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Evaluation of Predictor Factors of Non-Diabetic Nephropathy in Diabetic Patient's Biopsy Specimen in Labbafinejad Hospital

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ABSTRACT

Background and Aim: Nephropathy is one of the major complications in diabetic patients that causes high mortality worldwide. In diabetic patients, differentiating non-diabetic nephropathy from diabetic nephropathy is clinically essential in treating patients. The present study aimed to examine clinical, laboratory, demographic variables and their relationship with the type of non-diabetic nephropathy in diabetic patients.

Methods: Clinical, demographic and laboratory data of 104 diabetic patients who underwent renal biopsy in Labbafinejad Hospital in Tehran in 2009-2010 were assessed. Patients were categorized into two groups based on the type of nephropathy (whether diabetic or non-diabetic). The recorded data were statistically compared between the two groups at the time of kidney biopsy and six months later.

Results: In this study, 104 patients were studied. The mean age of patients was 57.2 ± 13.4 years, and 50% of patients were male. Shorter duration of diabetes, no insulin use, renal failure, higher mean arterial pressure, smaller kidneys, lack of diabetic retinopathy, lower GFR and higher serum creatinine in patients with diabetic nephropathy were identical with non-diabetic nephropathy group (in all cases) ($P < 0.05$).

Conclusion: The need for kidney biopsy in diabetic patients can be determined with acceptable accuracy using the mentioned demographic, clinical, imaging and laboratory data. This study showed that the six-month GFR index could be used as a prognostic marker in patients.

INTRODUCTION

Diabetes kidney disease (DKD) affects about 25 to 30 percent of diabetic people. As a result, diabetes is now the primary cause of chronic kidney disease (CKD) and end- stage renal disease (ESKD) around the world (1-3). Microvascular abnormalities in the kidney caused by hyperglycemia are responsible for diabetic nephropathy or diabetic kidney disease (DKD), as well as morbidity and mortality in patients (1, 4). Despite the fact that new therapeutic options are developing or understudied, diabetic nephropathy is now treated mostly with non-specific treatment (5).

Diabetics can develop kidney damage in a different way than people with DKD. Physicians are less inclined to do diagnostic kidney biopsies on these individuals because the clinical signs are often non-specific (kidney failure and proteinuria), and they may misdiagnose DKD and restrict

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access to certain treatments. A clinical challenge arises when a patient with diabetes mellitus and kidney failure or proteinuria is advised to undergo a kidney biopsy. Several studies have attempted to uncover clinical and laboratory criteria linked to the histopathologic diagnosis of non-diabetic kidney disease (NDKD) in order to limit biopsies to those most likely to benefit from various therapeutic strategies. Lack of diabetic retinopathy, short duration of diabetes, sudden onset of nephrotic syndrome or proteinuria with nephrotic amplitude, microscopic hematuria (significantly abnormally shaped blood cells), and low levels of glycosylated hemoglobin are all clinically accepted predictors of NDKD in diabetic patients (5, 6). However, the preceding findings may have limited generalizability in certain populations. For example, more than half of the data on Asian patients in a recent meta-analysis of 48 studies showed no definite evidence to differentiate between the two disorders (7).

Due to the uncertainty of the predictors of NDKD incidence, this study aimed to investigate the predictors of non-diabetic nephropathy based on biopsy specimens in diabetic patients.

MATERIALS and METHODS

In this routine database study, all type 2 diabetic patients referred to Tehran Labbafinejad Hospital from April 2011 to September 2017 and underwent kidney biopsy were included. The sampling method was convenience sampling. The inclusion criteria were type 2 diabetes and kidney biopsy. Exclusion criteria was defined as not having type 2 diabetes, not having a kidney biopsy for any reason, incomplete medical records.

During these years, 104 patients met this study's inclusion and exclusion criteria. Based on pathological findings, these patients were divided into two groups of patients with diabetic and non-diabetic nephropathy. Patients' information such as age and sex, height and weight and body mass index (BMI), blood pressure, dyslipidemia, smoking, family history of diabetic nephropathy, duration of diabetes, and the presence of diabetic retinopathy were collected through a questionnaire. History of RAAS inhibitors, statins, insulin and kidney biopsy indication was recorded.

Laboratory tests, including the creatinine level, 24-hour protein, GFR, and hematuria, were performed during the patients' biopsy. Patients in both pathological groups were followed for renal function six months after biopsy. The effect of pathology on renal function was then compared in the two groups.

This study was approved in ethical committee of Shahid Beheshti Medical University (IR.SBMU.MSP.REC.1398.507).

