Research Article

New-Onset Diabetes Mellitus in Patients with Idiopathic Membranous Nephropathy Undergoing Tacrolimus and Low-Dose Corticosteroid Therapy

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Keywords

New-onset diabetes mellitus · Idiopathic membranous nephropathy · Tacrolimus · Corticosteroid · Age

Abstract

Background: Idiopathic membranous nephropathy (IMN) is the most common cause of nephrotic syndrome in adults. Although various studies have demonstrated the efficacy of tacrolimus combined with corticosteroids for treating IMN, both tacrolimus and corticosteroids have been shown to be diabetogenic, particularly following organ transplantation. Furthermore, the frequency and risk factors for new-onset diabetes mellitus (NODM) in IMN patients treated with tacrolimus plus low-dose corticosteroids remain unclear. **Objectives:** To evaluate the incidence of NODM in IMN patients undergoing tacrolimus plus low-dose corticosteroid therapy and to confirm the risk factors for NODM development. **Methods:** This retrospective study recruited 72 eligible patients with biopsy-proven IMN from our center, between September 2013 and June 2018. All subjects were treated with tacrolimus plus low-dose corticosteroids for a minimum of 3 months. The primary outcome was NODM development during the follow-up period. The secondary outcome was complete or partial remission. Patients were divided into 2 groups: patients with NODM (NODM group) and those

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without NODM (No-NODM group). Demographic and clinical data at baseline and follow-up were assessed. **Results:** During follow-up, 31 of the 72 patients developed NODM (43.0%). The median time to occurrence was 3 months after treatment initiation. NODM patients were significantly older (median age 59 vs. 40 years) than No-NODM patients. Baseline fasting blood glucose levels were slightly higher in the NODM group; however, the difference was not significant ($p = 0.07$). Older age was an independent risk factor for NODM (OR 1.73 and 95% CI 1.20–2.47, $p = 0.003$). Overall kidney remission rates were 80.6%. There was no significant difference in remission rate between groups. There was a significant difference in development of pulmonary infection, which occurred in 7 NODM patients and only in 1 No-NODM patient ($p = 0.018$). IMN reoccurred in 5 NODM patients but only 1 No-NODM patient. **Conclusions:** Tacrolimus plus low-dose corticosteroid therapy was an efficient treatment for IMN; however, it was accompanied by increased NODM morbidity, which should be considered serious, due to the increased risk of life-threatening complications. Increasing age was a major risk factor for NODM in IMN patients treated with tacrolimus plus low-dose corticosteroid therapy.

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Introduction

Idiopathic membranous nephropathy (IMN) is the most common cause of nephrotic syndrome in adults. A previous study revealed that the frequency of membranous nephropathy (MN) increased over the study period, and long-term exposure to high levels of fine particles (PM 2.5) was associated with an increased risk of MN [1]. Although spontaneous remission occurs in approximately 30% of patients, many other patients require ongoing treatment with immunosuppressive drugs (ISDs). The Kidney Disease Improving Global Outcomes (KDIGO) guideline recommends a cyclical combination of cyclophosphamide and steroids as the first-line treatment for IMN [2]. Calcineurin inhibitors (CNIs) including tacrolimus and cyclosporine were recommended by the KDIGO as the only alternative regimens for initial therapy [2]. Several studies have demonstrated the efficacy of tacrolimus combined with corticosteroids as treatment for IMN [3–5]. A meta-analysis showed that efficacy of tacrolimus was comparable with that of cyclophosphamide for inducing renal remission of IMN patients within 1 year [6]. However, following application of tacrolimus for treatment of IMN, some patients developed hyperglycemia, indicating that these immunosuppressants can be diabetogenic. In general, corticosteroids and CNIs are considered to be the predominant factors for development of post-transplant diabetes mellitus [7].

