

Frequency of Non-Diabetic Renal Disease (NDRD) in Type II Diabetes Mellitus

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Abstract

Objective: To describe the frequency of NDRD in type II diabetic patients who underwent renal biopsy for deranged renal functions that includes haematuria, proteinuria in the nephrotic and non-nephrotic range and rapidly worsening renal failure.

Methods: A descriptive study was undertaken in the Department of histopathology at The Kidney Post-graduate Center, Karachi, Pakistan from January 2000 to May 2005. The renal biopsies of 73 patients of type II diabetes were evaluated when a renal disease other than diabetic glomerulosclerosis (DGS) was suspected because of unexplained haematuria, clinically significant proteinuria in nephrotic and non-nephrotic range and rapidly progressive renal failure or unexplained renal failure with normal sized kidney. Three groups of patients were defined on the basis of renal damage noted on light microscopy and immunofluorescence investigations. Group I was NDRD alone, group II NDRD with co-existent DGS and group III DGS alone. The relationship of histology with clinical profile in each group and duration of diabetes were noted and analyzed using SPSS 15 software.

Results: Of the 73 patients studied 46 were males and 27 were females (1.7:1). Group I and II tended to have a younger age group at presentation (49.26 ± 9.37 years and 49.0 ± 5.72 years respectively) than group III (53.62 ± 6.62 years). The mean duration of diabetes was 9.9 ± 10.42 years in group I, 7.5 ± 3.78 years in group II and 13.31 ± 1.71 years in group III. Among patients 30(41.1%) had NDRD alone, 06(8.21%) had NDRD co-existent with DGS, and 37(50.7%) had DGS alone. Focal segmental glomerulosclerosis (FSGS) and tubulointerstitial nephritis (TIN) were the most common lesion and accounted for 22.2% and 19.4% respectively. Amount of proteinuria was higher in patients of NDRD (3.064 ± 1.38 gms/24hrs in group I and 3.316 ± 0.97 gms/24hrs in group II) than those of DGS (2.815 ± 0.916 gms/24hrs) but it did not reach statistical significance. Serum creatinine was significantly raised in patients of group III (3.391 ± 0.927 mg/dl) versus group I (2.563 ± 0.95 mg/dl) and II (2.633 ± 0.952 mg/dl) (p 0.002). The presence of haematuria was seen in greater number in patients of NDRD (32.5% in group I and 33.3% in group II) versus DGS (in group III 29.6%), but it did not reach statistically significant values.

Conclusion: This study shows a high frequency of NDRD in type II diabetic patients who underwent a renal biopsy for impaired renal functions emphasizing the significance of biopsy in such patients in order to tailor their management accordingly.

Keywords: Type II diabetes, Diabetic glomerulosclerosis, Non-diabetic renal diseases (AASH & KMDC 18(1):1;2013)

Introduction

It has been well demonstrated that renal diseases in more than 95% of the patients, in patients suffering from insulin dependent diabetes mellitus (IDDM) or Type I diabetes for greater than 10 years, especially in the presence of diabetic retinopathy and neuropathy, is usually the result of diabetic nephropathy (DN) as proven histologically in greater than 95% of the patients^{1,2}.

Incidence of non-insulin dependent (NIDDM) or type II diabetes is increasing worldwide. Renal involvement is common during the course of this illness in spite of the correction of environmental factors^{3,4}. In retrospective studies of type II diabetic patients with renal involvement, 12-81% of their renal lesions were due to non-diabetic renal diseases with different spectrums of diseases identified in different series¹.

The presence of proteinuria is a strong predictive factor of renal failure in type II diabetic patients. However, if proteinuria or unexplained renal failure is seen in type II diabetic patients in the absence of

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retinopathy or noted in the early phase of diabetes it strongly rises a possibility of NDRD. In recent years emphasis is given on renal biopsy evaluation to establish the cause of renal pathology for an obvious prognostic significance, as several of the NDRD shown to have better renal outcome with treatment modalities⁵. The distinction between DN and NDRD is not always obvious on clinical grounds and often determined on renal biopsy⁶, thus altering therapeutic options.

In a limited number of prospective studies of type II diabetic patients with renal involvement, 23-39% of patients were found to have NDRD¹. The determination of NDRD in type II diabetic patients in our country is limited. Therefore, the study was undertaken to describe the frequency and spectrum of NDRD in Type II diabetic patients who underwent renal biopsy for impaired renal function including haematuria, proteinuria in the nephrotic and non-nephrotic range and rapidly worsening renal failure.

Patients and Methods

The renal biopsies of all the type II diabetic patients were included in this descriptive study. From January 2000 to May 2005, a total of 73 cases were identified and retrieved from the record of department of histopathology at The Kidney Post-graduate Center, Karachi.

