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CASE REPORT

Unusual phenotypes of diabetic nephropathy: A case report

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Abstract

Background The prevalence and incidence of diabetes mellitus (DM) are rapidly increasing worldwide. Diabetic kidney disease (DKD) is a chronic complication of DM and major cause of end-stage renal disease. The pathogenesis of DKD is complex, with various clinical features, pathological phenotypes, and poor therapeutic outcomes. DKD rarely occurs in patients without a history or evidence of DM. We herein report a case of diabetic nephropathy (DN) diagnosed using a renal biopsy in a patient with impaired glucose tolerance (IGT). Initially, DKD was considered to start with proteinuria preceding renal dysfunction, although in recent decades, many patients with DM without proteinuria develop renal insufficiency. Here, we also present a case of DN with normoalbuminuric renal insufficiency.

Case presentation We report a case of a 73-year-old man with no history of DM who presented with proteinuria, and a renal biopsy revealed mesangial proliferative glomerulopathy with mild acute tubular injury. Glucose metabolism was examined, and a 75 g oral glucose tolerance test showed IGT. Fundus examination revealed diabetic retinopathy. We also report a case of a 57-year-old man with DM with normoalbuminuric renal insufficiency, whose renal biopsy revealed renal tubulointerstitial damage but only mild glomerular injury.

Conclusion This study represents two cases of DKD with unusual presentations and highlights the role of renal tubular injury in the development of DKD. In patients without a history of clinically overt DM or proteinuria, DKD may still be considered. Thus, these cases may help clinicians to better understand DKD.

Keywords Impaired glucose tolerance · Diabetic nephropathy · Diabetic kidney disease · Normoalbuminuric diabetic kidney disease · Proteinuric diabetic nephropathy

Background

Diabetic kidney disease (DKD), the most common microvascular complication of diabetes mellitus (DM), has heterogeneous clinical characteristics, histopathology, and progression rates. Proteinuric DKD is characterized by sequential glomerular hyperfiltration, microalbuminuria, overt proteinuria, and eventually progressive renal function decline. However, a distinct group of patients present with renal insufficiency and vascular complications without proteinuria, known as normoalbuminuric diabetic kidney disease (NADKD), characterized by tubulointerstitial injury and fibrosis. In recent decades, studies have highlighted the role of renal tubular injury in DKD progression, by which kidney function decline may appear independently of proteinuria. Additionally, DKD can occur independently to clinical DM.

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Case report

Case 1

A 73-year-old man was admitted to our facility with lower extremity edema for 1 month. He had a history of hypertension with bad control for more than 1 year, with a blood pressure of up to 190/110 mmHg and use of oral sustained-release nifedipine tablets combined with telmisartan. He had no history of kidney disease and denied the use of nonsteroidal anti-inflammatory drugs (NSAIDs). The patient had no personal or family history of DM and no smoking history. On admission, his blood pressure was 186/103 mmHg and his body mass index was 21 kg/m^2. Laboratory test results revealed hemoglobin, 122 g/L; albumin, 30.5 g/L; serum creatinine, 101.9 μmol/L (reference range, 53–111 μmol/L); and serum uric acid, 459 μmol/L. The blood lipid results revealed normal levels of plasma triglycerides (1.15 mmol/L), total cholesterol (5.15 mmol/L), and LDL cholesterol (2.98 mmol/L). The anti-PLA-2R antibody test was negative (< 2 RU/mL). Thyroid function, IgA, IgG, IgM, C3, and C4 levels were normal. Tests for anti-sm, anti-JO-1, anti-dsDNA, antineutrophil cytoplasmic autoantibody (ANCA), and anti-glomerular basement membrane (GBM) antibodies were negative. Urinalysis revealed urine specific gravity of 1.011, urine occult blood (−), urine protein (2+), urine glucose (−), centrifugal urine erythrocyte 0–1 /HP, urinary Bence Jones protein (−), urinary microalbumin 1272.8 mg/L (0–30), urinary beta2-microglobulin 3.55 mg/L (0–0.24), urinary alpha1-microglobulin 65.86 mg/L (0–18), urinary transferrin 89.90 mg/L (0–2), urinary IgG 208.13 mg/L (0–10), urinary total protein 1650.38 mg/L (0–150), urine creatinine 4876.2 umol/L, urine albumin/creatinine ratio (UACR) 2309.9 mg/g (0–30), and 24 h urine protein 2315 mg. Cardiac color Doppler ultrasound revealed a normal left ventricular ejection fraction of 60%, normal ventricular wall thickness, and mild regurgitation of mitral, tricuspid, and aortic valves. Ultrasonography revealed normal-sized kidneys with multiple cystic echoes in the left kidney and increasing intrarenal arterial resistance index. The left kidney was 99 × 56 × 47 mm, and the right kidney was 97 × 47 × 44 mm.