The majority of current knowledge about the development of diabetes mellitus following the use of ISDs is derived from studies of steroid-induced diabetes in nonchronic kidney disease populations such as those with rheumatologic disease [8]. However, a better understanding of the incidence and outcomes of new-onset diabetes in patients with glomerulonephritis treated with ISD is lacking [9]. Furthermore, the incidence and risk factors for new-onset diabetes mellitus (NODM) in IMN patients treated with tacrolimus plus low-dose corticosteroids remain unclear. The effectiveness of this therapy may be attenuated by NODM, which is an important risk factor for infection in IMN patients. In addition, treatment for NODM increases the cost; therefore, alternative treatments should be considered for patients with these risk factors.

This retrospective study evaluates the incidence of NODM in IMN patients who received tacrolimus plus low-dose corticosteroid therapy and identifies risk factors for the development of NODM.

Fig. 1. Study screening process. Of the 150 patients who were screened for participation in the study, 78 patients were excluded, and 72 patients were enrolled in this study. IMN, idiopathic membranous nephropathy; ISD, immunosuppressive drug; NODM, new-onset diabetes mellitus.

Materials and Methods

Patients

A total of 150 patients from our center with biopsy-proven IMN were prospectively enrolled in this retrospective study between September 2013 and June 2018. Patients treated with other ISDs (cyclophosphamide, cyclosporine A, rituximab, or tripterygium) or conservative therapy ($n = 59$), those with a history of diabetes mellitus ($n = 9$) and those with a follow-up duration of <3 months ($n = 10$) were excluded from the study. A total of 72 patients with IMN were included in the study (Fig. 1). The study was approved by the Ethics Committee of Zhejiang Provincial People's Hospital. The need for informed consent was waived due to the retrospective study design.

Treatment

Oral prednisone was administered at an initial dose of 0.4 mg/kg/day and then reduced by 5 mg every 4 weeks to 10 mg/day for 6 months. Tacrolimus was administered at an initial dose of 0.05 mg/kg/day and adjusted according to target concentration to between 5 and 8 ng/mL [10]. Patients with hypertension received antihypertensive drugs to achieve a target level of $<130/80$ mm Hg. Anticoagulant therapy was initiated in patients with severe hypoalbuminemia (<20 g/L) [10].

Definitions

Occurrence of NODM following treatment was defined according to the American Diabetes Association guidelines [11]. This requires a patient to experience symptoms of diabetes accompanied by a random plasma glucose concentration of ≥ 11.1 mmol/L, a fasting plasma glucose concentration of ≥ 7.0 mmol/L, a 2 h plasma glucose concentration of ≥ 11.1 mmol/L during an oral glucose tolerance test (OGTT), or plasma HbA1c of $\geq 6.5\%$.

Patients were divided into 2 groups: patients with NODM (NODM group) and those without NODM (No-NODM group). The term remission includes both complete remission (CR) and partial remission (PR). CR was defined as proteinuria of <0.3 g/day following initiation of treatment, confirmed by 2 measurements, obtained at least 1 week apart, with a normal serum albumin concentration and a normal serum creatinine. PR was defined as proteinuria of <3.5 g/day and a 50% or greater reduction from peak values after treatment initiation, confirmed by 2 measurements, obtained at least 1 week apart.

Data Collection

Clinical, laboratory, and therapy data of the participants were recorded in the database of Department of Nephrology, Zhejiang Provincial People's Hospital, Hangzhou, China. Estimated glomerular filtration rate (eGFR) was calculated using the 2009 chronic kidney disease-EPI creatinine equation [10].

Statistical Analyses

All statistical analyses were performed using SPSS 19.0 software (SPSS, Inc. Chicago, IL, USA). Demographic and clinical data are expressed as proportions or means $\pm$ SD for normally distributed data or as medians with interquartile range for nonnormally distributed data. Differences in means between NODM and No-NODM groups were tested using a Student *t* test, and data expressed as medians were tested using the nonparametric Mann-Whitney U test. Categorical variables between the 2 groups were compared using a chi-square test. Logistic regression analysis was performed for univariate analysis; then, the variable with a *p* value of <0.01 in the univariate analysis was entered as the candidate variable in multivariate logistic regression model analysis, and an advanced logistic regression method was used for multivariate screening. The area under the receiver operating characteristic curve was used to evaluate the predictive value of the multivariate logistic regression model. All tests were bilateral, and a *p* value of < 0.05 was considered statistically significant in all analyses.

