Idiopathic membranous nephropathy in patients with diabetes mellitus: a diagnostic and therapeutic quandary!

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Abstract

Background: Proteinuria and renal dysfunction is common in diabetic patients and may occur due to variety of causes. Nondiabetic renal diseases (NDRD) account for 30% of the renal biopsies, and idiopathic membranous nephropathy (iMN) is a common non diabetic glomerular disease that can exist alone or in combination with diabetic nephropathy (DN). Immunosuppressants used in iMN may be associated with complications of worsening glycemic control and recurrent infections. There is a paucity of literature on the clinical course, outcomes and treatment adverse effects of patients with iMN and diabetes.

Methods: We retrospectively analyzed the data of all diabetics, evaluated for NDRD and found to have iMN, between January 2000 and June 2015 in our institute.

Results: A total of 134 patients with diabetes were biopsied for NDRD and 16 patients had iMN. Mean ± standard deviation age was 54 ± 11.77 years and the median duration of diabetes was 9.4 years. Twelve patients had isolated iMN and four patients had iMN coexisting with DN. Response rates of 18%, 35.71% and 63.63% were seen with Modified Ponticelli (MP) regimen, tacrolimus and mycophenolate mofetil (MMF), respectively. Five patients developed treatment-related adverse effects significant enough to necessitate a treatment change. Worsening glycemic control was the most common side effect. Adverse effects were less with the MMF compared with the MP regimen and tacrolimus-based regimen.

Conclusion: Patients with iMN coexisting with diabetes exhibit a poor response to the MP regimen. Treatment-related toxicity is less common with MMF in comparison with the MP regimen and tacrolimus-based regimen. An almost similar response was noted with MMF and tacrolimus-based regimen but there was more withdrawal from treatment due to toxicities observed in the latter.

Key words: diabetes mellitus, membranous nephropathy, nephrotic syndrome
Introduction
Membranous nephropathy (MN) is a frequent cause of adult nephrotic syndrome, with a reported incidence of 5–10 cases per million population per year in Northern Europe [1]. Studies have reported an apparent reversal in the trend of the late 20th century with regard to the frequencies of focal segmental glomerulosclerosis and idiopathic membranous nephropathy (iMN) [2–4]. MN is emerging as the most common cause of adult nephrotic syndrome. In about one-third of patients with MN an underlying cause such as infection, hematological or solid organ malignancy, systemic autoimmune disease or the use of drugs such as non-steroidal anti-inflammatory, penicillamine and intravenous gold can be identified [5]. In the remaining 70% of patients, the disease is regarded as primary or iMN.

Membranous glomerulopathy is a common cause of primary glomerular disease in diabetics [6–8]. It can occur either as an isolated lesion or superimposed with diabetic nephropathy (DN). Nephrotic syndrome occurs late in the course of DN, indicating an advanced stage of glomerular damage [9]. Pathological changes in DN are characterized by mesangial expansion forming nodular glomerulosclerosis, thickening of glomerular basement membrane and arteriolar hyalinization, and in later stages global glomerulosclerosis and marked interstitial fibrosis. An expeditious onset of the nephrotic syndrome in diabetic patients may result from either an accelerated progression of DN or development of another primary glomerulopathy such as membranous, minimal change or IgA nephropathy [9]. Coexistence of diabetes and MN may pose both diagnostic and therapeutic challenges to the treating physician. Both DN and MN can present as proteinuric illnesses and may be indistinguishable. Steroids and other immunosuppressive drugs such as calcineurin inhibitors used to treat iMN may worsen glycemic control and exacerbate infections in diabetics. Despite the common occurrence of MN as a nondiabetic primary glomerular disease, there is a paucity of data on its natural history, management and outcome in diabetics. Hence we performed a retrospective analysis of the clinical profile, diagnostic and therapeutic difficulties encountered in treating this subset of iMN.