Statistical analysis

Quantitative data with t-test and qualitative data with chi-square or Fisher's exact test were compared in three groups. Univariate, multivariate, and logistic regression analyses were used to determine the potential predictor of NDKD in which first the univariate analysis was used and in case of the significance at the level of < 0.2, the variables entered into the final multivariate model called "testimation bias" (8, 9). Finally, data were collected and statistically analyzed by SPSS 23 software.

RESULTS

In this study, 104 patients were studied, of which 50% were male, and the mean age of patients was 57.2 ± 13.4 years. The mean duration of diabetes in all patients was 9.8 years. Approximately 83% of patients had hypertension. Half (49.5%) of the patients were treated with insulin. More than 80% of patients used statins and RAAS inhibitors. Essential patients' information is shown in Table 1. Indications for renal biopsy in patients included the following:

Kidney biopsy specimens were examined and reported by two single pathologists. Fifty-nine patients (55.7%) had changes related to diabetic nephropathy in histopathological examinations, and 44 patients (41.5%) had changes related to other nephropathies. Acute tubular necrosis (ATN) was the most common cause of renal failure in diabetic patients after diabetic nephropathy (prevalence 11.8%). The results of histopathological changes are shown in Table 2.

Patients with pathological diagnoses of diabetic nephropathy and patients with non-diabetic causes of nephropathy were compared in terms of risk factors and baseline characteristics. (Table 3)

Personal history of diabetic retinopathy (66.1% vs. 25%), positive family history of diabetes (65.4% vs. 34.8%), lower GFR at biopsy (35.08 ± 22.6 vs. 51.3 ± 42.6 cc / min), and history of insulin therapy in patient's diabetic nephropathy was significantly more common with the pathological diagnosis. The duration of diabetes, although not statistically significant, can be clinically significant. Individuals with a longer duration of diabetes are more likely to have diabetic nephropathy, although this was not significant in the present study due to the small number of samples.

Patients with pathological diagnosis of non-diabetic kidney disease had a significant family history of chronic non-diabetic kidney disease (78% vs. 21.2%). Other clinical findings such as age, history of hypertension, mean arterial pressure, lipid disorders, glycemic control status (HBA1c level), and the presence or absence of hematuria and pyuria were not significantly different between patients in these two groups (P > 0.05). In the study of changes in renal function in

a 6-month follow-up, the GFR in diabetic patients was significantly lower than non-diabetic patients (34.02 ± 20 vs. 62.4 ± 38.02 ml/min, p-value: 0.00). In addition, the GFR reduction was higher among patients with nephropathy than diabetic patients with non-diabetic kidney disease (4.2 ± 1.88 vs. 1.2 ± 0.16 cc / min in 6 months, p-value: 0.02). This issue, along with the relative improvement of GFR in patients with non-diabetic nephropathy (from 51.3 ± 42.6 to 62.02 ± 38.02 cc / min), indicates that timely identification and appropriate treatment of non-diabetic causes of renal involvement can improve renal prognosis (Table 3).

Regression model to predict the type of nephropathy

Using data on age, sex, family history of diabetes and renal failure, and GFR and mean arterial pressure (MAP) of patients, the possibility of predicting the type of nephropathy in patients based on the Binary Logistic Regression model was investigated. According to the data in Table 4, 26.1% to 34.9% of the data variance can be justified using the current regression model. In 75.3% of cases, using a logistic regression model with current variables, different types of nephropathies in patients can be distinguished from each other. Based on the above tables, family history of renal failure, MAP and smaller kidney size in patients are significantly effective in distinguishing the type of renal failure.

Table 1. Basic information, comorbidity and drugs of patients under study

Subject	Result
Male (n / %)	52 (50%)
Age, mean ± SD (years)	57.2 ±13.4
BMI, mean ± SD (kg / m2)	29.48 ± 5.60
Duration of diabetes, mean ± SD (year)	9.80 ± 6.80
Hypertension (n / %)	86 (82.7%)
Dyslipidemia (n / %)	71 (68.3%)
Retinopathy (n / %)	50 (48%)
Smoking (n / %)	25 (24%)
Family History of Diabetes (n / %)	68 (65.4%)
Family history of CKD (n / %)	82 (78.8%)
Insulin treatment, (n / %)	51 (49.5%)
RAAS inhibitor, (n / %)	92 (89.3%)
Statin, (n / %)	84 (81.6%)

Table 2. Frequency distribution of the histopathology changes

Pathologic diagnosis	Frequency
ATN, (n / %)	12 (11.3%)
FSGS, (n / %)	10 (9.4%)
MGN, (n / %)	9 (8.5%)
Minimal Change, (n / %)	4 (3.8%)
IgA nephropathy, (n / %)	4 (3.8%)
Hypertensive nephropathy, (n / %)	2 (1.9%)
Amyloidosis, (n / %)	2 (1.9%)

Table 3. Comparison of patients with diabetic and non-diabetic nephropathy based on clinical, laboratory, and imaging findings