Results

Patient Characteristics

In total, 72 patients were enrolled in this study after screening (Fig. 1). There were 40 male and 32 female patients, and the median age was 51 years. The median follow-up period was 16.3 months (range 7.5–30.4 months). No patients had a family history of diabetes. Table 1 shows the comparison of the demographic and clinical variables between. Mean baseline proteinuria was 5.42 (range 3.78–9.1) g/day, albumin was 21.7 ± 5.3 g/L, median serum creatine was 74.4 (range 66.1–88.2) μ mol/L, and fasting blood glucose (FBG) was 4.9 ± 0.57 mmol/L. Only 40 patients were tested for blood PLA2R antibody (Ab) levels at baseline and 31 (77.5%) yielded positive results. Renal biopsies indicated stages I–II lesions in 70 patients and stage III lesions in 2 patients.

Morbidity of NODM

NODM occurred in 31 patients between 2 weeks and 24 months after treatment (median time to occurrence: 3 months). The cumulative frequency of NODM increased over time, and

Table 1. Baseline characteristics of the IMN patients receiving tacrolimus and low-dose corticosteroids treatments with or without NODM

	Total (n = 72)	NODM (n = 31)	No-NODM (n = 41)	p value
Follow-up time	16.3 (7.5–30.4)	15.9 (7.6–26.3)	16.9 (7.0–31.2)	0.95
Age, years	51 (33–62)	59 (49–68)	40 (29–59)	0.001
Male, n (%)	40 (55.6)	17 (54.8)	23 (56.1)	0.92
Family history of hypertension	2	0	2	0.50
Hypertension	19	10	9	0.33
BMI, kg/m ²	24.4±3.4	24.7±3.2	24.1±3.6	0.43
Albumin, g/L	21.7±5.3	21.3±4.4	22±5.9	0.60
FBG, mmol/L	4.9±0.57	5.07±0.49	4.83±0.61	0.07
Scr, µmol/L	74.4 (66.1–88.2)	71.4 (66.1–79.8)	76.1 (65.4–92.0)	0.27
eGFR, mL/min × 1.73 m ²	92.6±25.8	90.7±21.2	94.1±29	0.57
Uric acid, µmol/L	372±91	361±93	380±90	0.38
TG, mmol/L	2.1 (1.5–2.9)	2.1 (1.7–2.7)	2.0 (1.47–3.0)	0.40
LDL-c, mmol/L	5.4±2.7	4.93±3.0	5.74±2.3	0.20
24 h urine protein, g	5.42 (3.78–9.1)	6.1 (4.4–10.7)	4.81 (3.1–9.1)	0.29
PLA2R antibody positive ^a , n (%)	31 (77.5)	15	16	0.12
PLA2R antibody negative ^a , n (%)	9 (22.5)	4	5	
GC history, n	6	4	2	0.39
Pathological stage, n (%)				
Stage I	33 (45.8)	11 (35.5)	22 (53.7)	0.31
Stage II	37 (51.4)	18 (61.3)	19 (43.9)	
Stage III	2 (2.8)	1 (3.2)	1 (2.4)	

FBG, fasting blood-glucose; Scr, serum creatinine; BMI, body mass index; TG, triglyceride; GC history, history of glucocorticoid use before come to our hospital for treatment; LDL-C, low-density lipoprotein cholesterol; IMN, idiopathic membranous nephropathy; NODM, new-onset diabetes mellitus. ^a Only 40 patients were monitored blood level of PLA2R Ab at the base line. The other patients had no those PLA2R antibody data because we haven't implemented this testing technology yet when they were diagnosed.

