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Non-Diabetic Nephropathy in Diabetic Patients: Incidence, HbA1c Variability and Other Predictive Factors, and Implications

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Abstract

Purpose: Diabetes Mellitus (DM) is the leading cause of chronic kidney disease (CKD) in the population. In patients with diabetes mellitus, the incidence of non-diabetic nephropathy (NDNP) has been estimated to range from 3% to 82.9%. Personal judgment is frequently employed while deciding whether or not to do a kidney biopsy on diabetic patients. NDNP alters the prognosis and course of treatment for people with DM. In our study, we examined the incidence of NDNP concurrent with the progression of diabetes mellitus, as well as the laboratory and clinical indicators that could be utilized to forecast it.

Methods: A retrospective analysis of 76 diabetic patients who underwent KB was conducted. Based on the pathological diagnoses of these patients, they were categorized as DNP (diabetic nephropathy) or NDNP. The definition of HbA1C variability was determined by calculating the mean HbA1C and the average value of the HbA1C measurements, as well as the standard deviation (SD) for each participant.

Results: NDNP was detected in 50% of 76 patients. Among patients with NDNP, 36.8% had focal segmental glomerulosclerosis (FSGS), 23.6% had membranous glomerulonephritis, and 7.8% had IgA nephritis. The NDNP group exhibited significantly higher rates of female gender, absence of diabetic retinopathy, shorter time to diagnosis of diabetes mellitus, chronic kidney disease, and proteinuria, less intensive medication for diabetes mellitus, presence of hematuria and leukociduria, serological marker positivity, and non-HbA1C variability.

Risk factors for predicting non-diabetic nephropathy, as determined by multivariate analysis, included female gender, the absence of diabetic retinopathy, non-HbA1c variability and a positive serological test.

Conclusion: In this study, a significant number of diabetic patients with chronic kidney disease were diagnosed with NDNP. Identifying these patients allows for treatment of the specific underlying disease. Factors such as the absence of DR, non-HbA1c variability, female gender, and serological test positivity can predict NDNP and guide the clinician's decision on kidney biopsy. Further prospective studies are warranted to validate the efficacy of potential predictive factors like HbA1c variability.

Introduction

Diabetes mellitus (DM) is a significant public health concern in both industrialized and developing nations. Based on data from 2019, it was reported that 9.3 percent of the population, or 463 million individuals, were diagnosed with diabetes [1]. According to estimations, the global incidence of diabetes mellitus is expected to substantially escalate. Specifically, the number of individuals affected by diabetes is estimated to climb from 135 million in 1995 to 300 million by 2025. The substantial surge can be predominantly attributed to modifications in lifestyle and the escalating incidence of obesity. Sedentary lifestyle and a Westernized diet are significant contributors to the development of diabetes [2].

Diabetes mellitus and its complications, such as diabetic nephropathy (DN), represent a significant and growing global health challenge. DM is the most common cause of chronic kidney disease (CKD) and

30–40% of patients with DM develop diabetic kidney disease [3]. Based on data from the Turkish Society of Nephrology Registry, the prevalence of diabetes among patients initiating kidney replacement therapy in 2022 was determined to be 36.7%. These results demonstrate the severity of the risk by revealing that DM affects nearly two out of every five dialysis patients [4]. Glycemic control and its variability are critical factors in the management of diabetes and its complications. Hemoglobin A1c (HbA1c) variability has been studied in relation to various diabetic complications, including diabetic nephropathy, which is a significant cause of morbidity in diabetic patients [5]. The correlation between fluctuations in HbA1c and the onset of chronic kidney disease in individuals with type 2 diabetes suggests that renal health is influenced not only by the stability of glycemic control on average, but also by its variability. The available evidence indicates that reducing variations in HbA1c may offer supplementary safeguarding against the onset of microvascular problems, such as those that impact renal function [6].

In the literature, the prevalence of glomerular disease unrelated to diabetes or added to the course of DN in DM patients has been reported in the range of 3-82.9% [7]. The detection of non-diabetic nephropathy (NDNP) in patients with DM alters treatment and prognosis. IgA nephropathy, focal segmental glomerulosclerosis (FSGS), membranous glomerulonephritis (MGN), and various other primary glomerular diseases frequently respond favorably to individualized immunosuppressant therapy, in conjunction with conservative approaches including glycemic control, blood pressure regulation, and lipid-lowering therapy [7]. In light of recent technical advancements that have reduced the risk of problems following kidney biopsy (KB), numerous clinicians have posited that routine KB administration in diabetic patients could be advantageous, given the prevalence of NDNP [8]. It is well acknowledged that diagnostic biopsy is not mandatory for all patients; however, those who would benefit from the procedure should be assessed using clinical and laboratory data. Due to the lack of consensus regarding timing and indicators, the determination to conduct a KB is frequently predicated on individual judgment or protocols that focus on a single center [9].