Materials and methods
In this retrospective observational study, we analyzed the data of all diabetics, evaluated for nondiabetic renal disease (NDRD) and found to have iMN, between January 2000 and June 2015. The study was carried out in a major tertiary care center situated in the northern part of India. The demographic profiles, details of illness and hospitalization, management and outcomes of the patients were retrieved from the electronic Hospital Information System.

We included all patients with diabetes mellitus (DM) with iMN and excluded patients with known secondary causes like infection with hepatitis B or C virus or HIV, known malignancy, positive antibodies to double-stranded DNA, or current treatment with gold or penicillamine.

Management protocol
Supportive care was given to all patients with iMN with nephrotic syndrome including angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers to control proteinuria and to maintain blood pressure ≤130/80 mmHg (proteinuria <1 g/day) or ≤125/75 mmHg (proteinuria >1 g/day), statins for hyperlipidemia, dietary salt restriction and diuretics if edema was present.

The Modified Ponticelli (MP) regimen was started if the proteinuria was more than 4 g/day and more than 50% of the baseline value despite 6 months of supportive treatment, or if there was an unexplained >30% rise in the serum creatinine levels within 6–12 months of treatment initiation. The MP regimen included methyl prednisolone (1 g) given by parenteral route for three consecutive days, followed by oral prednisolone (0.5 mg/kg/day) for 27 days (Cycle A). Cycle A was followed by cyclophosphamide (2 mg/kg/day) orally for 1 month (Cycle B). Cycles A and B were continued at alternate months for three times each. The total duration of treatment was 6 months.

If there was no response within 4 months of starting of initial treatment, failure of MP regimen was considered and alternative therapy including macrolimost and steroids were started. Alternatives such as mycophenolate mofetil (MMF), rituximab and adrenocorticotropic hormone were considered if both tacrolimus and the MP regimen failed.

Definitions
Response: achievement of either complete remission or partial remission
Complete remission (CR): a decrease of 24-h urinary protein excretion to at least 500 mg/day at least 1-month duration with plasma creatinine stable at <1.5 mg/dL.
Partial remission (PR): a reduction in the rate of urinary protein excretion to between 0.5 and 2 g/day for at least 1-month duration with plasma creatinine stable at <1.5 mg/dL or decrease in proteinuria of >50% from baseline.
Treatment failure/nonresponder: if there is no CR or PR within 4 months of starting of given treatment.
Relapse: reappearance of proteinuria of >0.2 g/day in a patient who had either CR or PR. Renal failure: a persistent doubling of serum creatinine over the baseline values.

Results
A total of 136 patients with DM were evaluated during the study period and biopsied in suspicion of NDRD. Out of these 136 patients, 16 patients were found to have iMN in coexistence with DM. The duration of follow-up for MN ranged from 15 to 75 months.

Demographic and clinical characteristics
All patients were male with a mean age of 54 ± 11.77 years (range: 23–69 years) (Table 1). All patients except one had Type 2 DM. Indications of kidney biopsy were rapid-onset proteinuria or massive proteinuria, or both. The mean ± standard deviation proteinuria was 9.4 g ± 2.85 g/day. Diabetic retinopathy (DR) was present in only four patients. Other complications of DM such as distal sensory polyneuropathy were present in five patients and coronary artery disease was present in 5 of 16 patients. Of the 16 patients, 11 were stratified as having high risk and 5 as an having intermediate risk for progression to end-stage renal disease. Renal histopathology was suggestive of pure MN in 12 of 16 patients while the remaining 4 had MN (Figure 1) in coexistence with DN.
Table 1. Demographic and clinical characteristics of patients of iMN in coexistence with DM

