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The role of kidney biopsy in deciphering diabetic versus non-diabetic origin of kidney disease among patients with type 2 diabetes mellitus and nephrotic range proteinuria: A retrospective study

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ABSTRACT

Background: Diabetes mellitus (DM) is tightly associated with the increased prevalence of diabetic kidney disease (DKD). Nonetheless, severe renal function impairment and/or nephrotic range-proteinuria could also result from non-diabetic renal disease (non-DRD) among patients with DM. The 'Gold standard' for the differential diagnosis between DKD and non-DRD is kidney biopsy, although no real consensus exists. Thus, this study intends to associate the clinical and biochemical profile of patients with DM and renal disease with the histopathological data of kidney biopsy.In addition, we aimed to evaluate the role of kidney biopsy, especially when other causes, other than DM, are highly suspected among patients with DM and kidney disease.

Methods: Thirty two patients with T2DM and nephrotic range levels of proteinuria or with co-existing factors pointing towards a non-diabetic origin of kidney disease were studied, retrospectively. All 32 patients underwent kidney biopsy and were classified according to histopathological findings into 3 groups: a) isolated diabetic kidney disease (DKD), b) non-diabetic kidney disease (NDKD) and c) mixed kidney disease (MKD).

Results: Fifteen out of the 32 patients had findings of an isolated DKD, while 17 out of 32 patients suffered from NDKD (13 patients) or MKD (4 patients). DKD patients were younger ($p = 0.016$) and had a higher HbA1c value ($p = 0.069$, borderline statistical significance), while the NDKD patients had significantly shorter disease duration ($p = 0.04$). Furthermore, the incidence of diabetic retinopathy (DR) was lower among the NDKD patients ($p < 0.001$), who had also significantly less interstitial fibrosis ($p = 0.02$). Finally, the presence of DR, higher levels of interstitial fibrosis and longer T2DM duration were recognized as factors, which were positively associated with DKD.

Conclusion: This study advocates the usefulness of kidney biopsy in patients with T2DM and nephrotic range levels of proteinuria, especially when DR is absent and shorter disease duration is observed.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder, characterized by increased insulin resistance and dysfunction of beta pancreatic cells [1–4]. Excess body weight is a significant risk factor for T2DM and cardiometabolic disorders, contributing also to the severity of

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T2DM [5–13].The prevalence of T2DM has been increasing rapidly, especially during the last decades, affecting more than one tenth of the population [14]. T2DM has been associated with microvascular and macrovascular complications, such as cardiovascular disease (CVD), diabetic retinopathy (DR), and diabetic kidney disease (DKD) [15–17]. DKD is by far the most prevalent complication of T2DM and is linked to glomerular hyperfiltration, progressive albuminuria, decreased glomerular filtration rate and even end-stage renal disease (ESRD) [18]. Diagnosis of DKD is based on clinical 'clues', such as concomitance of other diabetic complications, absence of hematuria, gradual decline in renal function and is typically confirmed by the absence of other possible causes of chronic kidney disease (CKD) [19–23]. Diagnosis of DKD usually doesn't require a kidney biopsy, while in other cases of nephropathy in T2DM, kidney biopsy is absolutely indicated. Thus, a kidney biopsy is not mandatory for diagnosing DKD [24,25]. In sharp contrast, kidney biopsy should be considered for patients with diabetes with rapidly declining renal function and high suspicion of non-diabetic renal disease (NDKD) [26]. Interestingly, a variety of factors besides DM can negatively affect renal function and cause irreparable kidney injury. These factors comprise arterial hypertension, glomerulonephritis, genetic syndromes, atherosclerosis, various systemic autoimmune diseases and acute kidney injury [27]. The value of early and accurate differentiation between DKD and NDKD is high and reflects on the fact that treatment strategies are completely different between these two pathologic entities. In cases of NDKD and depending on the underlying cause, personalized treatment options are indicated to delay impairment of renal function, which may lead to irreparable damage to the kidneys [28]. Thus, kidney biopsy is of great importance regarding the diagnosis of NDKD and the subsequent treatment of patients [29]. Significant differences regarding the prognosis and overall survival exist among patients with DKD and NDKD [30]. Thus, kidney biopsy is unquestionably vital for the diagnosis of NDKD and will only be performed in case the suspicion of this pathologic entity is set.

Unfortunately, no established guidelines exist regarding patients with T2DM and renal failure, who should undergo kidney biopsy on accounts of suspecting other causes of nephropathy. It is well known that the incidence of NDKD in patients with T2DM varies significantly [31]. Among the factors contributing to this variability, the absence of criteria for patients presenting with renal insufficiency, who would benefit from kidney biopsy, may be the most important one. Until now, only a small number of studies have aimed at further evaluating our understanding of these criteria [24,32–35]. The aim of our study was to associate the clinical and laboratory data of patients with T2DM and DKD, NDKD and MKD with the histopathological data. In addition, we aimed to evaluate the role of kidney biopsy, especially when other causes, other than DM, are highly suspected among patients with DM and kidney disease.

2. Materials and methods

2.1. Patients and data collection

We retrospectively reviewed the files of patients with T2DM, who were subject to kidney biopsy at Evangelismos General Hospital of Athens, in a tertiary-care endocrinology, diabetology and nephrology referral center in Greece, between 2011 and 2020. The review process was organized and conducted by a team of endocrinologists and nephrologists. The medical records of the patients were used for the collection of the demographic and clinical data, which included among others, age, gender, body mass index (BMI), duration of T2DM before biopsy, diabetic treatment, grade of CKD and presence of DR. Regarding the clinical and biochemical data, the levels of albuminuria/proteinuria, signs of DR in fundus examination by an ophthalmologist, presence of red blood cells in the urine (URBC), arterial pressure levels and the number/type of antihypertensive agents, glycated hemoglobin (HbA1c) and number/type of antidiabetic agents, serum albumin, lipid profile and eGFR (estimated glomerular filtration rate) using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula were recorded. Depending on the histopathological findings, patients were classified into 3 groups: a) patients with isolated DKD, b) patients with NDKD and c) patients with MKD. Regarding histological findings, the grade of DKD and the level of interstitial renal fibrosis (IRF) and nephrosclerosis were estimated and related to treatment interventions. Kidney biopsy was performed in patients with DM and nephrotic range proteinuria as well as among patients with high clinical suspicion of non-diabetic origin of kidney dysfunction, such as co-existing hematuria and presence of red blood cells/urine sediment and/or rapidly declining renal function. All patients were followed up and overall survival, following kidney biopsy, was estimated. No complications were observed following kidney biopsy in our patients.Ethical approval was obtained by the Scientific and Ethics Committee of the hospital. All patients gave informed consentfor the performance of kidney biopsy.