A renal biopsy was performed. Light microscopy specimen revealed 18 glomeruli, glomerulomegaly with increased cross-sectional area and volume of glomeruli (Fig. 1A), two of which were globally and one segmentally sclerotic, and the remaining were hypertrophied with moderate mesangial cell proliferation, mesangial matrix hyperplasia (Fig. 1B, C), and GBM thickening (Fig. 1C). Some capillary tubes were narrow, some capillary loops showed hemangiomatous dilation, and mesangiolysis was observed (Fig. 1B). Tubular epithelial cells showed granular and vacuolar degenerations. Tubular dilatation, epithelial cell sloughing, interstitial edema, protein casts (Fig. 1A), and focal infiltration of lymphocytes and monocytes were observed. Arteriole walls were thickened with hyalinosis and intimal hyperplasia (Fig. 1C, D), leading to lumen stenosis. Immunofluorescence staining revealed 1 + granular staining for IgM in the segmental mesangium (Fig. 1E). Negative deposits of IgG, IgA, C3, C1q, PLA2R, and light-chain proteins were also observed. Electron microscopy showed that the GBMs were homogeneously thickened (350–700 nm), and the podocyte foot processes were extensively effaced. Mesangial low-electron-dense deposits were occasionally observed, and the

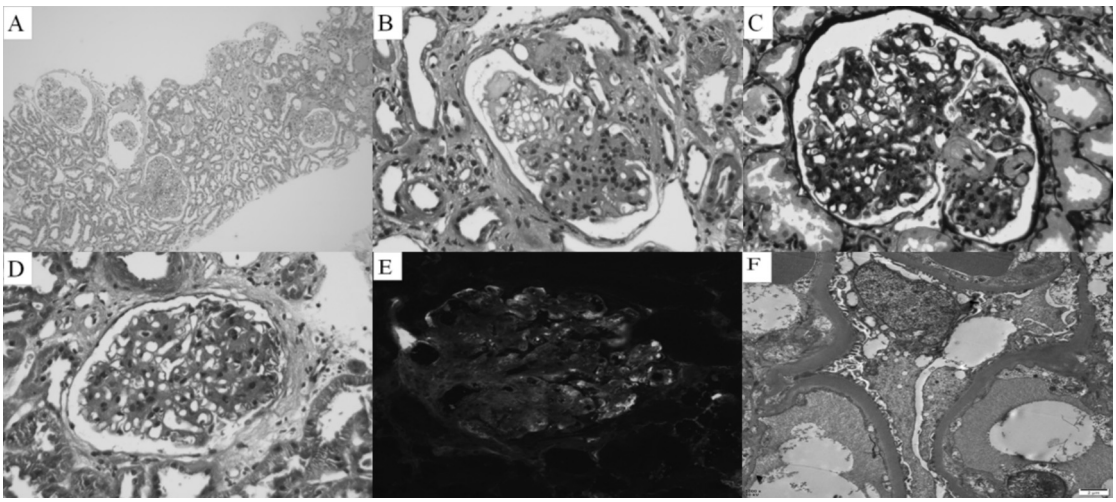

Fig. 1 The renal biopsy specimen in case 1. **A** Hematoxylin–eosin staining × 100. **B** Periodic Acid–Schiff staining × 400. **C** Periodic acid silver methenamine stain × 400. **D** Masson's Trichrome staining × 400. **E** Immunofluorescent staining × 400. **F** Electron microscopy × 5000