| Patient no. | Age (years)/gender | Type of DM/duration (years) | Indication of kidney biopsy | DR/other micro/macrovascular complication | SAlb mg/dL (onset/last) | SCr mg/dL (onset/last) | Anti PLA2R Ab | Risk stratification of iMN | Renal biopsy diagnosis | Follow-up duration (months) | Treatment | Outcome at last follow-up |
|-------------|--------------------|---------------------------|-----------------------------|-----------------------------------------|------------------------|------------------------|-----------------|---------------------------|--------------------------|--------------------------|-----------|-------------------------|
| 1           | 69/M 2/18          |                            | DR/CAD                      | 2.1/8.2 0.9/1.5                        | NA High                | MN + DN               | 19              | MP—CNI—MMF               | Relapse                  |                         |           |                         |
| 2           | 61/M 2/10          |                            | DR/PN/CAD                   | 1.9/7.5 1.1/1.3                        | NA Intermediate        | MN                    | 75              | MP                       | PR                       |                         |           |                         |
| 3           | 42/M 2/6           |                            | DR/None                     | 2.0/12.5 1.0/1.2                       | NA High                | MN                    | 29              | MP—CNI                   | PR                       |                         |           |                         |
| 4           | 62/M 2/9           |                            | DR/PN/CAD                   | 1.8/11.6 1.2/1.4                       | NA High                | MN                    | 33              | MP—CNI—MMF NR            |                         |                         |           |                         |
| 5           | 45/M 2/4           |                            | DR/None                     | 2.3/8.5 0.9/1.3                        | NA High                | MN                    | 47              | MP—CNI—MMF PR            |                         |                         |           |                         |
| 6           | 69/M 2/13          |                            | DR/None                     | 2.8/5.4 1.1/1.2                        | NA Intermediate        | MN + DN               | 23              | MP—CNI—MMF CR            |                         |                         |           |                         |
| 7           | 55/M 2/11          |                            | DR/PN/CAD                   | 2.3/10.4 1.0/1.4                       | NA High                | MN                    | 30              | MP—CNI—MMF NR            |                         |                         |           |                         |
| 8           | 51/M 2/9           |                            | DR/None                     | 2.0/13.1 1.2/1.6                       | NA High                | MN                    | 18              | MP—CNI—MMF NR            |                         |                         |           |                         |
| 9           | 48/M 2/7           |                            | DR/None                     | 3.0/4.9 0.9/1.3                        | 109.96 Intermediate    | MN                    | 20              | MP                       | CR                       |                         |           |                         |
| 10          | 56/M 2/5           |                            | DR/None                     | 2.0/12.1 1.1/1.3                       | NA High                | MN                    | 26              | MP—CNI—MMF CR            |                         |                         |           |                         |
| 11          | 50/M 2/4           |                            | DR/None                     | 1.8/11.6 1.2/1.4                       | NA High                | MN                    | 29              | MP—CNI—MMF PR            |                         |                         |           |                         |
| 12          | 23/M 1/12          |                            | DR/None                     | 2.9/6.0 1.7                            | NA Intermediate        | MN                    | 124             | MP—CNI—MMF ESRD          |                         |                         |           |                         |
| 13          | 67/M 2/19          |                            | DR/PN                       | 2.1/13.0 1.0/1.2                       | Nil High               | MN + DN               | 24              | MP—CNI—MMF               |                         |                         |           |                         |
| 14          | 57/M 2/9           |                            | DR/None                     | 2.8/5.9 1.1/1.1                        | 106.48 Intermediate    | MN                    | 16              | MP—CNI                   | CR                       |                         |           |                         |
| 15          | 61/M 2/12          |                            | DR/PN/CAD                   | 2.3/10.6 1.2/1.0                       | NA High                | MN + DN               | 38              | MP—CNI—MMF PR            |                         |                         |           |                         |
| 16          | 48/M 2/4           |                            | DR/None                     | 2.2/9.2 1.2/1.3                        | 1.73 High              | MN                    | 15              | MP—CNI                   | CR                       |                         |           |                         |

UP: urinary protein; SAlb: serum albumin; SCr: serum creatinine; Anti PLA2R Ab: anti-phospholipase A2 receptor antibody; M: male; rapid-onset proteinuria = 1; massive proteinuria = 2; PN: distal sensory polyneuropathy; CAD: coronary artery disease; CNI: calcineurin inhibitors; ESMD: end-stage renal disease.