2.2. Statistical analysis

Data were analyzed using SPSS for Windows, version 26.0 (IBM Corporation, Armonk, NY, USA). All binary variables were expressed in counts and percentages, as shown in tables. Continuous variables were described as mean ± standard deviation for normally distributed data. Student's t-test or one-way analysis of variance (ANOVA) was used for normally distributed data analysis, and the Mann-Whitney *U* test or Kruskal-Wallis test was used for skewed data analysis. Results were reported as the odds ratio (OR) and 95 % confidence interval (CI).The Kaplan-Meier method was used for survival analysis, while the log rank test was employed for comparisons. All probabilities were two-tailed, and a P-value of less than 0.05 was considered to be statistically significant.

3. Results

The number of patients with T2DM who underwent kidney biopsy was 32. Among them, 21 (65.6 %) were males and 11 (34.4 %) females (female to male ratio 0.52:1). All patients were subject to kidney biopsy for the first time in their life and no other kidney disease was known from their past medical history. Mean age of the patients was 61.8 ± 5 years (range: 29–89) and the patients had DM for 10.5 ± 0.8 years (range: 3–20). The patients had a mean follow-up of 24.8 years (range: 0–84). Mean HbA1c was 7.2 ± 1.6 % (range: 5–10.6). Mean values for serum albumin, serum creatinine, eGFR (CKD-EPI formula) and Total Protein in Urine (TPU) in urine were 3 ± 0.7 g/dl (range: 2–4.7), 2.5 ± 1.5 mg/dl (range: 0.6–6.2), 35.8 ± 23, mL/min/1.73 m^2 (range: 6–109) and 7.5 ± 2.8 gr (range: 3.9–14.9). Twenty three out of 32 patients (71.2 %) presented with nephrotic syndrome. Regarding IRF, 13 patients presented with <25 % IRF, 18 patients had IRF between 25 % and 50 % and only 1 patient was detected with >50 % IRF. Ten patients had positive urine sediment, while most of the studied patients were diagnosed with Grade III DKD (classification by Tervaert et al. [36]). Moreover, patients had a mean level of nephrosclerosis of 28.9 ± 17.4 % (0.1–62). Most patients (40 %) were being treated for T2DM with insulin, whereas 33 % were on oral antidiabetic therapy. Furthermore, 12 patients (37.5 %) had documented DR. All patients had arterial hypertension, with most of them (85 %) receiving two or more antihypertensive medications. Demographic and biochemical findings are presented in Table 1.

Moreover, based on the results of kidney biopsy, patients were classified into 3 groups: DKD (n = 15), NDKD (n = 13) and MKD (n = 4). Patients' characteristics and demographic data are presented in Table 2. Patients with DKD were significantly younger than the NDKD and MKD groups (54.1 vs 68.2 vs 70.5 years respectively, p = 0.016). The NDKD group of patients had a shorter duration of T2DM (8.4 vs 11.6 vs 13.3 years, respectively, p = 0.04), but had a longer medical follow-up though not statistically significant (33.2 vs 17.4 vs 25 years respectively, p = 0.31) in comparison to the DKD and MKD groups,

Table 1
Demographic and biochemical findings of all patients with T2DM included in the study (n = 32) that underwent kidney biopsy.

Characteristics	All patients n = 32
Gender (male) (N) (%)	21/32 (65.6 %)
Age (years)	61.8 ± 5
Duration of diabetes (years)	10.5 ± 5
Mean follow-up (years)	24.8 ± 27.3
Diabetic retinopathy (N)(%)	12/32 (37.5)
Serum Creatinine (mg/dl)	2.53 ± 1.5
eGFR (mL/min/1.73m^2)	35.8 ± 23.4
Nephrotic syndrome (N) (%)	23/32(71.2 %)
TPU (gr)	7.5 ± 2.8
Nephrosclerosis (%)	28.9 ± 17.4
HbA1c (%)	7.2 ± 1.6
Interstitial renal fibrosis (IRF) (N) (%)	
IRF<25 %	13/32 (40.6 %)
25 % ≤ IRF <50 %	18/32 (56.3 %)
IRF ≥50 %	1/32 (3.1 %)
Red blood cells in urine (urine sediment) (N) (%)	10/32 (31.3 %)
Arterial hypertension (N) (%)	32/32 (100 %)
Antihypertensive therapy with more than 2 agents (N) (%)	26/32 (85 %)
Antidiabetic therapy with insulin (N) (%)	13/32 (41 %)
Antidiabetic therapy with oral agents (N) (%)	11/32 (34.3 %)

Table 2
Patient characteristics and demographic data among the 3 groups of patients with T2DM.

Type of nephropathy	DKN n = 15	NDKD n = 13	MKD n = 4	P-value
Age (yrs)	54.1 ± 12.9 (29–74)	68.2 ± 14.1 (47–89)	70.5 ± 13.3 (51–79)	0.016
Duration of diabetes (yrs)	11.6 ± 4.5 (6–20)	8.4 ± 4 (4–20)	13.3 ± 8.3 (3–20)	0.04
Follow-up (ys)	17.4	33.2	25	0.31
DR (%)	9/15 (60 %)	1/13 (7.6 %)	3/4 (75 %)	<0.001
Creatinine (mg/dl)	2.4 ± 1.2 (0.9–5.2)	2.4 ± 1.62 (0.6–2.3)	3.78 ± 1.9 (1.4–6)	0.21
eGFR (mL/min/ 1.73 m^2)	37.5 ± 18.8 (11–77)	38.4 ± 29.4 (7–109)	21.3 ± 17.8 (6–47)	0.42
TPU (gr)	6.4 ± 1.7 (4–10)	8.7 ± 3 (4.5–14.9)	7.9 ± 4.3 (3.88–13)	0.08
IRF (%)				
IRF <25 %	3/15 (20 %)	8/13 (61.5 %)	2/4 (50 %)	0.02
25 % ≤ IRF <50 %	11/15 (73.3 %)	5/13 (38.5 %)	2/4 (50 %)	0.02
IRF ≥50 %	1/15 (6.7 %)	0/13 (0 %)	0/4 (0 %)	0.018
Nephrosclerosis (%)	27.1 ± 17.6 (54–62)	30.6 ± 19 (0.1–60)	30 ± 15.4 (14–50)	0.87
HbA1c (%)	7.9 ± 1.7 (5–10.6)	6.5 ± 1.4 (5.2–10.1)	6.8 ± 1.1 (5.6–8)	0.069