mesangial cells and matrix proliferated in the mesangium. The renal tubular epithelial cells showed vacuolar degeneration. There were no special lesions in the renal interstitium (Fig. 1F).

The renal biopsy findings revealed diabetic-like lesions. Therefore, we re-evaluated his glucose metabolism, the hemoglobin A1c level was 5.4%, and the fasting plasma glucose level from the fingertip was normal with a 2-h value of 8.9–10.3 mmol/L. Anti-islet cell, insulin, and anti-glutamic acid decarboxylase antibodies were all negative. An oral glucose tolerance test (OGTT) with 75 g glucose revealed impaired glucose tolerance (IGT) with fasting and 2-h glucose levels of 4.75 mmol/L (3.9–6.1) and 9.92 mmol/L (3.9–7.8), respectively. Insulin release test showed fasting and 2-h insulin levels of 3.99 μU/mL (1.1–17) and 75.34 μU/mL (9–53), respectively. C-peptide levels were 1.4700 ng/mL (0.69–2.45) at fasting and 12.090 ng/mL (2.7–10.5) at 2 h. IGT was diagnosed. "Cotton wool spots" were visible in the retina during ophthalmoscopy. Diabetic nephropathy (DN) was eventually considered. Telmisartan 40 mg qd was administered. Unfortunately, the patient was lost to follow-up after discharge.

Case 2

A 57-year-old man had elevated serum creatinine for 3 months and a history of DM exceeding 6 years. He received insulin to lower his blood glucose, but did not regularly monitor his blood glucose. He had hypertension for 1 year, with blood pressure reaching 140/90 mmHg. He denied NSAID usage. Upon admission, laboratory tests showed hemoglobin of 78 g/L, serum albumin 45.9 g/L, serum creatinine 236.8 μmol/L, glycosylated hemoglobin A1c 5.6%, parathyroid hormone 77.4 pg/mL, and C3 0.47 g/L. Ig A, IgG, and IgM levels were normal. Anti-GBM antibody and ANCAs were negative. Urinalysis revealed urinary protein (−), occult blood (−), urinary microalbumin 11.9 mg/L (0–30), urinary beta2-microglobulin 0.15 mg/L (0–0.24), urinary alpha1-microglobulin 39.40 mg/L (0–18), UACR 9.4 mg/g (0–30), and urinary protein 126 mg/24 h. Urinary ultrasonography revealed normal-sized kidneys with normal echogenicity. Fundus examination showed patchy hemorrhages and cotton wool exudates.

Renal biopsy was performed, and light microscopy revealed the biopsy specimen contained 13 glomeruli; 6 were global sclerosis, and others presented mild mesangial cell and matrix increase and GBM thickening (Fig. 2B, C). Renal tubular interstitial changes showed vacuolar and granular degeneration of renal tubular epithelial cells, epithelial cell sloughing (Fig. 2A), protein casts, tubular lumen dilatation, tubular brush border shedding, and tubular atrophy (approximately 60%). Arteriolar hyalinosis, arterial wall thickening, intimal fibrosis and intimal mucoid edema, and stenosis, or even occlusion, of the lumen were seen (Fig. 2B). Immunofluorescence showed linear (1 +) deposition of IgG along glomerular capillary loops (Fig. 2E). Electron microscopy revealed capillary endothelial cell vacuoles degeneration, homogeneous GBM thickening (400–750 nm), and extensive podocyte foot process fusion (Fig. 2F). No electron-dense deposits were observed in mesangial regions. Mild mesangial proliferative DN and ischemic kidney injury were diagnosed. On discharge, he was prescribed telmisartan, ferrous succinate, and erythropoietin. Serum creatinine was 180.6 μmol/L and hemoglobin 104 g/L at 10 days post-discharge. After 2 months, serum creatinine was 181.3 μmol/L and proteinuria 134 mg/24 h.