The utility of KB in clinical practice for DM patients lies in its ability to detect the NDNP, hence facilitating the prompt initiation of disease-specific and suitable treatment [10]. The objective of this research is to investigate the prevalence of NDNP concurrent with the progression of DM and to identify potential diagnostic indicators for its detection. Furthermore, the existing body of literature lacks significant research investigating the impact of HbA1c variability on the differentiation between DNP and NDNP. It is intended that this research adds to this gap in the knowledge.

Methods

A data set was prepared by retrospectively analyzing the clinical and byochemical findings of patients with DM who were followed up in our nephrology clinic between 2014 and 2022 and who underwent KB to elucidate renal pathology. The following information was documented: demographic data, clinical manifestations, concurrent medical conditions, medications, current blood tests (including urea, creatinine, CRP, albumin, hemogram, lipid levels, parathormone, HbA1c, serological tests, sedimentation, and proteinuria level), kidney ultrasound results, and biopsy reports. Antinuclear antibody (ANA),

antiphospholipase A2 receptor antibody (AntiPLA2R), anti-HIV antibody, extractable nuclear antigen antibodies (ENA), antineutrophil cytoplasmic antibodies (ANCA), and serum protein electrophoresis comprised the serological testing for systemic diseases. Patients who tested positive for these tests were classified as serology positive.

In prior studies, indicators of HbA1c variability have included both the standard deviation (SD) and coefficient of variation (CV). In our research, the standard deviation was implemented. The determination of HbA1C variability involved the computation of both the mean and standard deviation (SD) of HbA1C for every individual patient. SD values are computed by multiple studies and adjusted for the number of HbA1c measurements. This is due to the fact that the SD value can be affected by the number of HbA1c readings; fewer measurements result in a bigger SD. The corrected HbA1c SD was calculated using the following formula: $SD/\sqrt{[n/(n-1)]}$ [2, 11, 12]. SD was computed in our study by utilizing the greatest and lowest HbA1c values recorded for a minimum of two years of follow-up for each patient, up until the date of biopsy, in accordance with the given formula. The computed average SD was 1.17. Patients whose HbA1C SD was greater than 1.17 were classified as "HbA1C variability," whereas those whose HbA1C SD was less than 1.17 were classified as "non-HbA1C variability."

The exclusion criteria are as follows: age below 18, absence of a diagnosed diabetes mellitus, inadequate patient data, and renal biopsy failure to procure diagnostic tissue.

For statistical analyses, SPSS (version 23.0: SPSS, Chicago, IL, U.S.A. 23) software was utilized. Descriptive statistical approaches employed for categorical data were number and percent, while mean ± standard deviation was utilized for continuous numerical variables with and without normal distribution. For ordinarily distributed numerical variables, the Independent Sample T test was applied; for non-normally distributed variables, the Mann Whitney U test was utilized; and for categorical variables, the chi-square test was applied. In binary logistic regression, variables that were significant in univariate analysis and did not exhibit multicollinearity were incorporated. Utilizing a backward LR technique, multivariate analysis was conducted. The risk estimates were provided in the form of adjusted odds ratios (AOR) and 95% confidence intervals (OR and AOR, respectively) (CI). The Hosmer-Lemeshow statistic was employed in logistic regression analysis to ascertain the degree of model fit. Receiver operating characteristic (ROC) analyses were performed to determine whether any of the parameters were significantly more predictive than the others in multivariate analysis. Later, the area under the curve (AUC) was calculated. A value of $p < 0.05$ was considered statistically significant.

The methods utilized in this investigation were authorized by the Haydarpaşa Numune Research and Training Hospital Clinical Research Ethics Committee (Approval No. HNEAH-KAEK 2022/205), and all procedures conducted in the study adhered to the ethical standards outlined in the 1964 Declaration of Helsinki.