Abbreviations: DKD: Diabetic Kidney Disease; DR: Diabetic Retinopathy; eGFR: estimated Glomerular Filtration Rate; IRF: Interstitial Renal Fibrosis; MKD: Mixed Kidney Disease; NDKD: Non Diabetic Kidney Disease; TPU: Total Protein in Urine.

respectively. DR was less frequent among the NDKD group (7.6 vs 60 vs 75 %, p < 0.001), while the same observation applied for IRF (38.5 vs 50 vs 73.3 %, p = 0.02). Regarding the levels of nephrosclerosis, no statistically significant difference was observed between the 3 groups (27.1 vs 30.6 vs 30 %, p = 0.87), while almost 1 out of 3 patients suffered from nephrosclerosis. HbA1c values were higher among the DKD, when compared to the NDKD and MKD groups (7.9 vs 6.5 vs 6.8 %, respectively, p = 0.069, of borderline statistical significance). eGFR levels did not differ significantly among the 3 groups (37.5 vs 38.4 vs 21.3, p = 0.42). The same observation applied for TPU levels, though patients from the NDKD group had higher levels than the DKD and MKD groups (8.7 vs 6.4 vs 7.9 respectively, p = 0.08, of borderline statistical significance).

Regarding the overall survival after kidney biopsy, 8/15 patients from the DKD group died during the follow-up, while 0/13 patients from the NDKD group and 3/4 patients from the MKD group were not alive at the end of the follow-up. Thus, the overall survival of the 3 groups was 46.7 %, 100 % and 25 % for the DKD, NDKD and MKD groups, respectively (p = 0.001) (Fig. 1).

Table 3 depicts patients with NDKD and MKD according to their specific diagnoses (Table 3). Notably, all patients with NDKD and MKD received appropriate therapy based on their histological findings in kidney biopsy. In addition, the level of IRF together with the stage of DN in kidney biopsy was taken into account for choosing intensification of treatment among patients with T2DM.

Finally, we conducted unadjusted regression statistical analysis of the risk for DN regarding long time duration since T2DM diagnosis (>10 years), middle age (>45 years), moderate or poor glycemic control (7 %< HbA1c ≤ 8 % vs HbA1c >8 %), presence of DR and/or IRF. The presence of DR (OR 4.88. % 95 CI: 1.06–22.38, p = 0.041), the presence of high extent of IRF (>25 %) (OR 5.71.% 95 CI:1.16–28.1, p = 0.032) and longer duration time since the diagnosis of T2DM (>10 years) (OR 5.04. % 95 CI: 1.1–22.96, p = 0.036) were factors that were positively associated with DKD (Table 4).

4. Discussion

Despite the great improvement in the diagnostic procedures and treatment modalities for patients with T2DM, very often, impaired renal function in these patients is 'labeled' as diabetic nephropathy, although it is the result of other cause/illness, not related to DM. Thus, kidney

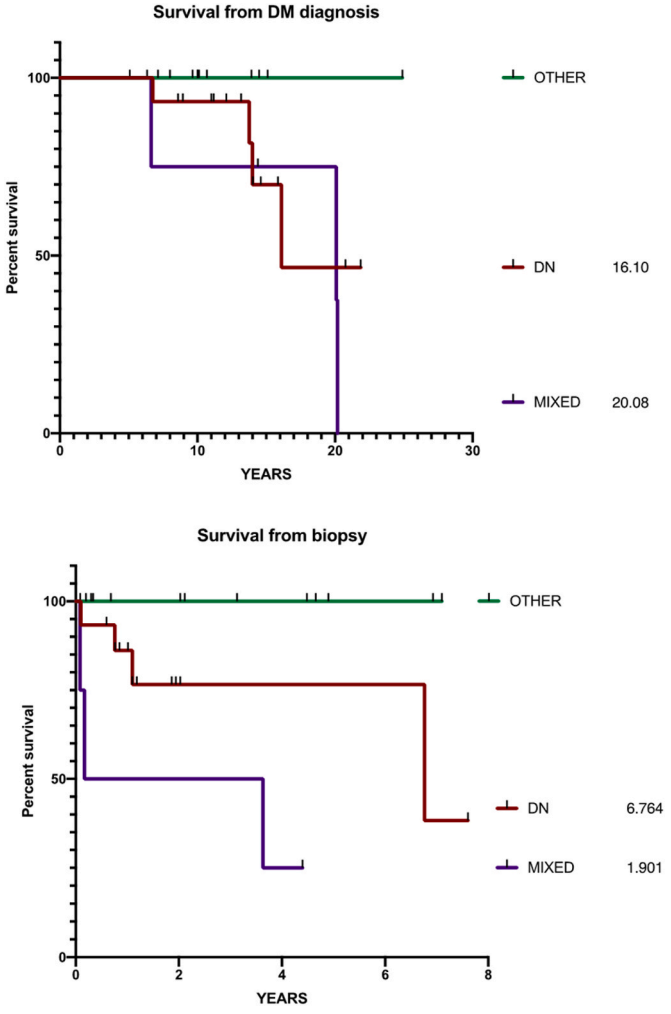

Fig. 1. Overall survival of patients from diagnosis of T2DM as well as following kidney biopsy, depending on cause of nephropathy.

Table 3
Different histological types of nephropathy among patients with NDKD and MKD (n = 17).