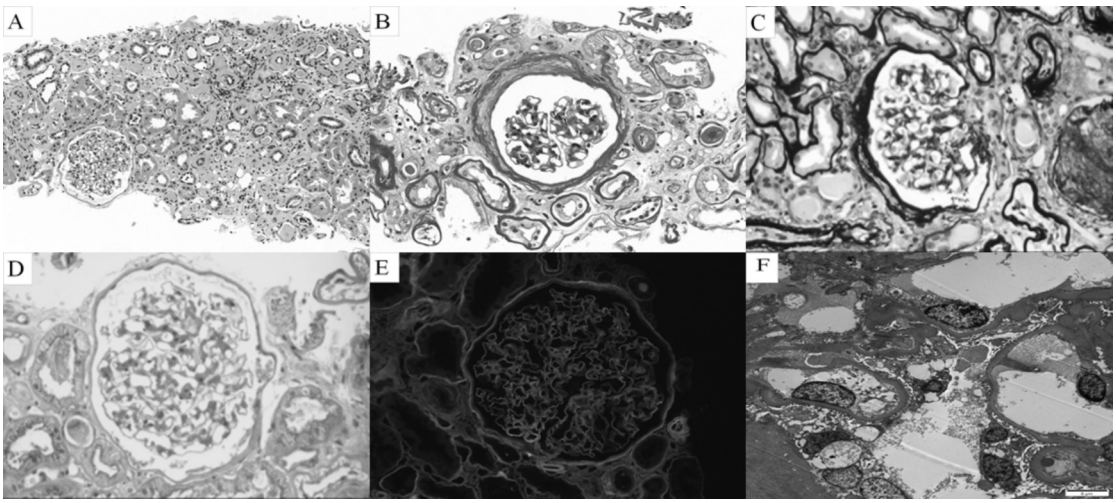

Fig. 2 The renal biopsy specimen in case 2. **A** Hematoxylin–eosin staining × 100. **B** Periodic Acid–Schiff staining × 200. **C** Periodic acid silver methenamine stain × 400. **D** Masson's Trichrome staining × 400. **E** Immunofluorescent staining × 400. **F** Electron microscopy × 3000

Discussion

The criteria and timing of a kidney biopsy remain controversial and lack consensus in DM patients. DN is a histologic diagnostic term confirmed by renal biopsy, and DKD is a broader diagnostic term, covering both histological diagnosis and clinical diagnosis. Initially, increased urinary albumin excretion was considered to be the first clinical event of DKD. In 1992, Lane et al. first described DM patients who experienced a progressive decline in renal function without albuminuria [1]. Over recent decades, growing evidence suggests that a portion of DM patients have renal insufficiency without clinically significant proteinuria. This phenotype, known as NADKD, was defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 with UACR < 300 mg/g and was characterized by mesangial expansion, tubulointerstitial damage, and vascular lesions but mild typical glomerular lesions [2, 3]. Epidemiological data have demonstrated that the prevalence of NADKD ranges from 14 to 57% [4], varying by region and study, and is likely to increase in the future. This phenotype may become the predominant form of kidney damage in patients with type 2 diabetes. However, the normoalbuminuric phenotype may be overlooked in clinical work. Therefore, the latest diagnostic criteria for DKD include decreased eGFR or persistent presence of elevated albuminuria [5]. The pathology, clinical features, and prognosis of patients with DKD without proteinuria differ from those with proteinuria. Patients without proteinuria typically have lower eGFR decline and lower risk of adverse renal prognosis than those with proteinuria [2]. In case 2, pathological changes were mainly tubulointerstitial injury and vascular lesions, with minor glomerular lesions. Hypertension may also be involved in kidney damage progression.