Fig. 1. Images from a case of iMN with early DN. Periodic acidSchiff (A×20 and B×40) and silver stain (C×40) showing argyrophillic spikes (red arrow) and one nodule of exudative lesion (black and blue arrows) characteristic of diabetes.

Table 2. Response and adverse effects of different regimens used to treat patients with iMN in coexistence with DM

| Regimen                        | Responders | Relapse | Switch to other treatment (NR + IT + R) | Mean proteinuria before TT | Cytopenias | Infections | Worsening of diabetes |
|--------------------------------|------------|---------|----------------------------------------|----------------------------|------------|------------|-----------------------|
| MP regimen, N = 16            | 3 (2 CR + 1 PR) | 1       | 14 (11 + 2 + 1)                         | 9.40 ± 3.14 g/day          | 6          | 4          | 7                     |
| CNI, N = 14                   | 4 (2 CR + 2 PR) | 1       | 11 (6 + 4 + 1)                          | 10.28 ± 2.81 g/day         | 0          | 2          | 11                    |
| MMF, N = 11                   | 7 (4 CR + 3 PR) | 1       | 4 (3 + 0 + 1)                           | 8.92 ± 2.32 g/day          | 2          | 1          | 0                     |

NR: nonresponder; IT: intolerant; R: relapse; TT: treatment; CNI: calcineurin inhibitors.

**Management and outcome**

All patients (n = 16) with iMN were treated with the MP regimen after adequate supportive management (Figure 1 and Table 2). Of the 16 patients, only 3 (18%) patients had responded to the MP regimen and the remaining 13 (82%) patients were switched to tacrolimus and low-dose steroids. Persistent cytopenias and recurrent infections were contributory to poor tolerance and a switch in the regimen in two patients. One patient who relapsed after treatment with the MP regimen was treated subsequently with tacrolimus and low-dose steroids.

Of the 14 patients who were treated with tacrolimus and low-dose steroids, only 4 patients (28.57%) had responded and the remaining 10 patients (71.43%) were switched to MMF and low-dose steroids. Of these 10 patients, 4 patients were unable to tolerate tacrolimus. They had a persistent worsening of diabetes even on insulin therapy. One patient developed ketosis during treatment with tacrolimus. One patient relapsed after...
treatment with tacrolimus and low-dose steroids and was treated subsequently with MMF and low-dose steroids.

Of the 11 patients who were treated with MMF and low-dose steroid, 7 patients (63.63%) had responded to treatment. The remaining three (27.27%) nonresponders were managed with supportive treatment and planned for rituximab therapy but were lost to follow-up. One patient who relapsed after treatment with MMF and low-dose steroid was treated subsequently with supportive management.

**Adverse effects of treatment**

Of the 16 patients of iMN with coexisting DM, 5 patients (31.25%) developed treatment-related side effects significant enough to necessitate a regimen switch (Table 2). The most common cause of switch was worsening of diabetes (three patients) followed by cytopenias (one patient) and recurrent infections (one patient). Immunosuppression was not stopped in any patient treated with MMF owing to treatment-related toxicity.

**Discussion**

To the best of our knowledge, we report the largest data set in the literature to date on the clinical behavior and management of iMN in coexistence with DM. In this study, we have observed that patients with iMN in coexistence with DM responded poorly to the MP regimen, which is contrary to our logical belief. They had better response to MMF in comparison with the MP and tacrolimus-based regimen. Treatment-related toxicity was also seen less with MMF in comparison with the MP and tacrolimus-based regimen.

The incidence of these NDRDs varies between 18% and 80% among different studies based on the indication used for renal biopsy [10, 11]. MN is a common primary glomerular disease seen in diabetic patients [6–8]. Others include IgA nephropathy, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis and minimal change disease [12].