Type of NDKD patients	Number of patients
Membranous Glomerulonephritis	5
Glomerulosclerosis (+ Focal Segmental Glomerulosclerosis -FSGS)	3
Hypertensive Nephropathy (benign nephrosclerosis)	2
Membranoproliferative Glomerulonephritis	2
Minimal Change Disease	1
Type of MKD patients	
DKD + Hypertensive Nephropathy	2
DKD + Diffuse Proliferative Glomerulonephritis (DPGN)	1
DKD + IgA Nephropathy	1

Table 4
Unadjusted odds ratios for the logistic regression estimates for the relationship between isolated diabetic nephropathy and various risk factors.

Factors	DKD	NDKD and MKD	Odds Ratio (OR)	95 % Confidence Interval (CI)	P value
Population	15	17			
Age >45 years	12	11	2.18	0.43–10	0.34
Disease duration >10 years	11	6	5.04	1.1–22.96	0.036
Diabetic retinopathy	9	4	4.88	1.06–22.38	0.041
7 %≤ HbA1c ≤ 8 %	3	2	1.87	0.27–13.1	0.52
HbA1c > 8 %	7	3	4.08	0.81–20.38	0.086
Interstitial renal fibrosis (IRF) (>25 %)	12	7	5.71	1.16–28.1	0.032

dysfunction of non-diabetic origin goes under-diagnosed or mis-diagnosed, resulting in inadequate and inappropriate medical treatment. Therefore, it is of utmost importance to recognize and differentiate non-diabetic from diabetic nephropathy in its early stages in order to select and initiate suitable therapeutic measures.

In our study, 15 (46.9 %) patients were diagnosed with DKD, while 13 (40.6 %) and 4 (12.5 %) patients suffered from NDKD and MKD, respectively, according to the histopathological data. In the past, the prevalence of DKD has been reported to be up to 94 %, reflecting perhaps the relative lack of performing renal biopsy among patients with T2DM [37]. However, Fiorentino et al., in their meta-analysis of 48 studies in 2017, noted that the prevalence of DKD has been ranging from 6.5 % to 94 % [38]. Interestingly, 94 % was the estimated prevalence in a study published in 1998, whereas 6.5 % was the prevalence reported from a study published in 2013 [37,39]. Despite these huge differences in the reported prevalence of DKD, after 2000, the reported prevalence of DKD ranges from 6.5 % to 73.85 %, which is still a wide range [37, 40]. We reported 46.9 % of our patients having DKD, while 40.6 % had NDKD and 12.5 % MKD. Nevertheless, we might have a selection bias, as we have performed kidney biopsy in selected patients with T2DM. Notably, the prevalence of NDKD among patients with T2DM observed in other studies markedly varied depending on numerous factors, such as the ethnic background of patients, disease duration and severity and co-existence of other diabetes complications, for example DR [41–48].

Therefore, regarding the potential indicators, which could be helpful towards the clinical differentiation between diabetic and non-diabetic kidney dysfunction, no consensus has been achieved yet. Regarding the role of DR as an indicator of diabetic nephropathy, the vast majority of studies support its role in predicting DKD versus NDKD [43,49–55]. It is noteworthy that Dong et al. reported that absence of DR had a sensitivity of 92.11 % and a specificity of 82.29 % in predicting NDKD [55]. However, in a recent meta-analysis, DR was not powerful enough to confirm the presence of DKD or exclude NDKD [56]. In our study, the presence of DR was associated with significantly increased risk for DKD rather than NDKD (OR 4.88; % 95 CI: 1.06–22.38, p = 0.041).

Furthermore, in our study, longer duration of T2DM (>10 years) was observed to be associated with increased risk for DKD, when compared to the non-diabetic origin CKD. Increased T2DM duration has been correlated with DKD versus NDKD in most studies, thus far [21,57–61]. In particular, Prakash et al. have reported that DKD is the predominant type of kidney dysfunction in patients with duration of T2DM > 10 years, whereas NDKD is the most prominent form among patients with duration of T2DM < 5 years [62]. Nevertheless, this distinction in the duration of T2DM, although helpful, is not so accurate in predicting the diabetic versus the non-diabetic origin of kidney dysfunction.

Finally, identification of enhanced IRF, as documented by an IRF>25 % in the histopathological findings among patients with T2DM was associated with increased odds of DKD (OR 5.71; % 95 CI:1.16–28.1, p = 0.032). IRF is known to be tightly associated with DKD and its rapid progression, which often leads to ESRD [63,64]. Notably, IRF exhibits an additive value regarding prognosis of kidney dysfunction among patients with T2DM [64]. Other studies have also confirmed that increased IRF is observed in patients with diabetic nephropathy compared to those suffering from kidney disease of a non-diabetic origin [29,63–68]. It is noteworthy that Gonzalez et al. have reported that IRF may be present among patients with T2DM and eGFR >90 mL/min/1.73 m^2 [69]. Nonetheless, more studies are needed to further evaluate the potential predictive role of IRF in cases of DKD.

In conclusion, certain clinical factors, such as duration of DM and presence of DR seem to be positively associated with DKD among patients with T2DM. Despite this observation, the discrimination between DKD and NDKD seems to be tempting and often discerned. Thus, in cases where there is significant doubt regarding the cause of CKD in patients with T2DM, kidney biopsy should be discussed and thoroughly suggested, based on an individualized approach for each patient.

This study has several limitations. The retrospective design of the study and its relatively small sample size do not allow for definite findings, which could be applied among patients with T2DM and kidney dysfunction. Due to the small sample size of patients, only unadjusted logistic regression analyses were performed.In addition, a selection bias is possible as we have not performed kidney biopsy in all patients with T2DM and co-existing nephropathy. Furthermore, this study was conducted exclusively in a single center in Athens, Greece and was not multi-ethnic.

5. Conclusion

This study highlights the usefulness of kidney biopsy and its findings in patients with T2DM presenting levels of albuminuria equivalent to that of nephrotic syndrome. Patients who have T2DM and suffer from NDKD can be differentiated from those with DKD and receive the appropriate therapy based on the underlying cause. In cases of DKD, intensification of medical treatment, especially in the era of SGLT-2 inhibitors is needed in order to delay renal function impairment and prevent or reverse further kidney damage [70–73]. In conclusion, the detection of nephrotic syndrome-proteinuria in patients with T2DM should prompt the clinicians to perform kidney biopsy, in particular among patients who do not have DR, who have a shorter duration of T2DM or in patients who present with T2DM and a positive urinary sediment.