Growing clinical studies have indicated that microangiopathy is unusual in NADKD patients compared to macroangiopathy. The incidence of diabetic retinopathy (DR) in patients with DKD varies by region and race. Overall, the patients with type 2 diabetes have a much lower prevalence of DR than those with type 1 diabetes, DR is less frequent in the normoalbuminuric than in the albuminuric phenotype [3]. Based on a multicenter study of 15,773 patients with type 2 diabetes, 1673 (10.61%) had NADKD. Of these individuals, 1280 (76.51%) had absent DR, 218 (13.03%) had non-proliferative DR, and 175 (10.46%) had proliferative DR. Whereas, of 1286 patients with albuminuric DKD, 539 (41.91%) had DR [6], thus indicating that the normoalbuminuric phenotype correlated less strongly with DR than the albuminuric one. Similarly, another study also showed that DM patients with normoalbuminuria had a lower prevalence of DR than those with proteinuria (28% vs 45%) [7]. Studies have shown that patients with normoalbuminuria more frequently experienced coronary heart disease than those with proteinuria (47.1% vs 29.5%) [8]. This indicates that renal insufficiency in NADKD is closely related to macroangiopathy instead of microangiopathy. Literature studies have shown that the pathogenic mechanisms of renal insufficiency in NADKD may involve macrovascular disease, metabolic syndrome, arteriosclerosis, obesity, aging, smoking, hypertension, female sex, lipid toxicity, inflammation, and use of renin–angiotensin–aldosterone system inhibitors, instead of hyperglycemia or microangiopathy [4]. Therefore, when these risk factors are present in DM patients, the possibility of developing NADKD should be considered. Further studies on vascular lesions have shown that intrarenal arteriosclerosis was the main cause of decreased kidney function, without affecting urinary albumin excretion [8]. The literature suggests that noninvasive biomarkers can identify decreased eGFR and tubular injury, and the levels of neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, cystatin C, monocyte chemoattractant protein-1, and retinol-binding protein were increased in NADKD [4, 9]. However, whether they can help identify NADKD needs to be further validated and evaluated in more studies.

The pathogenesis of renal injury due to IGT is complex and only partially understood. Patients usually exhibit hyperinsulinemia after glucose loading and insulin resistance. Studies show that high levels of insulin can activate Mir-7977/SIRT3 signal transduction, lead to renal tubule damage by inducing oxidative stress, and lead to reabsorption dysfunction by inhibition of cubilin expression [10]. Therefore, renal damage caused by hyperglycemia already appears in IGT. Nephropathy in IGT is characterized by impaired renal tubule reabsorption. Studies show that albuminuria occurs due to proximal renal tubular damage with associated albumin malabsorption, rather than damage to the glomerular filtration membrane. The glomerular filtration membrane can be almost normal in IGT [11]. Impaired glucose metabolism (IGM) may underlie DN development without DM, with hypertension, obesity, and tobacco use accelerating its progression [12].

DKD can occur in patients without diabetes, but it is rare. Nodular glomerulosclerosis, first used to describe DN, was considered a typical pathological feature of DN. In 1962, Ellenberg reported a case of DN without obvious DM [13]. Subsequent reports presented nodular glomerulosclerosis lesions with DM later diagnosed. The category involves patients with IGM, who may have impaired fasting glucose or IGT. Most (> 90%) DN cases without diabetes are nodular glomerulosclerosis (corresponding to Class III DN); a few cases are diffuse mesangial sclerosis (Class IIa and IIb of DN) [12]. Our patient in case 1 denied a DM history;