The mean age of the patients in our cohort was 54 ± 11.77 years with a striking male predilection similar to the findings observed by Mami et al. [13]. The median duration of diabetes was 108 months (range: 48–228 months). The median duration of diabetes in the study done by Mami et al. was 71.4 months [13]. These findings are in accordance with the study done by Prakash et al., who concluded that NDRD is more common in patients with short duration of diabetes (<10 years duration) [14]. The indications for renal biopsy in our study included rapid-onset proteinuria in 50% of the patients, while the remaining had massive proteinuria or a combination of both. The mean ± standard deviation proteinuria was 9.4 ± 2.85 g/day. This is contrary to the findings of Mak et al., who showed that non-nephrotic range proteinuria is a predictor of NDRD. However, there were no cases of MN in their series [11]. DR was absent in 12 patients (75%) in our cohort. Four patients (25%) with DR had either iMN or a combination of iMN and DN. Prakash et al. showed that DR can be seen in 40% of the patients with non-DN either alone or in combination with DN [10]. Interestingly, among these four patients who had DR only one patient had DN and it was coexistent with iMN. Among the four patients who had features of DN in biopsy, only one had DR. These findings are consistent with the observation by Prakash et al., that, DR is a poor predictor of DN as DN can be present in 50% of the patients without DR [10]. Twelve patients (75%) had isolated MN and four patients (25%) had a combination of DN and MN. In the case series reported by Yoshikawa et al. features suggestive of diabetic glomerulosclerosis were seen in 12 of the 15 patients with MN [15].

The treatment of MN relies on immunosuppression in individuals who have not derived benefit from supportive therapy. Delaying immunosuppression in patients with iMN categorized as high risk could result in disease progression and may be associated with more frequent and severe adverse effects. There is no published literature examining the response to immunosuppressive medications in iMN patients with diabetes. Current knowledge of immunosuppression is derived from studies on isolated iMN. Alkylating agents with steroids are the most widely used initial immunosuppressive therapy for iMN.

The response rate to MP regimen is as high as 93% [16]. However, in our study, only 18% of the patients responded to the MP regimen. Calcineurin inhibitors are used in patients who are unresponsive to other immunosuppressive medications, including alkylating agents, with response rates varying from 56% to 85% [17, 18]. The majority of CRs occur after 6 months of treatment and the number increases with the duration of therapy [17–19]. However, only 28.57% patients responded while similar percentages of patients were intolerant to the tacrolimus-based regimen. In contrast, however, 63.63% of the patients responded to MMF. Studies examining the role of MMF in the treatment of iMN have produced mixed results [20–22]. Two randomized controlled trials demonstrated a similar efficacy of MMF as compared to alkylating agents, with a response rate of ~65% [20, 21]. A similar response rate to MMF was seen in our study. The reason for this poor response to alkylating agents and tacrolimus and a fair response to MMF remains elusive and needs further study. Adverse effects related to treatment were observed with all the regimens. However, adverse effects requiring treatment withdrawal were seen only with the MP regimen and tacrolimus, and not MMF. Worsening of the control of diabetes was the most common adverse effect and was more common in patients treated with tacrolimus.

Limitations of our study include its retrospective nature and the relatively small number of patients. The major strength of our study is being largest dataset in the literature to date on clinical behavior and management of iMN in coexistence with DM.

In conclusion, our study presents a descriptive account of the clinical course, treatment outcomes and adverse effects of patients with iMN and diabetes. In this largest series of patients with iMN coexisting with DM, an unforeseen poor response to the MP regimen was observed. Treatment-related toxicity was also less common with MMF in comparison with the MP regimen and tacrolimus-based regimen. An almost similar response was noted with the MMF and tacrolimus-based regimens. However, treatment-related toxicities leading to withdrawal of treatment were observed frequently in tacrolimus-based regimen.

**Conflict of interest statement**

None declared.

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