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Ethical approval

All participants have given their informed consent for the

performance of kidney biopsy. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Scientific and Ethics Committee of Evangelismos Hospital.

CRediT authorship contribution statement

Efstratios Kardalas: Methodology, Conceptualization. **Aggeliki Paikopoulou:** Investigation, Data curation. **Dimitra A. Vassiliadi:** Software, Methodology. **Dimitris Kounatidis:** Writing – original draft, Investigation. **Natalia G. Vallianou:** Writing – original draft. **Christine Vourlakou:** Data curation. **Irene Karampela:** Writing – original draft. **Maria Dalamaga:** Writing – review & editing. **Marinella Tzanela:** Conceptualization. **Theodora Stratigou:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that there is no conflict of interest.

References

[1] Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. Lancet 2017;389(10085):2239–51. https://doi.org/10.1016/S0140-6736(17)30058-2.

[2] Vallianou NG, Geladari EV, Kounatidis D, Geladari CV, Stratigou T, Dourakis SP, Andreadis EA, Dalamaga M. Diabetes mellitus in the era of climate change. Diabetes Metab 2021;47(4):101205. https://doi.org/10.1016/j.diabet.2020.10.003.

[3] Dalamaga M, Karmaniolas K, Chamberland J, Nikolaidou A, Lekka A, Dionyssiou-Asteriou A, Mantzoros CS. Higher fetuin-A, lower adiponectin and free leptin levels mediate effects of excess body weight on insulin resistance and risk for myelodysplastic syndrome. Metabolism 2013;62(12):1830–9. https://doi.org/10.1016/j.metabol.2013.09.007.

[4] Papadavid E, Vlami K, Dalamaga M, Giatrakou S, Theodoropoulos K, Gyftopoulos S, Stavrianeas N, Papiris S, Rigopoulos D. Sleep apnea as a comorbidity in obese psoriasis patients: a cross-sectional study. Do psoriasis characteristics and metabolic parameters play a role? J Eur Acad Dermatol Venereol 2013;27(7):820–6. https://doi.org/10.1111/j.1468-3083.2012.04580.x.

[5] Koliaki C, Dalamaga M, Liatis S. Update on the obesity epidemic: after the sudden rise, is the upward trajectory beginning to flatten? Curr Obes Rep 2023;12(4):514–27. https://doi.org/10.1007/s13679-023-00527-y.

[6] Papadavid E, Gazi S, Dalamaga M, Stavrianeas N, Ntelis V. Palmoplantar and scalp psoriasis occurring during anti-tumour necrosis factor-alpha therapy: a case series of four patients and guidelines for management. J Eur Acad Dermatol Venereol 2008;22(3):380–2. https://doi.org/10.1111/j.1468-3083.2007.02335.x.

[7] Dalamaga M, Karmaniolas K, Nikolaidou A, Papadavid E. Hypocalcemia, hypomagnesemia, and hypokalemia following hydrofluoric acid chemical injury. J Burn Care Res 2008;29(3):541–3. https://doi.org/10.1097/BCR.0b013e3181711152.

[8] Vallianou N, Kounatidis D, Christodoulatos GS, Panagopoulos F, Karampela I, Dalamaga M. Mycobiome and cancer: what is the evidence? Cancers 2021;13(13):3149. https://doi.org/10.3390/cancers13133149.

[9] Kassi E, Dalamaga M, Faviou E, Hroussalas G, Kazanis K, Nounopoulos Ch, Dionyssiou-Asteriou A. Circulating oxidized LDL levels, current smoking and obesity in postmenopausal women. Atherosclerosis 2009;205(1):279–83. https://doi.org/10.1016/j.atherosclerosis.2008.11.006.

[10] Papadavid E, Katsimbri P, Kapniari I, Koumaki D, Karamparpa A, Dalamaga M, Tzannis K, Boumpas D, Rigopoulos D. Prevalence of psoriatic arthritis and its correlates among patients with psoriasis in Greece: results from a large retrospective study. J Eur Acad Dermatol Venereol 2016;30(10):1749–52. https://doi.org/10.1111/jdv.13700.

[11] Karampela I, Kandri E, Antonakos G, Vogiatzakis E, Christodoulatos GS, Nikolaidou A, Dimopoulos G, Armaganidis A, Dalamaga M. Kinetics of circulating fetuin-A may predict mortality independently from adiponectin, high molecular weight adiponectin and prognostic factors in critically ill patients with sepsis: a prospective study. J Crit Care 2017;41:78–85. https://doi.org/10.1016/j.jcrc.2017.05.004.

[12] Stratigou T, Dalamaga M, Antonakos G, Marinou I, Vogiatzakis E, Christodoulatos GS, Karampela I, Papavassiliou AG. Hyperirisinemia is independently associated with subclinical hypothyroidism: correlations with cardiometabolic biomarkers and risk factors. Endocrine 2018;61(1):83–93. https://doi.org/10.1007/s12020-018-1550-3.

[13] Spyrou N, Vallianou N, Kadillari J, Dalamaga M. The interplay of obesity, gut microbiome and diet in the immune check point inhibitors therapy era. Semin Cancer Biol 2021;73:356–76. https://doi.org/10.1016/j.semcancer.2021.05.008.

[14] Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol 2018;14(2):88–98. https://doi.org/10.1038/nrendo.2017.151.

[15] Gregg EW, Sattar N, Ali MK. The changing face of diabetes complications. Lancet Diabetes Endocrinol 2016;4(6):537–47. https://doi.org/10.1016/S2213-8587(16)30010-9.

[16] Das T, Islam K, Dorji P, Narayanan R, Rani PK, Takkar B, Thapa R, Moin M, Piyasena PN, Sivaprasad S. Health transition and eye care policy planning for people with diabetic retinopathy in south Asia. Lancet Reg Health Southeast Asia 2024;27:100435. https://doi.org/10.1016/j.lansea.2024.100435.

[17] Dalamaga M, Karmaniolas K, Lekka A, Antonakos G, Thrasyvoulides A, Papadavid E, Spanos N, Dionyssiou-Asteriou A. Platelet markers correlate with glycemic indices in diabetic, but not diabetic-myelodysplastic patients with normal platelet count. Dis Markers 2010;29(1):55–61. https://doi.org/10.3233/DMA-2010-0726.