Results

Seventy-six patients, 37 of whom were female (49%) and the mean age was 54.7 ± 11.3 years. Proteinuria persisted for an average of 3.1 ± 3.2 years, while the mean duration of DM was 9.7 ± 7.8 years. 65 patients (85.5%) had hypertension, 18 patients (23.7%) had coronary artery disease, 22 patients (28.9%) had acute kidney injury, 33 patients (43.4%) had CKD, and 43 patients (28.9%) had diabetic retinopathy (DR) (56.5%). Additional parameters are detailed in Table 1.

Table 1
Clinical findings, biochemical, radiological and pathological parameters of the patients

Parameter	Results
Gender / Female (%)	37 (%49)
Age-years (Mean ± SD)	54.7 ± 11.3
Hypertension (%)	65 (%85.5)
Diabetic retinopathy (%)	43 (%56.5)
Coronary Artery Disease (%)	18 (%23.7)
Acute kidney injury (%)	22 (%28.9)
CKD (%)	33 (%43.4)
Hemodialysis (%)	11 (%14.5)
Haematuria (%)	27 (%35)
Leukociduria (%)	17 (%22.4)
CPD (by USG) (%)	35 (%46)
Positive serology (%)	19 (%25)
Duration of diabetes-years (Mean ± SD)	9.7 ± 7.8
Duration of CKD-years (Mean ± SD)	1.4 ± 2.7
Hemoglobin g/dl (Mean ± SD)	11.7 ± 3
HbA1c (at biopsy) % (Mean ± SD)	7.9 ± 2
Creatinine mg/dl (Mean ± SD)	1.7 ± 1.2
CRP mg/L (Mean ± SD)	13.3 ± 28
eGFR ml/min (Mean ± SD)	59.5 ± 33.3
Serum Albumin g/dl (Mean ± SD)	3.1 ± 0.8
LDL mg/dl (Mean ± SD)	145.3 ± 73.2
Triglyceride mg/dl (Mean ± SD)	218.4 ± 121.1
PTH pg/mL (Mean ± SD)	97.9 ± 73.1
Duration of proteinuria-years (Mean ± SD) (n:62)	3.1 ± 3.2
Sedimentation mm/hr (Mean ± SD) (n:68)	53.8 ± 30
Proteinuria gr/day (Mean ± SD)	7 ± 6.1

Parameter	Results
Albuminuria g/day (Mean ± SD) (n:50)	4.4 ± 3.6

SD; standard deviation, CKD; chronic kidney disease, CPD; renal parenchymal disease, USG; ultrasound, HbA1c; percentage of glycosylated hemoglobin, eGFR; Estimated Glomerular Filtration Rate, CRP; C-Reactive Protein, LDL; low-density lipoprotein, PTH; Parathyroid hormone

On the basis of biopsy diagnoses, NDNP was identified in fifty percent of the seventy-six individuals. Of the patients with NDNP, 14 (36.8%) were diagnosed with FSGS, 9 (23.6%) with MGN, and 3 (7.8%) with IgA nephritis (Fig. 1).

The number of serology positive patients was as follows according to the tests: AntiPLA2R positivity in 7 patients, ANA positivity in 6 patients, ANCA positivity in 4 patients and M spike in serum protein electrophoresis in 2 patients.

A statistical analysis was conducted to compare demographic, clinical, and biochemical findings between the two groups of patients, referred to as DNP and NDNP (Table 2). Upon individual analysis of the HbA1c levels of the patients before the biopsy, the mean standard deviation (Hba1c-SD) for each patient was 1.17 ± 1.09. Upon dividing the patients into two groups based on their individual HbA1c-SD (1.17 vs. 1.17>), it was observed that 24 (63%) of the patients in the DNP group and 4 (10%) in the NDNP group had HbA1c variability. Variability in HbA1c varied considerably across the two groups (p:0.001). Additional factors that were found to be significantly more prevalent in the NDNP group were the following: female gender (68.4% vs. 28.9%, p:0.001), less intensive medication for DM (oral antidiabetic use (86.8% vs. 63.2%, p:0.017)), hematuria (52.6% vs. 18.4%, p:0.002), leukociduria (39.5% vs. 5.3%, p:0.017) and positive serological markers (42.1% vs. 7.9%, p:0.001). Besides that, DR (94.7% vs. 18.4%, p:0.001), CKD (68.4% vs. 18.4%, p:0.001), coronary artery disease (34.2% vs. 13.2%, p:0.004), longer time to diagnosis of DM (13.2 ± 8 vs. 6.1 ± 5.9 years, p:0.001), of CKD (2.3 ± 3.1 vs. 0.6 ± 1.9 years, p:0.001) and of proteinuria (4.4 ± 2.7 vs. 2 ± 3 years, p:0.001), more intensive medication for DM (insulin use (78.9% vs. 26.3%, p:0.001), lower hemoglobin (10.9 ± 2.8 vs. 12.4 ± 3, p:0.04) and eGFR (46 ± 24 vs. 73 ± 36, p:0.001), higher HbA1c (8.98 ± 2.3 vs. 6.9 ± 1.05, p:0.001), Parathormone (118 ± 85 vs. 75 ± 48, p:0.02) and albuminuria (4.9 ± 3.7 vs. 3.6 ± 3.3, p:0.03) (excluding the patient with minimal change disease from the analysis) were significantly more frequent in the DNP group. The incidence of serum albumin, proteinuria, acute phase reactants, blood lipids, and ultrasound-detected renal parenchymal disease was comparable across the two groups.