however, a renal biopsy revealed mesangial proliferative glomerulopathy, showing GBM thickening, arteriolar hyalinosis, and mesangial expansion. Efferent arteriole hyalinosis is more specific than afferent arteriole for DN, yet neither afferent nor efferent arterioles were well distinguished because of the specimen section angle. Main pathological changes were similar to DN, the OGTT result met the diagnostic criteria of IGT, and fundoscopy revealed DR; hence, Class IIb DN was diagnosed. Metabolic syndrome involves IGM, arterial hypertension, and obesity. Obesity-related kidney injury is characterized by glomerular enlargement, mesangial matrix expansion, and podocyte depletion [14], and the histological appearance of diabetes-related and obesity-related renal disease is similar. In Case 1, the patient's BMI was 21 kg/m^2, which did not meet the diagnostic criteria for obesity; hence, obesity-associated renal injury can be ruled out. Hypertensive nephropathy is a clinical diagnostic term characterized by left ventricular hypertrophy, hypertensive retinopathy, microproteinuria, and decreased renal function, and its pathological features are arteriolar wall hypertrophy, afferent arteriole hyalinosis, lumen stenosis, ischemic or hypertrophic glomerulopathy, and eventually tubulointerstitial scarring. Despite the absence of left ventricular hypertrophy, the patient in Case 1 had poorly controlled hypertension, and tubulointerstitial lesions lacked specificity, so the possibility of hypertensive renal injury cannot be ruled out. Hypertensive kidney disease superimposed upon DKD, as well as age-related kidney senescence, accelerated the progression of chronic kidney disease. IgA nephropathy could be excluded by immunofluorescence staining without IgA deposition. The GBM was thickened, but the absence of electron-dense deposits in the GBM and no positive expression of IgG by immunofluorescence indicated that membranous nephropathy could be excluded. Ig light chain isotype restriction was not observed by immunofluorescence staining; hence, we excluded monoclonal immunoglobulin deposition disease.

Elevated levels of pro-brain natriuretic peptide (BNP) may be associated with heart failure (HF) in patients with hypertension, and the value of BNP tests helps rule out HF, but we ignored it. Due to normal left ventricular systolic function and no chest distress, we inferred that pro-BNP levels in Case 1 were probably normal. Moreover, BNP testing may guide best treatment practices, such as angiotensin receptor neprilysin inhibitor therapy. Postprandial plasma glucose levels in case 1 were slightly elevated, but due to normal hemoglobin A1c level and the risk of hypoglycemia in older adults, no hypoglycemia medication was administered. In Case 1, we prescribed an angiotensin receptor blocker (ARB) to reduce proteinuria by lowering glomerular hypertension. Unfortunately, follow-up data after discharge are missing, including further glucose monitoring, urinary protein, and serum creatinine. The second OGTT was not performed. The patient in case 2 was also treated with ARB and showed some renal function recovery.

A continuous glucose monitoring system (CGMS) can provide detailed blood glucose parameters, including time in range (TIR), which is a novel indicator for blood glucose metabolic control. A CGMS may be more appropriate for pre-diabetics and diabetics with nephropathy due to poor TIR. Moreover, the use of a CGMS may help in the diagnosis of hidden DM. However, it is not widely available in our facility, and we plan to gradually implement it in the future.

Conclusions

In conclusion, DKD may occur in people without overt DM and should be noted in those without proteinuria. Tubular injury plays an important role in DKD pathogenesis, renal biopsies should be proactively performed if no contraindications exist for renal puncture, and glucose metabolism and fundus should be examined to specify an appropriate diagnosis and treatment schedule.

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Author contribution WXT, LLN, WJC, WLY, and LXW analyzed and interpreted the patient clinical data. LLN performed pathological analysis and interpretation. WXT drafted and wrote the manuscript. LSH reviewed the manuscript. All authors contributed to the writing process and read and approved the final manuscript.

Data availability All data are included in the manuscript.