[18] Phillips PCA, de Sousa Loreto Aresta Branco M, Cliff CL, Ward JK, Squires PE, Hills CE. Targeting senescence to prevent diabetic kidney disease: exploring molecular mechanisms and potential therapeutic targets for disease management. Diabet Med 2024:e15408. https://doi.org/10.1111/dme.15408.

[19] Qi C, Mao X, Zhang Z, Wu H. Classification and differential diagnosis of diabetic nephropathy. J Diabetes Res 2017;2017:8637138. https://doi.org/10.1155/2017/8637138.

[20] Zhou T, Fang YL, Tian TT, Wang GX. Pathological mechanism of immune disorders in diabetic kidney disease and intervention strategies. World J Diabetes 2024;15(6):1111–21. https://doi.org/10.4239/wjd.v15.i6.1111.

[21] Pugliese G, Penno G, Natali A, Barutta F, Di Paolo S, Reboldi G, Gesualdo L, De Nicola L, Italian Diabetes Society and the Italian Society of Nephrology. Diabetic kidney disease: new clinical and therapeutic issues. Joint position statement of the Italian Diabetes Society and the Italian Society of Nephrology on "The natural history of diabetic kidney disease and treatment of hyperglycemia in patients with type 2 diabetes and impaired renal function". J Nephrol 2020;33(1):9–35. https://doi.org/10.1007/s40620-019-00650-x.

[22] Kounatidis D, Vallianou NG, Psallida S, Panagopoulos F, Margellou E, Tsilingiris D, Karampela I, Stratigou T, Dalamaga M. Sepsis-associated acute kidney injury: where are we now? Medicina (Kaunas) 2024;60(3):434. https://doi.org/10.3390/medicina60030434.

[23] Marouga A, Dalamaga M, Kastania AN, Kroupis C, Lagiou M, Saounatsou K, Dimas K, Vlahakos DV. Circulating resistin is a significant predictor of mortality independently from cardiovascular comorbidities in elderly, non-diabetic subjects with chronic kidney disease. Biomarkers 2016;21(1):73–9. https://doi.org/10.3109/1354750X.2015.1118536.

[24] Tong X, Yu Q, Ankawi G, Pang B, Yang B, Yang H. Insights into the role of renal biopsy in patients with T2DM: a literature review of global renal biopsy results. Diabetes Ther 2020;11(9):1983–99. https://doi.org/10.1007/s13300-020-00888-w.

[25] Doshi SM, Friedman AN. Diagnosis and management of type 2 diabetic kidney disease. Clin J Am Soc Nephrol 2017;12(8):1366–73. https://doi.org/10.2215/CJN.11111016.

[26] Bermejo S, Pascual J, Soler MJ. The large spectrum of renal disease in diabetic patients. Clin Kidney J 2017;10(2):255–6. https://doi.org/10.1093/ckj/sfw137.

[27] Levey AS, Eckardt KU, Dorman NM, Christiansen SL, Hoorn EJ, Ingelfinger JR, et al. Nomenclature for kidney function and disease: report of a kidney disease: improving global outcomes (KDIGO) consensus conference. Kidney Int 2020;97(6):1117–29. https://doi.org/10.1016/j.kint.2020.02.010.

[28] Erdogmus S, Kiremitci S, Celebi ZK, Akturk S, Duman N, Ates K, Erturk S, et al. Non-diabetic kidney disease in type 2 diabetic patients: prevalence, clinical predictors and outcomes. Kidney Blood Press Res 2017;42(5):886–93. https://doi.org/10.1159/000484538.

[29] Santoro D, Torreggiani M, Pellicanò V, Cernaro V, Messina RM, Longhitano E, Siligato R, Gembillo G, Esposito C, Piccoli GB. Kidney biopsy in type 2 diabetic patients: critical reflections on present indications and diagnostic alternatives. Int J Mol Sci 2021;22(11):5425. https://doi.org/10.3390/ijms22115425.

[30] Yang Z, Feng L, Huang Y, Xia N. A differential diagnosis model for diabetic nephropathy and non-diabetic renal disease in patients with type 2 diabetes complicated with chronic kidney disease. Diabetes Metab Syndr Obes 2019;12:1963–72. https://doi.org/10.2147/DMSO.S223144.

[31] Bermejo S, González E, López-Revuelta K, Ibernon M, López D, Martín-Gómez A, Garcia-Osuna R, Linares T, et al. Risk factors for non-diabetic renal disease in diabetic patients. Clin Kidney J 2020;13(3):380–8. https://doi.org/10.1093/ckj/sfz177.

[32] Tan HZ, Choo JCJ, Fook-Chong S, Chin YM, Chan CM, Tan CS, Woo KT, Kwek JL. Development and validation of a novel nomogram to predict diabetic kidney disease in patients with type 2 diabetic mellitus and proteinuric kidney disease. Int Urol Nephrol 2023;55(1):191–200. https://doi.org/10.1007/s11255-022-03299-x.

[33] Hsieh JT, Chang FP, Yang AH, Tarng DC, Yang CY. Timing of kidney biopsy in type 2 diabetic patients: a stepwise approach. BMC Nephrol 2020;21(1):131. https://doi.org/10.1186/s12882-020-01794-w.

[34] Ghani AA, Al Waheeb S, Al Sahow A, Hussain N. Renal biopsy in patients with type 2 diabetes mellitus: indications and nature of the lesions. Ann Saudi Med 2009;29(6):450–3. https://doi.org/10.4103/0256-4947.57167.

[35] Wang X, Li J, Huo L, Feng Y, Ren L, Yao X, Jiang H, Lv R, Zhu M, Chen J. Clinical characteristics of diabetic nephropathy in patients with type 2 diabetic mellitus manifesting heavy proteinuria: a retrospective analysis of 220 cases. Diabetes Res Clin Pract 2019;157:107874. https://doi.org/10.1016/j.diabres.2019.107874.

[36] Tervaert TW, Mooyaart AL, Amann K, Cohen AH, Cook HT, Drachenberg CB, Ferrario F, Fogo AB, Haas M, de Heer E, Joh K, Noël LH, Radhakrishnan J, Seshan SV, Bajema IM, Bruijn JA, Renal Pathology Society. Pathologic classification of diabetic nephropathy. J Am Soc Nephrol 2010;21(4):556–63. https://doi.org/10.1681/ASN.2010010010.