Table 2
Evaluation of the statistical significance of clinical and biochemical findings in diabetic and non-diabetic nephropathy groups

Parameter	DNP (n = 38)	NDNP (n = 38)	P value (p < 0.05)
Gender (Female) (%)	11 (%28.9)	**26 (%68,4)**	**0.001**
Hypertension (%)	34 (%89.5)	31 (%81.6)	0.32
Diabetic retinopathy (%)	**36 (%94.7)**	7 (%18.4)	**0.001**
Coronary Artery Disease (%)	**13 (%34,2)**	5 (%13.2)	**0.03**
Acute kidney injury (%)	12 (%31.6)	10 (%26.3)	0.6
CKD (%)	**26 (%68.4)**	7 (%18.4)	**0.001**
ACEi/ARB use (%)	33 (%86.7)	27 (%71.1)	0.091
Antiaggregant use (%)	15 (%39.8)	11 (%28.9)	0.333
Statin use (%)	17 (%44.7)	11 (%28.9)	0.15
OAD use (%)	24 (%63.2)	**33 (%86.8)**	**0.017**
Insulin use (%)	**30 (%78.9)**	10 (%26.3)	**0.001**
Hematuria (%)	7 (% 18.4)	**20 (%52.6)**	**0.002**
Leukociduria (%)	2 (%5.3)	**15 (%39.5)**	**0.001**
CPD (by USG)	20 (%52.6)	15 (%39.5)	0.2
Positive serology (%)	3 (%7.9)	**16 (%42.1)**	**0.001**
HbA1c variability (%)	**24 (%63)**	4 (%10)	**0.001**
Nephrotic syndrome clinical* (%)	10 (%26.3)	12 (%31.6)	0.6
Age-years (Mean ± SD)	53.8 ± 8.6	55.5 ± 13.5	0.5
Duration of diabetes-years (Mean ± SD)	**13.2 ± 8**	6.1 ± 5.9	**0.001**
Duration of CKD-years (Mean ± SD)	**2.3 ± 3.1**	0.6 ± 1.9	**0.001**
Hemoglobin g/dl (Mean ± SD)	**10.9 ± 2.8**	12.4 ± 3	**0.04**

Proteinuria > 3.5 g/day, albumin < 3 g/dl, presence of edema. The p value was 0.06 when albuminuria, MCD was included and 0.03 when excluded. SD; standard deviation, CKD; chronic kidney disease, CPD; renal parenchymal disease, OAD; oral antidiabetic drugs, USG; ultrasound, HbA1c; percentage of glycosylated hemoglobin, eGFR; Estimated Glomerular Filtration Rate, CRP; C Reactive Protein, LDL; low-density lipoprotein, PTH; Parathyroid hormone, ACEi; angiotensin converting enzyme inhibitors, ARB; angiotensin-receptor blocker, DNP, diabetic nephropathy; NDNP, non-diabetic nephropathy*

Parameter	DNP (n = 38)	NDNP (n = 38)	P value (p < 0.05)
HbA1c (at biopsy) % (Mean ± SD)	**8.98 ± 2.3**	6.9 ± 1.05	**0.001**
Creatinine mg/dl (Mean ± SD)	**2.1 ± 1.2**	1.3 ± 1	**0.001**
CRP mg/L (Mean ± SD)	10.4 ± 19.6	16.4 ± 36.2	0.9
eGFR ml/min (Mean ± SD)	**46 ± 24**	73 ± 36	**0.001**
Serum Albumin g/dl (Mean ± SD)	3.2 ± 0.6	3 ± 1.1	0.4
LDL mg/dl (Mean ± SD)	131 ± 53	159 ± 88	0.2
Triglyceride mg/dl (Mean ± SD)	204 ± 112	232 ± 129	0.3
PTH pg/mL (Mean ± SD)	**118 ± 85**	75 ± 48	**0.02**
Duration of proteinuria-years (Mean ± SD)	**4.4 ± 2.7** (n = 27)	2 ± 3 (n = 35)	**0.001**
Sedimentation mm/hr (Mean ± SD)	54 ± 25	53 ± 34	0.8
Proteinuria gr/day (Mean ± SD)	7.1 ± 5.3	7 ± 6.9	0.3
Albuminuria g/day** (Mean ± SD)	**4.9 ± 3.7** (n = 25)	3.6 ± 3.3 (n = 24)	**0.03**