Only those renal tissues for biopsy were included that contained cortical region with 5-10 glomeruli with obvious histological details of glomeruli, tubulointerstitium and blood vessels. The biopsies with advanced nephrosclerosis, those containing less than 04 glomeruli or consisting of medullary region only, were excluded. The renal biopsy was considered necessary by the clinicians in type II diabetic patients when NDRD was suspected because of unexplained haematuria, significant proteinuria in nephrotic and non-nephrotic range, rapidly progressive renal failure and unexplained renal failure with normal sized kidney. The biopsy was not performed if a patient had a long history of diabetes with severe multi-organ disease, such as ret-

inopathy; in these patients the diagnosis of DN was considered.

Renal tissue obtained by needle biopsy was examined by light microscopy and immunofluorescence microscopy. Sections were stained with haematoxylin and eosin, Masson's trichome, periodic Acid-Schiff, silver methamine, and when required by Congo red stain. Tissues were tested against human immunoglobulin G (IgG), IgA, IgM, C3c, and C1q for immunofluorescence study.

The morphological criteria of diabetic glomerular lesion included diffuse mesangial sclerosis with or without Kimmelstiel-Wilson nodule, microaneurysms, basement membrane thickening, lesions such as fibrin caps and capsular drops, arteriolar hyalinosis and linear IgG positivity along the glomerular basement membrane. The diagnosis of DGS was made when at least three of the above features were present in the tissue biopsies⁷. NDRD was diagnosed and categorized in the light of clinical and histological features and the immuno-flourescence profile of the renal lesion.

Based on the biopsy findings, patients in this study were divided into 3 groups. Group I NDRD only group II NDRD with co-existing DGS and group III DGS only. The clinical and biochemical parameters were recorded at the time of renal biopsy that included age, sex, and duration of diabetes, serum creatinine, 24 hr urinary protein and systolic and diastolic blood pressures. Furthermore, the relationship between clinical and histological findings were compared.

Statistical analysis was performed using SPSS version 15.0 for windows. Data was expressed as mean±SD for continuous variables. Frequency and percentage were computed for qualitative and categorical variables (eg. gender, number of patients). Student's t-test and ANOVA were used to compare two and multiple parameters respectively (like age, duration of diabetes, serum creatinine, blood pressure and proteinuria). Chi square test was applied on variables such as gender and haematuria at re-

nal biopsy. $p < 0.05$ was considered as statistically significant.

Results

Table 1 shows that, among the 73 patients in this study, 30(41.1%) had NDRD alone (group I), 06(8.21%) had NDRD with co-existing DGS (group II) and 37 (50.7%) had DGS alone (group III). It also depicts the base line patient profile at the time of renal biopsy. The number of males were 46 and 27 were females (M:F: 1.7:1). Patients of NDRD (group I and II) tended to have younger age (49.26 ± 9.37 years and 49 ± 5.72 years respectively) as compared to group III (53.62 ± 6.62 years) though difference among groups was not significant ($p = 0.06$). There was no significant difference in mean duration of diabetes between group I (9.9 ± 10.42 years), group II (7.5 ± 3.78 years) and group III (13.31 ± 1.71 years) ($p = 0.051$).

Table 2 illustrates the different percentages of NDRD with focal segmental glomerulosclerosis (FSGS) being the most common (22.2%) followed by tubulointerstitial nephritis (TIN) (19.44%) and post-infectious glomerulonephritis (16.66%).

Table 3 lists the clinical and biochemical characteristics of type II diabetic patients in this study. Proteinuria was higher in patients of NDRD (3.06 ± 1.38 gms/24hrs in group I) and 3.32 ± 0.97 gms/24hrs in group II) than those of DGS (2.81 ± 0.91 gms/24hrs) but it did not reach statistical significance ($p = 0.48$). Serum creatinine was significantly raised ($p = 0.002$) in patients of group III (3.39 ± 0.92 mg/dl) versus group I (2.56 ± 0.95 mg/dl) and II (2.63 ± 0.95 mg/dl).

The presence of haematuria was seen in greater number in patients of NDRD (32.5% in group I and 33.3% in group II) versus DGS, group III (29.6%), but it did not reach statistically significant values. Mean systolic and diastolic blood pressures were higher in group III (152 ± 9 mmHg, 94 ± 6 mmHg) as compared to group I (135 ± 13 mmHg, 86 ± 8 mmHg) and group II ($148 \pm$

11 mmHg, 93 ± 8 mmHg) which were statistically significant ($p < 0.001$).