Fig. 2. The cumulative frequency of NODM increased over time during follow-up time.

the 2-, 4-, 8-, 12-, 16-, 24-, and 36-month frequency rates were 4.2, 15.3, 20.8, 23.6, 30.6, 34.7, and 40.28%, respectively (Fig. 2). The median time to occurrence was 3 months after treatment initiation. The median HbA1c was 7.85%. The median FBG level was 9.37 mmol/L (Table 2).

Table 2. Comparison of outcomes and complications

	Total	NODM	No-NODM	p value
Follow-up time	16.3 (7.5–30.4)	15.9 (7.6–26.3)	16.9 (7.0–31.2)	0.95
HbA1c, % ^a	–	7.85 (6.75–9.83)	–	
FBG, mmol/L	5.93 (4.71–8.7)	9.37 (7.63–12.7)	4.73 (4.43–5.1)	0.000
Time after ISD therapy, month	–	3 (1–6)	–	
Life outcomes				
Live	71	30	41	0.43
Died	1	1	0	
Kidney outcomes, n (%)				
CR	40 (55.6)	20 (64.5)	20 (48.8)	0.069
PR	18 (25)	8 (25.8)	10 (24.4)	
CR + PR	58 (80.6)	28 (90.3)	30 (73.2)	
NR	14 (19.4)	3 (9.7)	11 (26.8)	
Remission time, month	6.75 (4.0–11.5)	7.25 (5.8–11.7)	5.1 (3.1–10.64)	0.22
eGFR (remission), mL/min	91.3±23.1	86.7±23.86	95.6±22.2	0.15
Fk506, ng/mL	5.0±2.42	5.61±2.51	4.61±2.33	0.17
Recurrence, n (%)	6 (8)	5 (16.1)	1 (2.4)	0.08
Severe lung infection, n (%)	8 (11)	7 (22.6)	1 (2.4)	0.02
Severe lung infection occur time	4 (2.25–6)	4 (3–6)	2	–

Fk506 (ng/mL): The plasma concentration of tacrolimus; eGFR (mL/min/1.73 m²), calculated by the CKD-EPI formula for remission patients. FBG, fasting blood-glucose; CR, complete remission; PR, partial remission; NR, no remission; eGFR, estimate glomerular filtration rate. ^a The blood level of HbA1c was not conducted in the No-NODM group because their normal fasting blood-glucose level.

Fig. 3. **a** Age distribution in 2 groups; NODM. **b** The proportion of NODM in 2 different age groups. NODM, new-onset diabetes mellitus.

Characteristics of Patients with NODM

Patients with NODM were significantly older than those without NODM (median age 59 vs. 40 years, $p = 0.001$; Fig. 3a). Baseline FBG was higher in the NODM group, but the difference was not significant (median level 5.07 vs. 4.83, $p = 0.07$). Family history of hypertension, personal history of hypertension, body mass index, serum albumin level, serum creatinine, eGFR, low-density lipoprotein cholesterol, triglycerides, 24-h urinary protein, hyperuricemia, PLA2R antibody positivity, pathological stage, and history of glucocorticoid use did not differ between NODM and No-NODM groups.

Table 3. Predictive factors of NODM after initiation of tacrolimus and low-dose corticosteroids therapy

	Univariate		Multivariate	
	HR and 95% CI	p value	HR and 95% CI	p value
Age at baseline (per 10 years)	1.75 (1.24–1.48)	0.002	1.73 (1.20–2.47)	0.003
Male	1.05 (0.41–2.69)	0.92		
Hypertension	1.69 (0.59–4.87)	0.33		
GC history	2.89 (0.49–16.9)	0.24	2.5 (0.32–19.4)	0.381
Overweight	1.77 (0.69–4.54)	0.24	1.67 (0.52–4.74)	0.34
Albumin, g/L	0.98 (0.89–1.07)	0.60		
FBG, mmol/L	2.18 (0.92–5.15)	0.08	2.07 (0.79–5.43)	0.14
eGFR	1.21 (0.58–2.51)	0.61		
Hyperuricemia	0.46 (0.22–1.39)	0.17		
TG, mmol/L	1.19 (0.88–1.61)	0.26		
LDL-C, mmol/L	0.88 (0.72–1.07)	0.20		
24 h-urine protein, g	1.05 (0.95–1.17)	0.34		

GC history, history of glucocorticoid use. Overweight: BMI ≥ 24 . FBG, eGFR (mL/min/1.73 m²), calculated by the CKD-EPI formula for remission patients. Hyperuricemia: male ≥ 420 μ mol/L and female ≥ 380 μ mol/L. TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; NODM, new-onset diabetes mellitus; FBG, fasting blood-glucose. eGFR, estimate glomerular filtration rate; HR, hazard ratio.

