic renal disease.

In the present study, total cholesterol, LDL cholesterol and serum triglyceride levels were significantly higher in subjects with non-diabetic renal disease compared to subjects with diabetic nephropathy. Renal disease is accompanied by characteristic alteration of lipoprotein metabolism, which appears as a consequence of nephrotic syndrome or renal insufficiency. Nephrotic syndrome results in increased concentrations of both cholesterol and triglyceride rich apoB containing lipoproteins and renal insufficiency is characterised by an accumulation of intact or partially metabolised triglyceride - rich apoB containing lipoproteins. In contrast, it is also suggested that hypercholesterolemia could play a role in the progression of glomerulosclerosis and that LDL is mitogenic and cytotoxic for the mesangial cells. Scavenger receptor uptake of LDL particles by monocytes and macrophages results in mesangial foam cells. Greco et al in a review suggested that lipid nephrotoxicity leads to renal injury and that lipids play a synergistic role with other risk factors in the progression of renal disease both in diabetic and non-diabetic renal disease.

One of the limitations of the study is that it was carried out on a highly selected population. As we had used an algorithm based on arbitrary cutoffs such as proteinuria > 1 g/day, it is difficult to determine the exact percentage of patients having non-diabetic renal disease. This is because patients who were not recruited for biopsy studies like those with proteinuria < 1 g/day might also have non-diabetic renal disease.

**Conclusion**

Our study suggests even in those suspected to have non-diabetic renal disease clinically many may have diabetic nephropathy. A shorter duration of diabetes and massive proteinuria associated with hyperlipidemia would be clinical pointers to a non-diabetic cause. Our study suggests that the indications for performing a renal biopsy should be evaluated carefully and it should not by any means be routinely performed in type 2 diabetic patients with proteinuria unless there are clear indications. The justification for doing a renal biopsy at all in this group of patients with suspected non-diabetic renal disease however is that some of these glomerulopathies may respond quite dramatically to steroids or other specific treatments and thus help the occasional patient who otherwise would have been miss-classified as diabetic nephropathy.
References