Discussion

DN is a long term complication in type II diabetic patients which progresses to end-stage renal disease. However, in recent years, the medical literature has reported the presence of non-diabetic often treatable renal diseases in type II diabetic patients^{2,8}. Therefore, in the present study we observed the prevalence and nature of NDRD in type II diabetic patients who underwent renal biopsy for impaired renal functions. Based on morphological features and immunofluorescence investigation, the 73 cases in this study were divided into 3 groups of renal lesions. In this series the frequency of NDRD is 49.31% (group I and II), whereas 58.9% of the patients demonstrated DGS (group II and III).

The real frequency of NDRD in type II diabetic patients is difficult to assess as different studies published over the last several years reported a prevalence ranging from 12% to 81% which are unrelated to or coexistent with DGS⁹. This broad variability is not easy to explain. From the review of the relevant literature it has been observed that this variability possibly relates to certain factors that includes policies in different institutions for renal biopsy, the population being investigated and the small size of the study. Significant discrepancies are also evident, when ethnically homogenous populations belonging to the same geographic area were studied. Most of the earlier studies were not supported by the morphological data and therefore, they are unable to clarify this question. However, when morphological data were available as in two series in Denmark and Finland, the real frequency of NDRD alone or coexistent with DGS ranged from 9% to 18%^{10,11}, whereas a study conducted in India reported a prevalence of 81% of NDRD in type II diabetic patients¹². The factor which can resolve this issue up to some extent, is the policies adapted towards renal biopsies in various institutions. In centers which pursue restricted policy, renal biopsies were performed only when NDRD was

suspected due to atypical renal symptoms. Whereas, the centers that pursue unrestricted policy, renal biopsy was performed in type II diabetic patients with proteinuria > 0.5 gm/day alone or associated with hematuria, or impairment in renal functions.

In our institution, the nephrologists are following the current practice of restricted policy and are doing renal biopsies in type II diabetic patients suspected for NDRD of unexplained haematuria, clinically significant proteinuria in nephrotic and non-nephrotic range, rapidly progressive renal failure, or unexplained renal failure with normal sized kidneys. In fact, NDRD alone are more prevalent than without DGS in studies following restricted policy¹³, this finding is also noted in the present study. Conversely, DGS alone or co-existent with NDRD is seen in more number of studies using unrestricted policy. Regardless of the fact that the policies in different institutions are influencing the prevalence result of renal disease in diabetes, the matter of significance is the detection of NDRD in type II diabetic patients for obvious therapeutic and prognostic implications⁸.

The prognosis of NDRD depends on the nature of that lesion and the time of its occurrence in the course of diabetes mellitus. It is evident from the literature that NDRD with DGS have a significantly worse outcome than those without DGS⁷. Furthermore, the renal outcome of patients with DGS is probably not altered by co-existing nephropathy. Much more important is the detection of NDRD without DGS which might favorably be influenced by the therapy. For instances, it is well known that post infectious glomerulonephritis, MCD and perhaps FSGS, membranous glomerulonephritis (MGN) and some form of IgA nephropathy respond to specific treatment¹⁴. Spontaneous remission of acute proliferative glomerulonephritis has also been reported⁵. In our study FSGS was the most common NDRD followed by TIN. In a similar study conducted in United States which reported FSGS (21%) the most common lesion in type II diabetic patients whereas in a local study done in nondiabetic pa-

tients, in which (AIN 32%), the most prevalent NDRD followed by diffuse proliferative glomerulonephritis (17%)¹⁵.

The presence of proteinuria did not accurately predict the presence or severity of DN in type II diabetic patients, but if significant proteinuria seen earlier than expected in these patients, it is a clue to a possible presence of NDRD¹⁶. As shown in this study significant proteinuria in all the three groups of type II diabetic patients which is comparable to a study done by Gianna et al¹³. It is to be noted that proteinuria of more than 2 gm/day is associated with disease progression and adverse outcome, and protein as such is tubulotoxic. This high proteinuria applies not only in type II diabetes but also in patients with NDRD alone or co-existing with DGS¹⁷.

Deterioration of renal functions either earlier in the course of diabetes or at an accelerated pace should also arouse suspicion of NDRD¹⁸. In the present study sudden decline in renal functions were not only seen in NDRD but also noted in patients with DGS, and this is probably related to difficulty in estimating the precise duration of diabetes. In fact, many of these patients had severe changes of diabetes of longer duration accompanied with organizing fibro epithelial crescents in the glomeruli. The presence of such crescents in DGS has been reported to be associated with aggressive clinical course¹⁹. Therefore, unexplained or rapid deterioration in renal function is the poor predictor of NDRD. Urinary abnormality such as haematuria with the absence of urinary tract infection is an indicator of both DN and NDRD, however if it is seen in earlier course of type II diabetic patients it is a clue towards NDRD²⁰. In our study of type II diabetic patients, haematuria was also noticed in both DGS and NDRD and in our opinion red blood cells in the urine require evaluation for the possible presence of NDRD.