Proteinuria > 3.5 g/day, albumin < 3 g/dl, presence of edema. The p value was 0.06 when albuminuria, MCD was included and 0.03 when excluded. SD; standard deviation, CKD; chronic kidney disease, CPD; renal parenchymal disease, OAD; oral antidiabetic drugs, USG; ultrasound, HbA1c; percentage of glycosylated hemoglobin, eGFR; Estimated Glomerular Filtration Rate, CRP; C Reactive Protein, LDL; low-density lipoprotein, PTH; Parathyroid hormone, ACEi; angiotensin converting enzyme inhibitors, ARB; angiotensin-receptor blocker, DNP, diabetic nephropathy; NDNP, non-diabetic nephropathy*

When the renal biopsies of the patients were analyzed according to the pathological findings, as expected, classical diabetic nephropathy findings were more frequent in the DNP group. In addition, findings of chronic nephropathy, including sclerosis, tubular atrophy and interstitial fibrosis were significantly more frequent in the DNP group (Table 3).

Table 3
Frequency of renal biopsy pathology findings in DNP and NDNP patients

	DNP	NDNP	P value (p < 0.05)
Number of sclerosed glomeruli (Mean ± SD)	**7.2 ± 4.7**	4.39 ± 5.96	**0.029**
Sclerosis rate*, % (Mean ± SD)	**37.4 ± 19.1**	18.3 ± 18.1	**0.001**
Moderate to severe tubular atrophy/fibrosis, n (%)	**33 (%86.8)**	11 (%28.9)	**0.001**
Nodular mesangial expansion, n (%)	**27 (%71)**	5 (%13)	**0.001**
Arteriolar Hyalinosis, n (%)	**34 (%89)**	8 (%21)	**0.001**

* Ratio of sclerosed glomerulus/total glomerulus. DNP, diabetic nephropathy; NDNP, non-diabetic nephropathy

Using multivariate analysis, the parameters identified as significant between the two groups by univariate analysis were examined. Female sex (OR 11.7; 95% CI 1.91–71.7; p:0.008), absence of DR (OR 24.3; 95% CI 3.89–152; p:0.001), non-HbA1c variability (OR 16.34; 95% CI 2.57–103.6; p:0.003), and a positive serological test (OR 9.44; 95% CI 1.1–80; p:0.040) were identified as risk factors in predicting NDNP when cholinearity-indicating parameters were excluded (Table 4).

Table 4
Factors predicting NDNP according to multivariate analysis

Parameter	p value	Exp(B)	95% CI
Gender (Female)	0.008	11.7	1.91–71.77
Absence of DR	0.001	24.3	3.89–152
Non-HbA1c varibilty	0.003	16.34	2.57–103.6
Positive serology	0.040	9.44	1.1–80

HbA1c; percentage of glycosylated hemoglobin, DR; diabetic retinopathy

When the predictive factors for DNP-NDNP discrimination were included in the receiver operating characteristic (ROC) analysis, DR had the highest area under the curve (AUC) and HbA1c variability had the second highest AUC. The parameter with the highest specificity was serological marker and the second highest was HbA1c variability. The parameter with the highest sensitivity was DR (Table 5).