[37] Schwartz MM, Lewis EJ, Leonard-Martin T, Lewis JB, Batlle D. Renal pathology patterns in type II diabetes mellitus: relationship with retinopathy. The

Collaborative Study Group. Nephrol Dial Transplant 1998;13(10):2547–52. https://doi.org/10.1093/ndt/13.10.2547.
[38] Fiorentino M, Bolignano D, Tesar V, Pisano A, Biesen WV, Tripepi G, D'Arrigo G, Gesualdo L, ERA-EDTA Immunonephrology Working Group. Renal biopsy in patients with diabetes: a pooled meta-analysis of 48 studies. Nephrol Dial Transplant 2017;32(1):97–110. https://doi.org/10.1093/ndt/gfw070.
[39] Zhuo L, Ren W, Li W, Zou G, Lu J. Evaluation of renal biopsies in type 2 diabetic patients with kidney disease: a clinicopathological study of 216 cases. Int Urol Nephrol 2013;45(1):173–9. https://doi.org/10.1007/s11255-012-0164-6.
[40] Zhang PP, Ge YC, Li SJ, Xie HL, Li LS, Liu ZH. Renal biopsy in type 2 diabetes: timing of complications and evaluating of safety in Chinese patients. Nephrology 2011;16(1):100–5. https://doi.org/10.1111/j.1440-1797.2010.01369.x.
[41] Lee YH, Kim KP, Kim YG, Moon JY, Jung SW, Park E, et al. Clinicopathological features of diabetic and nondiabetic renal diseases in type 2 diabetic patients with nephrotic-range proteinuria. Medicine (Baltim) 2017;96(36):e8047. https://doi.org/10.1097/MD.0000000000008047.
[42] Chandrashekhar P, Kaul A, Bhaduaria D, Prasad N, Jain M, Patel M, Gupta A. Rapidly progressive renal failure in type 2 diabetic versus non-diabetic patients: changing trends, natural history, and outcome in an Indian tertiary care center. Saudi J Kidney Dis Transpl 2023;34(6):514–9. https://doi.org/10.4103/sjkdt.sjkdt_380_20.
[43] Imtiaz S, Salman B, Nasir K, Drohlia MF, Ahmad A. Clinical variables differentiating diabetic from nondiabetic kidney disease in patients with diabetes: a single-center study. Saudi J Kidney Dis Transpl 2017;28(2):307–12. https://doi.org/10.4103/1319-2442.202794.
[44] Xu X, Feng J, Cui Y, Li P, Dong J, Liao L. Renal effects and safety between Asian and non-Asian chronic kidney disease and type 2 diabetes treated with nonsteroidal mineralocorticoid antagonists. J Diabetes 2024;16(6):e13566. https://doi.org/10.1111/1753-0407.13566.
[45] Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. Clin J Am Soc Nephrol 2017;12(12):2032–45. https://doi.org/10.2215/CJN.11491116.
[46] Wang J, Han Q, Zhao L, Zhang J, Wang Y, Wu Y, Wang T, et al. Identification of clinical predictors of diabetic nephropathy and non-diabetic renal disease in Chinese patients with type 2 diabetes, with reference to disease course and outcome. Acta Diabetol 2019;56(8):939–46. https://doi.org/10.1007/s00592-019-01324-7.
[47] Gopaliah LR, Sudakaran I, Nalumakkal SV, Narayanan R, Vareed BM. Spectrum of biopsy-proven renal diseases: a single center experience. Saudi J Kidney Dis Transpl 2018;29(2):392–400. https://doi.org/10.4103/1319-2442.229295.
[48] Liu S, Guo Q, Han H, Cui P, Liu X, Miao L, Zou H, Sun G. Clinicopathological characteristics of non-diabetic renal disease in patients with type 2 diabetes mellitus in a northeastern Chinese medical center: a retrospective analysis of 273 cases. Int Urol Nephrol 2016;48(10):1691–8. https://doi.org/10.1007/s11255-016-1331-y.
[49] Luyckx VA, Tuttle KR, Abdellatif D, Correa-Rotter R, Fung WWS, Haris A, Hsiao LL, Khalife M, Kumaraswami LA, Loud F, Raghavan V, Roumeliotis S, Sierra M, Ulasi I, Wang B, Lui SF, Liakopoulos V, Balducci A. World Kidney Day Joint Steering Committee. Mind the gap in kidney care: translating what we know into what we do. J Fam Med Prim Care 2024;13(5):1594–611. https://doi.org/10.4103/jfmpc.jfmpc_518_24.
[50] Sakaci T, Ahbap E, Basturk T, Ortaboz M, Ozagari AA, Mazı EE, Eken KG, Hasbal NB, Unsal A. Determinants of non-diabetic kidney diseases in type 2 diabetic patients: twenty years of single center experience. Clin Nephrol 2024;101(5):207–21. https://doi.org/10.5414/CN111093.
[51] Wei S, Pan X, Xiao Y, Chen R, Wei J. The unique association between the level of plateletcrit and the prevalence of diabetic kidney disease: a cross-sectional study. Front Endocrinol 2024;15:1345293. https://doi.org/10.3389/fendo.2024.1345293.
[52] Harada K, Akai Y, Sumida K, Yoshikawa M, Takahashi H, Yamaguchi Y, Kubo A, Iwano M, Saito Y. Significance of renal biopsy in patients with presumed diabetic nephropathy. J Diabetes Investig 2013;4(1):88–93. https://doi.org/10.1111/j.2040-1124.2012.00233.x.
[53] Jiang S, Yu T, Zhang Z, Wang Y, Fang J, Yang Y, Liu L, Li W. Diagnostic performance of retinopathy in the detection of diabetic nephropathy in type 2 diabetes: a systematic review and meta-analysis of 45 studies. Ophthalmic Res 2019;62(2):68–79. https://doi.org/10.1159/000500833.
[54] Li Y, Su X, Ye Q, Guo X, Xu B, Guan T, Chen A. The predictive value of diabetic retinopathy on subsequent diabetic nephropathy in patients with type 2 diabetes: a systematic review and meta-analysis of prospective studies. Ren Fail 2021;43(1):231–40. https://doi.org/10.1080/0886022X.2020.1866010.