Both systolic and diastolic blood pressures were raised in type II diabetic patients in our study but they were significantly higher in patients of DGS alone or co-existent with NDRD. High blood pressures if accompanied with severe proteinuria

Table 1. Demographics in three groups:

| Characteristics | Group I- NDRD only | Group II- NDRD with DGS | Group III - DGS only | p-value |
|------------------------------|--------------------|-------------------------|----------------------|---------|
| Number of patient | 30 | 6 | 37 | - |
| Gender : Male/Female | 26/4 | 4/2 | 16/11 | 0.940 |
| Age (years) | 49.26 ± 9.37* | 49.0 ± 5.72 | 53.62 ± 6.62 | 0.062 |
| Duration of Diabetes (years) | 9.9 ± 10.42 | 7.5 ± 3.78 | 13.31 ± 1.71 | 0.051 |

* Mean ± SEM

Table 2. Frequency of Non- Diabetic Renal Diseases

| Types of Non-Diabetic Renal Disease | Not Coexisting With DGS | Coexisting with DGS | Total (%) |
|-------------------------------------|-------------------------|---------------------|-------------|
| FSGS | 7 | 1 | 08 (22.22%) |
| TIN | 5 | 2 | 07 (19.44%) |
| Post infectious GN | 4 | 2 | 06 (16.66%) |
| MGN | 3 | 0 | 03 (8.33%) |
| Amyloidosis | 3 | 0 | 03 (8.33%) |
| MCD | 3 | 0 | 03 (8.33%) |
| IgA Nephropathy | 1 | 1 | 02 (5.55%) |
| CrGN | 2 | 0 | 02 (5.55%) |
| HTN | 2 | 0 | 02 (5.55%) |
| Total | 30 | 6 | 36 (100%) |

MGN, Membranous glomerulonephritis; FSGS, Focal segmental glomerulosclerosis;
MCD, Minimal change disease; TIN, Tubulointerstitial nephritis; CrGN, Crescentic glomerulonephritis

Table 3. Clinical and Biochemical features in three groups of Type II diabetic renal diseases (n= 73)

| Clinical and Biochemical features | Group I -NDRD Only (n=30) | Group II -NDRD with DGS (n=06) | Group III -DGS Only (n=37) | p-value |
|-----------------------------------|------------------------------|-----------------------------------|-------------------------------|---------|
| Ser. Creatinine (mg/dl) | 2.56 ± 0.95 | 2.63 ± 0.952 | 3.39 ± 0.93 | 0.002 |
| Proteinuria (gms/24hr) | 3.06 ± 1.38 | 3.32 ± 0.97 | 2.81 ± 0.92 | 0.48 |
| Haematuria at renal biopsy (%) | 32.50% | 33.30% | 29.60% | 0.94 |
| Systolic Blood Pressure (mmHg) | 135.33 ± 13.22 | 148.33 ± 11.69 | 152.43 ± 9.25 | <0.001 |
| Diastolic Blood Pressure (mmHg) | 86.66 ± 8.023 | 93.33 ± 8.165 | 94.59 ± 6.05 | <0.001 |

p<0.05 Statistically significant NDRD (non diabetic renal disease) , NDRD with DGS (diabetic glomerulosclerosis) and DGS (diabetic glomerulosclerosis)

can accelerate the decline in glomerular filtration rate and may lead to end-stage renal disease²¹. This may explain more marked disturbed renal functions in our patients of DGS with significantly higher serum creatinine and proteinuria. Therefore, emphasis is given to anti-hypertensive treatment in patients of DGS or NDRD with high blood pressures to prevent or slowing down of the progression of renal damage²².

Conclusion

Frequency of NDRD in Type II diabetic patients in this study (either isolated or superimposed on underlying diabetic glomerulosclerosis) was found to be 49.31%. Our study indicated that in type II diabetic patients with impaired renal functions such as haematuria, proteinuria in the nephrotic and non-nephrotic range and rapidly worsening renal failure, the pathological renal damage is not easily predictable on clinical and laboratory grounds. There is high frequency of NDRD in patients of type II diabetes that occur alone or co-existent with DGS. The

determination of these renal lesions has obvious clinical implications and probably benefited from treatment modalities. In conclusion, our result emphasizes the need of renal biopsy evaluation in type II diabetic patients who presented with deranged renal functions that will help in determining the patient management and prognosis.

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