Risk Factors for NODM

Univariate logistic regression indicated that age and baseline FBG level were risk factors for NODM (Table 3). Since the relationship between being overweight (body mass index ≥ 24) and insulin resistance is clear, being overweight was included in the further analysis. We add history of glucocorticoid use in multivariate analysis because of its side effect of raising blood sugar. A multivariate logistic regression model was established with NODM as a dependent variable and age, history of glucocorticoid use, being overweight, and FBG level as independent variables.

Age was identified as the only independent risk factor for NODM in patients with IMN following tacrolimus plus low-dose corticosteroid therapy (OR 1.73, 95% CI 1.20–2.47, $p = 0.003$). The risk of developing NODM increased 1.73 times for every 10 years of age (Table 3). The predictive value of the multivariate logistic regression model was 0.723. The cutoff value of age for developing NODM was 45.5 years, based on the Youden index. The area under curve was 0.73 ($p = 0.001$). Only 14.3% patients who were younger than 45.5 years developed NODM, and 61.4% patients who were older than 45.5 years developed NODM, suggesting that tacrolimus plus low-dose corticosteroid therapy should be avoided in IMN patients older than 45.5 years, taking into consideration the increased risk of developing NODM (Fig. 3b).

Outcomes and Complications of NODM

The median follow-up time was 16.3 months (range 7.5–30.4). One patient in the NODM group died due to severe pneumonia. The median FBG level was 9.37 and 4.73 mmol/L in NODM and No-NODM groups and the difference was significant. The overall kidney remission of patients was 80.6%; CR was 64.5 and 48.8% in NODM and No-NODM groups, respectively. PR was 25.8 and 24.4% in NODM and No-NODM groups, respectively. The total remission rate was not significantly different between the groups ($p = 0.069$). The median remission time was 7.3 and 5.1 months in NODM and No-NODM groups; however, the difference was not significant. The eGFR of remission patients was 86.7 ± 23.86 and 95.6 ± 22.2 mL/min in NODM and No-NODM groups, respectively, however, no significant difference was revealed. Recur-

rence reoccurred in 5 NODM patients but only one No-NODM patient; however, this was not significantly different between groups, respectively. There was a significant difference in development of pulmonary infection, which occurred in 7 NODM patients and only 1 No-NODM patient ($p = 0.018$).

Discussion/Conclusion

The morbidity of NODM in patients with IMN undergoing tacrolimus plus low-dose corticosteroid therapy was high (40.28%), and the cumulative frequency increased over time. The median age in this study was 51 years old, and the range between the first quartile and the third quartile was 33–62 years. This age range was both representative of and similar to that reported in previous studies of MN [12, 13]. Older age was the only risk factor for NODM, suggesting that older age should be carefully considered when developing treatment strategies for IMN patients, in order to avoid NODM. An age of <45.5 years was associated with a lower incidence of NODM (14.3%), which is consistent with the results of another recently published study that focused on IgA nephropathy treated with methylprednisolone pulse therapy [9].

Recent studies demonstrated that greater proteinuria and methylprednisolone use were significantly associated with NODM, especially in patients older than 50 years. Although these studies included several kinds of glomerulonephritis with various ISD treatments [14, 15], older age was the major risk factor identified for NODM in these studies. These results suggest that IMN patients who are older than 45.5 years might not be suitable for tacrolimus plus low-dose corticosteroid therapy and should consider alternative ISD treatments.