Characteristics	DKD (n= 61)	NDKD (n=43)	P-value
Age, mean ± SD (year)	56.41 ± 11.8	58.25 ± 11.4	0.42
BMI, mean ± SD (kg / m2)	29.48 ± 4.6	29.57 ± 5.8	0.93
Duration of diabetes, mean ± SD (year)	11.22 ± 6.7	7.95 ± 6.4	0.16*
Hypertension (n / %)	1.14 ± 0.49	1.23 ± 0.42	0.23
Dyslipidemia (n / %)	51 (83%)	33 (77%)	0.21
Retinopathy (n / %)	39 (64%)	11 (25%)	0.01*
Smoking (n / %)	25 (40%)	32 (75%)	0.11
Family History of Diabetes (n / %)	40 (65.4%)	15 (34.8%)	0.01*
Family history of CKD (n / %)	13 (21.2%)	33 (78%)	0.01*
GFR at Biopsy, mean ± SD	35.08 ± 22.6	51.3 ± 42.6	0.01*
MAP, mean ± SD	96.5 ± 10.3	93.9 ± 8.11	0.16
Insulin treatment, (n / %)	35 (59.3%)	16 (36.4%)	0.02*
RAAS inhibitor, (n / %)	53 (89.8%)	39 (88.6%)	0.86
Statin, (n / %)	47 (79.7%)	37 (84.1%)	0.56
HbA1c, mean ± SD	7.57 ± 1.95	18.5 ± 7.05	0.22
FBS, mean ± SD	134.1 ± 62.7	126.2 ± 47.01	0.41
Cholestrol, mean ± SD	187.4 ± 67.4	203.4 ± 100.3	0.33
GFR at 6 months, mean ± SD	34.02 ± 20	62.4 ± 38.02	0.00
Right Kidney size	106.6 ± 15.17	109.52 ± 10.9	0.12
Left Kidney size	109.2 ± 12.7	112.7 ± 19.5	0.22
Mean Kidney size	107.9 ± 11.1	111.1 ± 13.1	0.18
GFR decrease (after 6 months)	4.2 ± 1.88	1.2 ± 0.16	0.02*

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Table 4. Logistic regression to predict risk factors associated with nephropathy in two groups of patients

Risk factor	P-value	Adjusted OR	Lower CI 95%	Upper CI 95%
Family history of renal failure	0.001*	3.75	3.14	4.09
MAP	0.221	1.88	0.88	1.99
Smaller kidney	0.328	1.01	0.91	1.23
Duration of diabetes	0.001*	4.81	3.70	5.12

DISCUSSION

In the present study, 104 patients were assessed and 50% were male. The mean age was 57.2 years. Out of 104 patients included in the study, the pathological diagnosis was 61 patients with diabetic nephropathy (55%), and 43 patients had pathological findings other than diabetic nephropathy. ATN was the most common cause of non-diabetic nephropathy in diabetic patients. Pathological diagnosis of non-diabetic kidney disease had a significant relationship with family history of chronic non-diabetic kidney disease. The GFR in diabetic patients was significantly lower than non-diabetic patients; and also, GFR reduction rate was higher among patients with nephropathy than diabetic patients with non-diabetic kidney disease. Diabetes is the crucial cause of kidney failure worldwide (10, 11). Diabetes is a vital predictor of kidney failure along with other diabetes- related complications, including diabetic retinopathy (12). According to published articles, in general, estimates show that 20-40% of patients with diabetes have one of the renal complications of diabetes (13, 14). Patients with diabetes can develop non-diabetic kidney disorders such as glomerular (membranous nephropathy), tubulointerstitial, or vascular diseases in addition to diabetic nephropathy. The early etiological therapy of individuals with non-diabetic renal disease is critical for greatly slowing or totally stopping the progression of chronic kidney disease to end-stage renal failure. Diabetic nephropathy is almost always associated with clinical symptoms such as persistent proteinuria, hypertension, and rapidly progressive renal failure. The validity of this clinical procedure is well accepted in patients with type 1 diabetes, but in patients with type 2 diabetes, the validity of clinical trials is still unclear. The study of whether non-diabetic nephropathies have an increased risk in people with diabetes also requires further investigation (15-18).

Due to the importance of this issue, this study examined diabetic patients who underwent a biopsy.

Out of 104 patients included in the study, the pathological diagnosis was 61 patients with diabetic nephropathy (55%), and 43 patients had pathological findings other than diabetic nephropathy. ATN was the most common cause of non-diabetic nephropathy in diabetic patients.