Table 5
AUC, sensitivity and specificity values of the parameters found to be significant in predicting NDNP

Parameter	AUC	95%CI	Sensitivity	Specifcity	P value
Absence of DR	0.816	0.719–0.912	0.816	0.816	< 0.001
Non-HbA1c varibilty	0.763	0.656–0.871	0.632	0.895	< 0.001
Gender (Female)	0.711	0.594–0.827	0.711	0.711	0.002
Positive serology	0.671	0.55–0.792	0.579	0.911	0.01

HbA1c; percentage of glycosylated hemoglobin, DR; diabetic retinopathy, ROC; Receiver operating characteristic, AUC; Area under the curve

Discussion

Around 3% of individuals diagnosed with type 2 diabetes mellitus have evident nephropathy at the moment of diagnosis, whereas an additional 20%-30% develop nephropathy at a later stage in their lives. Diagnosing diabetic individuals for renal damage as soon as possible is critical. In addition to decreasing the necessity for renal replacement therapy, it also mitigates the significant morbidity and death rates that are commonly linked to impaired renal function [13]. However, increasing evidence suggests that many patients with diabetes who are followed as DNP have features typical of NDNP or diabetic nephropathy in overlap histology with other nephropathies [7]. Diabetic individuals who present with active urine sediment, quick onset nephrotic syndrome, or rapid decline in renal function are deemed to warrant a biopsy. [13]. According to the classical premise, KB is indicated when a differential diagnosis that could affect clinical care is required. It is widely acknowledged that NDNP has a better prognosis than DNP, as renal lesions in DNP are considered difficult to reverse. In contrast, NDNP is often treatable and may even be reversible [14]. Detection of these pathologies by KB in diabetic patients will affect renal survival. Clinicians may utilize clinical and biochemical indicators that forecast NDNP to aid in the determination of the necessity of a biopsy [15]. In this study, we analyzed the frequency of non-diabetic nephropathy in patients with diabetes mellitus, as well as the clinical and laboratory findings that may help predict its occurrence.

The prevalence of NDNP in patients with DM varies significantly across different regions [16, 17]. In our study, non-diabetic nephropathy was found in half of diabetic patients. The substantial heterogeneity observed in the prevalence of NDNP among studies could potentially be attributed to the divergent judgments rendered by hospitals and physicians regarding the necessity of renal biopsy. Additionally, regional differences in the prevalence of DM and its accompanying complications may have an effect on the incidence of NDNP. The high frequency of NDRD detected in our study suggests that nephrologists appropriately select only diabetic patients for biopsy who are considered atypical for DNP or have clinical features suspicious for NDNP.

While the literature lists numerous histopathological diagnoses for NDNP, IgA nephritis, FSGS, and membranous nephropathy are the most prevalent [18, 19]. In the study of Erdogmus et al., NDNP was identified at a frequency of 50%, with membranous nephropathy being the most prevalent disease in this cohort [20]. In the study conducted by Heybeli et al. FSGS was most frequently detected in the NDNP group [21]. The increased occurrence of FSGS symptoms in our cohort of patients may be ascribed to the greater incidence of comorbidities, including obesity, diabetes mellitus, metabolic syndrome, and hypertension. These diseases may result in FSGS due to hyperfiltration-induced glomerular injury.

DNP symptoms often take a long time to become apparent and are therefore often not diagnosed in the early stages. [16]. As a result, when conventional inducers of renal biopsy in DM patients are absent, patients are often observed until advanced stages, with the majority of patients opting not to have KB. Thus, it is not surprising that patients with DNP, as in our study, have more chronic changes in the pathological findings compared to those with NDNP.

Clinical characteristics that have been previously demonstrated to be predictive of renal involvement in diabetic patients by NDNP include hematuria, acute kidney failure, abrupt onset of proteinuria, and proteinuria in the absence of retinopathy or neuropathy [14, 16]. In our study, female gender, absence of DR, non-HbA1c variability, positive serology were found to be risk factors in predicting non-diabetic nephropathy.

In the clinical setting, serological tests (ANA, ANCA, ENA, protein electrophoresis) are often performed on diabetic patients with acute kidney failure and proteinuria with a sudden onset or increase. Serological tests have been investigated for their utility in differentiating between DNP and NDNP. The literature indicates that serological tests may have some diagnostic value in NDNP, but their efficacy varies. When pre-biopsy serological tests were matched with pathological diagnoses in the Swedish population, the presence of antiphospholipid antibodies and low complement levels were found to reduce the likelihood of DNP the most. [22]. Positive serological testing, as anticipated, aids the clinician in the differential diagnosis of NDNP in DM patients and in the determination of whether to do a biopsy. Positive serological marker results were identified as the risk factor with the greatest specificity in our study.