[55] Dong Z, Wang Y, Qiu Q, Zhang X, Zhang L, Wu J, Wei R, Zhu H, Cai G, Sun X, Chen X. Clinical predictors differentiating non-diabetic renal diseases from diabetic nephropathy in a large population of type 2 diabetes patients. Diabetes Res Clin Pract 2016;121:112–8. https://doi.org/10.1016/j.diabres.2016.09.005.
[56] Ren D, Kang W, Xu G. Meta-analysis of diagnostic accuracy of retinopathy for the detection of diabetic kidney disease in adults with type 2 diabetes. Can J Diabetes 2019;43(7):530–537.e4. https://doi.org/10.1016/j.jcjd.2019.04.002.
[57] Yan H, Zhou Q, Wang Y, Tu Y, Zhao Y, Yu J, Chen K, Hu Y, Zhou Q, Zhang W, Zheng C. Associations between cardiometabolic indices and the risk of diabetic kidney disease in patients with type 2 diabetes. Cardiovasc Diabetol 2024;23(1):142. https://doi.org/10.1186/s12933-024-02228-9.
[58] Liang S, Zhang XG, Cai GY, Zhu HY, Zhou JH, Wu J, Chen P, Lin SP, Qiu Q, Chen XM. Identifying parameters to distinguish non-diabetic renal diseases from diabetic nephropathy in patients with type 2 diabetes mellitus: a meta-analysis. PLoS One 2013;8(5):e64184. https://doi.org/10.1371/journal.pone.0064184.
[59] Demirelli B, Boztepe B, Şenol EG, Boynueğri B, Bildacı YD, Gümrükçü G, Canbakan M, Öğütmen MB. Non-diabetic nephropathy in diabetic patients: incidence, HbA1c variability and other predictive factors, and implications. Int Urol Nephrol 2024;56(9):3091–100. https://doi.org/10.1007/s11255-024-04066-w.
[60] Wan KS, Hairi NN, Mustapha F, Mohd Yusoff MF, Mat Rifin H, Ismail M, Moy FM, Ahmad NA. Prevalence of diabetic kidney disease and the associated factors among patients with type 2 diabetes in a multi-ethnic Asian country. Sci Rep 2024;14(1):7074. https://doi.org/10.1038/s41598-024-57723-6.
[61] Koye DN, Magliano DJ, Nelson RG, Pavkov ME. The global epidemiology of diabetes and kidney disease. Adv Chron Kidney Dis 2018;25(2):121–32. https://doi.org/10.1053/j.ackd.2017.10.011.
[62] Prakash J, Gupta T, Prakash S, Bhushan P, Usha Sivasankar M, Singh SP. Non-diabetic renal disease in type 2 diabetes mellitus: study of renal - retinal relationship. Indian J Nephrol 2015;25(4):222–8. https://doi.org/10.4103/0971-4065.144420.
[63] Kim WJ, Oh T, Heo NH, Kwon K, Shin GE, Jeong SH, Lee JH, Park S, Cho NJ, Gil HW, Lee EY. Kidney biopsy can help to predict renal outcomes of patients with type 2 diabetes mellitus. Kidney Res Clin Pract 2024. https://doi.org/10.23876/j.krcp.23.059.
[64] Misra PS, Szeto SG, Krizova A, Gilbert RE, Yuen DA. Renal histology in diabetic nephropathy predicts progression to end-stage kidney disease but not the rate of renal function decline. BMC Nephrol 2020;21(1):285. https://doi.org/10.1186/s12882-020-01943-1.
[65] Eadon MT, Schwantes-An TH, Phillips CL, Roberts AR, Greene CV, Hallab A, Hart KJ, et al. Kidney histopathology and prediction of kidney failure: a retrospective cohort study. Am J Kidney Dis 2020;76(3):350–60. https://doi.org/10.1053/j.ajkd.2019.12.014.
[66] Zhang Y, Jin D, Kang X, Zhou R, Sun Y, Lian F, Tong X. Signaling pathways involved in diabetic renal fibrosis. Front Cell Dev Biol 2021;9:696542. https://doi.org/10.3389/fcell.2021.696542.
[67] Singh S, Patel PS, Archana A. Heterogeneity in kidney histology and its clinical indicators in type 2 diabetes mellitus: a retrospective study. J Clin Med 2023;12(5):1778. https://doi.org/10.3390/jcm12051778.
[68] Kaawele S, Elkeraie A, Youssef E, Elrggal M, Elrggal M, Zyada R, Esmail W. Spectrum of nondiabetic kidney diseases in patients with type 2 diabetes mellitus who underwent kidney biopsy in Egypt. Kidney Blood Press Res 2024;49(1):377–84. https://doi.org/10.1159/000538852.
[69] González J, Jatem E, Roig J, Valtierra N, Ostos E, Abó A, Santacana M, García A, Segarra A. Usefulness of urinary biomarkers to estimate the interstitial fibrosis surface in diabetic nephropathy with normal kidney function. Nephrol Dial Transplant 2022;37(11):2102–10. https://doi.org/10.1093/ndt/gfac185.
[70] Vallianou NG, Tsilingiris D, Kounatidis D, Lempesis IG, Karampela I, Dalamaga M. Sodium-glucose cotransporter-2 inhibitors in obesity and associated cardiometabolic disorders: where do we stand? Pol Arch Intern Med 2022;132(10):16342. https://doi.org/10.20452/pamw.16342.
[71] Lempesis IG, Apple SJ, Duarte G, Palaiodimos L, Kalaitzopoulos DR, Dalamaga M, Kokkinidis DG. Cardiometabolic effects of SGLT2 inhibitors on polycystic ovary syndrome. Diabetes Metab Res Rev 2023;39(6):e3682. https://doi.org/10.1002/dmrr.3682.
[72] Kounatidis D, Vallianou NG, Stratigou T, Voukali M, Karampela I, Dalamaga M. The kidney in obesity: current evidence, perspectives and controversies. Curr Obes Rep 2024. https://doi.org/10.1007/s13679-024-00583-y.
[73] Vallianou NG, Christodoulatos GS, Kounatidis D, Dalamaga M. Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor: in the heart of the problem. Metabol Open 2021;10:100089. https://doi.org/10.1016/j.metop.2021.100089.