There was no difference between the samples in terms of gender in this study. In a study published in 2020, Maric-Bilkan et al. examined the evidence in studies on diabetic nephropathy and the differences in its incidence in males and females (18). Maric-Bilkan et al. emphasized that the incidence of diabetic nephropathy in men and women has been reported differently in many studies. These differences are attributed to race, disease progression, age, and type of diabetes. Therefore, to clarify the relationship between the incidence of diabetic nephropathy and gender, more detailed studies with more segregation of the study population are necessary (18). The mean age of patients in this study was 57.2 years. In 60-year-old studies, the typical age of onset of diabetic nephropathy has been reported. Diabetic nephropathy also appears to be relevant about 9 to 11 years after the onset of symptoms of diabetes. In this study, patients with an average of 9.2 years after diagnosis of diabetes had kidney problems. The findings of this study concerning the age and time of onset of diabetic nephropathy after diagnosis are consistent with the findings of previous studies (19, 20).

In this study, patients were divided into two groups of patients with diabetic and non-diabetic nephropathy. Although it may provide more accurate results, dividing patients into more subgroups was not possible due to the researchers' limited access to patients to achieve the appropriate sample size and the limited cooperation of patients. Patients with diabetic and non-diabetic nephropathy were compared in terms of clinical, demographic, laboratory, and imaging indicators. This study initially found that the presence of diabetic retinopathy is significantly associated with diabetic nephropathy. In the study of Sheila Bermejo et al., diabetic retinopathy was associated with diabetic nephropathy. Considering the similar damage mechanism in diabetic nephropathy and diabetic retinopathy in diabetic patients, the association of these two complications with each other does not seem far- fetched (20). Both complications indicate vascular disease and poor blood sugar control. However, the pathophysiology of non-diabetic nephropathy is different from the pathophysiology of retinopathy in diabetic patients. Olugbenga E. Ayodele et al. reported genetic susceptibility, hypertension, uncontrolled blood

sugar, renal hyperfiltration, hyperlipidemia, and age as risk factors for diabetic nephropathy (21). In addition to diabetic retinopathy, having a family history of diabetes and insulin therapy was more common in people with diabetic nephropathy. Patients with diabetic nephropathy had lower GFR at biopsy. In a study published in 2016 by Sheila Bermejo et al., they examined the predictors of non-diabetic nephropathy in diabetic patients (20). Based on data published in a study by Sheila Bermejo et al., most cases of non-diabetic nephropathy in diabetic patients were IgA nephropathy. Shorter duration of diabetes, absence of diabetic retinopathy, older age, lower proteinuria, and higher GFR associated with non-diabetic nephropathy were detected in patients (20).

Olugbenga E. Ayodele et al. reported that increasing the duration of diabetes is a risk factor associated with diabetic nephropathy, which is consistent with the present study. Although Olugbenga E. Ayodele et al. identified hypertension as a risk factor for diabetic nephropathy (21), the obtained results suggest that higher blood pressure appears to be associated with non-diabetic nephropathy in patients. Higher MAP was also identified in the dual logistic regression model predicting non-diabetic nephropathy.

This study found no relationship between statin use and the renin-angiotensin-aldosterone inhibitors and nephropathies understudy. In a systematic review of Xue Shen et al., based on previous studies and data from 2866 patients, statin use was found to be associated with improved renal function in diabetic patients, especially patients with type2 diabetes (22). However, no study has been published on the prognosis of statins or RAAS inhibitors with nephropathy in diabetic patients.

In the present study, using the clinical data used in this study, up to 75% of cases, the type of diabetic nephropathy can be determined without the need for biopsy and based on clinical and laboratory findings. The variables used in the regression model of this study were examined. According to these findings, family history of renal failure, MAP, and smaller kidney size in patients can significantly predict the type of diabetic nephropathy in patients, and age and gender are invaluable data.

In addition, a 6-month follow-up of patients showed that patients with diabetic nephropathy had a more significant GFR decline over time. Accordingly, diagnosis of non-diabetic nephropathy and appropriate intervention can improve the prognosis of patients.

CONCLUSION

It seems that the duration of diabetes, family history of renal failure, MAP, kidney size, insulin use, presence or absence of diabetic retinopathy, and GFR at biopsy are assistive data to predict the type of nephropathy in diabetic patients. Based on the data of this study, larger kidney size, longer duration of diabetes, no family history of renal failure, presence of diabetic retinopathy, insulin injection, and lower MAP is associated with diabetic nephropathy in diabetic patients.

The limitation of this study was relatively small sample size. It is suggested that in future studies with larger sample sizes, temporal changes in other variables and their relationship with the type of nephropathy be performed. Also, it is necessary to study the types of non-diabetic nephropathy separately to examine the relationship between genetic background, racial and environmental variables, diet, and occupational and personal encounters with the type of nephropathy.

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CONFLICT OF INTEREST

All authors declare no conflicts of interest.

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