Both male and female genders have been demonstrated to be predictors of NDNP in the literature [23, 24]. In our study, more male dominance was found in the DNP group and female gender was found to be a risk factor for NDNP. There may be several reasons for this. Firstly, in studies conducted in diabetic patients, the prevalence of clinically diagnosed DNP was found to be lower in women, and it was stated that this may be related to the protective effects of estrogen [25]. In a study conducted in Turkey investigating the frequency of DNP by blood-urine analyses, it was found to be significantly more frequent in males (female 22.9% vs. male 29.2%, $p = 0.007$). [26]. Secondly, autoimmune diseases are known to occur more frequently in women [27]. Finally, it is known that FSGS, the most frequently detected renal pathology in the NDNP group, is mostly due to secondary/adaptive causes and obesity is

one of these causes. The prevalence of obesity is higher in women in Turkey [28]. From this point of view, it may be realistic to assume that female gender is a risk factor for NDNP.

Diabetic retinopathy is a microvascular complication of DM that may share pathogenetic pathways with DNP. When retinopathy coexists with nephropathy, it is considered a potential indicator of renal complications [7, 16]. The KDOQI 2007 guidelines state that if DR with albuminuria is present, the cause of CKD may be attributed to DNP [29]. Therefore, retinopathy can be considered as an indicator of DNP [30]. In our study, DR was detected more frequently in patients with DNP than in the NDNP group and the absence of DR was determined to be a risk factor for NDNP. In the ROC analysis, it was found to be the most successful parameter in differentiating NDNP from DNP.

The HbA1c value is widely regarded as the most reliable method for assessing glycemic control. Long-term glycemic control is the primary risk factor for the development of micro and macrovascular complications in diabetic patients, as evidenced by cumulative research [31]. In the literature, it has been repeatedly reported that elevated HbA1c is a risk factor in predicting DNP. [32–34]. In this study, the parameters indicating uncontrolled diabetes (such as intensive diabetes treatment and HbA1c levels) were significantly more common in the DNP group. These results suggest that higher HbA1c levels in DM patients with kidney disease are associated with a higher likelihood of DNP, while lower HbA1c levels are more likely to be associated with NDRD. In contrast, the ACCORD trial found that intensive treatment aimed at achieving normal HbA1c levels for 3.5 years did not significantly reduce major cardiovascular events compared with standard treatment. Moreover, it increased mortality [35]. In order to test their hypothesis that HbA1c variability in intensive therapy would be associated with all-cause mortality, Sheng et al. performed a post hoc analysis of the ACCORD trial. HbA1c variability is a significant predictor of all-cause death, as shown by the research [36]. Recent studies have found that HbA1c variability, expressed as intrapersonal SD or coefficient of variance, is also an independent risk factor for diabetic complications in type 2 patients [37]. It may even be a more reliable measure of glycemic control than the mean HbA1C in type 2 DM [12, 38]. In the short term and in a limited number of measurements, the HbA1c value may be influenced by various factors, such as anemia treatment, uremia, and laboratory errors. For this reason, analysis of HbA1c variability calculated separately for each patient over at least two years and more than two measurements may be more valuable in detecting diabetes complications such as DNP. In our study, HbA1c variability was found to be a risk factor in DNP-NDNP discrimination. A sudden rise in HbA1c levels may indicate uncontrolled diabetes, while a sudden decrease in HbA1c levels may be due to reduced insulin degradation and renal gluconeogenesis caused by CKD associated with DNP. The higher frequency of patients with stable HbA1c levels in the NDNP group can therefore be interpreted in this context. Currently, there are no studies investigating HbA1c variability between DNP and NDNP. Therefore, these findings in our study reveal the importance of HbA1c variability and encourage its clinical use.

While proteinuria levels remained constant, patients diagnosed with DNP had a considerably higher incidence of albuminuria when the patient with minimal change disease (MCD) was eliminated. This may be the result of people with NDNP having a greater urine transit of non-albumin proteins, specifically

multipl myeloma and MN. Although a lack of significance was shown in the multivariate analysis, it may be more advantageous to measure urine protein and albumin concurrently. A biopsy is recommended for diabetic patients who have been prediagnosed with NDNP and are experiencing rapid and growing proteinuria [30]. The length of DM has been shown as a strong predictor of DNP in prior research [39]. The effect of proteinuria duration, however, has received little research attention. We found that the duration of proteinuria in NDNP patients was considerably shorter in our study. In the multivariate analysis, however, we failed to identify any significant differences. It is critical to emphasize that clinicians may still find the duration of proteinuria to be a valuable criterion.