Declarations

Ethics approval and consent to participate This case report was approved by the ethics committee of Harrison International Peace Hospital.

Consent for publication The patients provided written informed consent for the publication of this case report.

Competing interests The authors declare no competing interests.

References

1. Lane PH, Steffes MW, Mauer SM. Glomerular structure in IDDM women with low glomerular filtration rate and normal urinary albumin excretion. Diabetes. 1992;41(5):581–6. https://doi.org/10.2337/diab.41.5.581.
2. Chang DY, Li MR, Yu XJ, Wang SX, Chen M, Zhao MH. Clinical and pathological characteristics of patients with nonproteinuric diabetic nephropathy. Front Endocrinol (Lausanne). 2021;12:761386. https://doi.org/10.3389/fendo.2021.761386.
3. Porrini E, Ruggenenti P, Mogensen CE, Barlovic DP, Praga M, Cruzado JM, Hojs R, Abbate M, de Vries AP. Non-proteinuric pathways in loss of renal function in patients with type 2 diabetes.

Lancet Diabetes Endocrinol. 2015;3(5):382–91. https://doi.org/10.1016/S2213-8587(15)00094-7.
4. Deng L, Li W, Xu G. Update on pathogenesis and diagnosis flow of normoalbuminuric diabetes with renal insufficiency. Eur J Med Res. 2021;26(1):144. https://doi.org/10.1186/s40001-021-00612-9.
5. American DA. Standards of medical care in diabetes-2019 abridged for primary care providers. Clin Diabetes. 2019;37(1):11–34. https://doi.org/10.2337/cd18-0105.
6. Penno G, Solini A, Zoppini G, Orsi E, Zerbini G, Trevisan R, Gruden G, Cavalot F, Laviola L, Morano S, et al. Rate and determinants of association between advanced retinopathy and chronic kidney disease in patients with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicenter study. Diabetes Care. 2012;35(11):2317–23. https://doi.org/10.2337/dc12-0628.
7. Kramer HJ, Nguyen QD, Curhan G, Hsu CY. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. JAMA. 2003;289(24):3273–7. https://doi.org/10.1001/jama.289.24.3273.
8. Chen C, Wang C, Hu C, Han Y, Zhao L, Zhu X, Xiao L, Sun L. Normoalbuminuric diabetic kidney disease. Front Med. 2017;11(3):310–8. https://doi.org/10.1007/s11684-017-0542-7.
9. An N, Wu BT, Yang YW, Huang ZH, Feng JF. Re-understanding and focusing on normoalbuminuric diabetic kidney disease. Front Endocrinol (Lausanne). 2022;13:1077929. https://doi.org/10.3389/fendo.2022.1077929.
10. Gao Z, Wang Z, Zhu H, Yuan X, Sun M, Wang J, Zuo M, Cui X, Han Y, Zhang Y, et al. Hyperinsulinemia contributes to impaired-glucose-tolerance-induced renal injury via mir-7977/SIRT3 signaling. Ther Adv Chronic Dis. 2020;11:2040622320916008. https://doi.org/10.1177/2040622320916008.
11. Dickson LE, Wagner MC, Sandoval RM, Molitoris BA. The proximal tubule and albuminuria: really! J Am Soc Nephrol. 2014;25(3):443–53. https://doi.org/10.1681/ASN.2013090950.
12. López-Revuelta K, Abreu AA, Gerrero-Márquez C, Stanescu RI, Marín MI, Fernández EP. Diabetic Nephropathy without Diabetes. J Clin Med. 2015;4(7):1403–27. https://doi.org/10.3390/jcm4071403.
13. Ellenberg M. Diabetic nephropathy without manifest diabetes. Diabetes. 1962;11:197–201.
14. Maric-Bilkan C. Obesity and diabetic kidney disease. Med Clin North Am. 2013;97(1):59–74. https://doi.org/10.1016/j.mcna.2012.10.010.