A meta-analysis indicated that glucocorticoid-induced hyperglycemia occurs fairly frequently; the rate at which patients developed glucocorticoid-induced hyperglycemia or diabetes was 32.3% ($p = 0.003$) and 18.6% ($p = 0.002$), respectively [8]. The study patients showed a higher incidence of NODM, partly due to superimposed effects of low-dose corticosteroid and tacrolimus. The possible mechanism of diabetogenic effects of tacrolimus was considered to be decreased insulin secretion due to islet cell necrosis and increased insulin resistance, observed in a rat model of tacrolimus-induced diabetes [16]. Glucose tolerance progressively declines with age [17], which might be caused by the shortened telomeres of β and α cells [18] and age-related changes to DNA methylation in human islet cells [19]. These two effects may explain the main study finding that older age was the only risk factor for the development of NODM. A study has revealed that liver transplant patients with NODM may benefit from conversion to cyclosporine from tacrolimus, as this can lead to improved glucose metabolism [20]. Since cyclosporine is the second-line ISD for IMN according to KDIGO [2], it could be a suitable alternative for these patients who develop NODM. However, further confirmation of these findings in a prospective, randomized comparative study is required.

Tacrolimus plus low-dose corticosteroid therapy was an efficient treatment for IMN. A systematic review and meta-analysis of 21 clinical trials showed that CNIs are promising alternatives to CTX for IMN patients and tacrolimus shows more lasting therapeutic effects and fewer side effects [21]. The present study showed that the overall remission was 80.6%, which is similar to that reported in published studies [22, 23]. Rituximab was considered as another effective therapy for IMN [24]. However, IMN patients are unlikely to be prescribed rituximab in our developing country (China), as it is not covered by medical insurance for IMN treatment now. Furthermore, a multicenter prospective study indicated that low-dose rituximab is poorly effective in patients with IMN, which might

explain the higher costs [25]. Several clinical studies have demonstrated that rituximab is more effective for refractory MN [26], indicating that tacrolimus plus low-dose corticosteroid therapy is efficient and could be a first-line choice for MN patients who cannot afford the high cost of rituximab.

The NODM group had a higher incidence rate of pulmonary infection than the No-NODM group following tacrolimus plus low-dose corticosteroid therapy. One patient died due to severe pulmonary infection and extremely high glucose levels. The overall time to occurrence of pulmonary infection for NODM patients was 4 months (range 3–6). Although the remission rate was similar in both groups, this result suggests that development of NODM leads to worse outcomes, and it should be tightly controlled.

There are several limitations in this retrospective study. First, an OGTT was not performed for all patients before treatment initiation; therefore, patients with impaired OGTT but normal FBG levels may have been included. Therefore, an OGTT test should be performed before initiation of ISD in future studies. Second, the study sample size was small. Further studies are required to assess the incidence and outcomes of NODM in MN with ISD treatment.

Tacrolimus plus low-dose corticosteroid therapy was efficient for treatment of IMN but was accompanied by a high frequency of NODM. Frequency of NODM should be considered serious, due to the increased risk of life-threatening complications. Increasing age was a major risk factor for NODM in IMN patients undergoing tacrolimus plus low-dose corticosteroid therapy. Older IMN patients might not be suitable for tacrolimus plus low-dose glucocorticoid therapy, and these patients should consider alternative ISD treatments.

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Statement of Ethics

The research was approved by the Ethics Committee of Zhejiang Provincial People's Hospital. The need for informed consent was waived because of the retrospective study design.

Disclosure Statement

The authors declare that they have no competing interests. The authors have no conflicts of interest to declare.

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Author Contributions

L.S., M.C., and Q.H.: conceptualization. L.S., J.J., J.G., B.Y., and B.X.: data curation. L.S.: formal analysis. L.S., B.X., and Y.L.: investigation. L.S., Q.H., and M.C.: methodology. M.C. and Q.H.: supervision. L.S.: writing the original draft. L.S., M.C., and Q.H.: writing, review, and editing. All authors read and approved the final manuscript.

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