Our study had limitations. As our study was based on information collected from electronic medical records, we encountered missing data and difficulties in accessing the results of some previous laboratory tests, which are common limitations of retrospective studies. The main limitation of our findings relates to the retrospective design and the possibility of selection bias. The traditional criteria used to decide on KB in the diabetic patient may have increased or decreased the effectiveness of the parameters studied as risk factors. A reliable way to address this issue would be prospective studies in which renal biopsies are performed in all patients with diabetes to determine the predictive effects of clinical factors and/or laboratory tests. However, selection bias appears to be present in the few prospective studies published to date with discordant results. Finally, although pathological findings overlapped in some patients, patients were divided into two groups based on the histological findings seen in the foreground. In some publications, patients were classified as diabetic, nondiabetic and patients with combined nephropathies. In our study, it was preferred to divide the patients into two groups both in order not to reduce the statistical power by dividing the groups and because the prominent pathological findings and clinical findings could be distinguished despite overlap.

In conclusion; the absence of diabetic retinopathy, non-HbA1c variability, female gender and serology positivity were found to be risk factors in predicting non-diabetic nephropathy. In conjunction with conventional variables, gender and HbA1c variability were identified as significant determinants in distinguishing DNP from NDNP. By using these factors, the current selection criteria for renal biopsy in patients with DM can be improved, and it is possible to determine which individuals might benefit from particular treatment measures to prevent renal dysfunction caused by NDNP or DNP. Prospective studies must validate the efficacy of HbA1c variability as shown in our research.

Declarations

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Competing Interests: The authors have declared that no conflict of interest exists.

Ethical approval: The methods utilized in this investigation were authorized by the Haydarpaşa Numune Research and Training Hospital Clinical Research Ethics Committee (Approval No. HNEAH-KAEK 2022/205), and all procedures conducted in the study adhered to the ethical standards outlined in the 1964 Declaration of Helsinki.

Author Contribution

B.D., Bu.B., Ba. B. wrote the main manuscript textB.D. prepared figureE.G.S prepared tables.Y.D.B., G.G., collected dataB.D. analyzed the dataConception or design, authorship: M.B.Ö., M.C.All authors reviewed the manuscript

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Figures

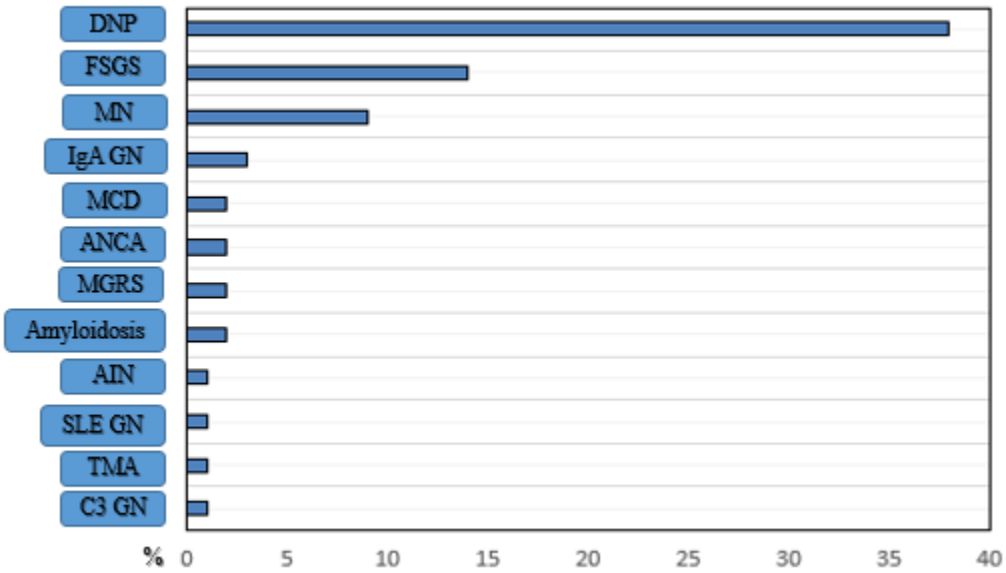


Figure 1

Frequency of pathological diagnoses in patients with DM who underwent renal biopsy.

TMA; thrombotic microangiopathy, C3 GN; C3-related glomerulonephritis, MGRS; monocolonal gammopathy of renal significance, FSGS; focal segmental glomerulosclerosis, DNP; diabetic nephropathy, IgA GN; IgA nephropathy, ANCA; antineutrophil cytoplasmic antibodies, AIN; Acute interstitial nephritis, SLE GN; Lupus nephritis, MCD; Minimal change disease, MN; Membranous nephropathy.