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1. Introduction

Diabetes mellitus (DM) is the most frequent cause of chronic kidney failure in both developed and developing countries [1]. Diabetic nephropathy, also known as Kimmelstiel-Wilson syndrome or nodular diabetic glomerulosclerosis or intercapillary glomerulonephritis, is a clinical syndrome characterized by albuminuria (>300 mg/day or >200 mcg/min) confirmed on at least two occasions 3-6 months apart, permanent and irreversible decrease in glomerular filtration rate (GFR) (Table 1), and arterial hypertension [2]. The syndrome was first described by a British physician Clifford Wilson (1906-1997) and American physician Paul Kimmelstiel (1900-1970) in 1936 [3].

| | Decline in glomerular filtration rate (ml/min/year) | |
|------------------|---|-----------|
| | Type 1 | Type 2 |
| Diabetes | | |
| Normoalbuminuria | 1,2 - 3,6 | 0,96 |
| Microalbuminuria | 1,2 - 3,6 | 2,4 |
| Proteinuria | 9,6 - 12 | 5,4 - 7,2 |

Table 1. Decline in glomerular filtration rate in various stages of type 1 and type 2 diabetes. Available: <http://emedicine.medscape.com/article/238946-overview>. Accessed 2012 May 14

Diabetic nephropathy is a chronic complication of both type 1 DM (beta cell destruction – absolute lack of insulin) and type 2 DM (insulin resistance and/or decreased secretion of insulin) [4]. There are five stages in the development of diabetic nephropathy.

Stage I: Hypertrophic hyper filtration. In this stage, GFR is either normal or increased. Stage I lasts approximately five years from the onset of the disease. The size of the kidneys is increased by approximately 20% and renal plasma flow is increased by 10%-15%, while albuminuria and blood pressure remain within the normal range.

Stage II: The quiet stage. This stage starts approximately two years after the onset of the disease and is characterized by kidney damage with basement membrane thickening and mesangial proliferation. There are still no clinical signs of the disease. GFR returns to normal values. Many patients remain in this stage until the end of their life.

Stage III: The microalbuminuria stage (albumin 30-300 mg/dU) or initial nephropathy. This is the first clinically detectable sign of glomerular damage. It usually occurs five to ten years after the onset of the disease. Blood pressure may be increased or normal. Approximately 40% of patients reach this stage.

Stage IV: Chronic kidney failure (CKF) is the irreversible stage. Proteinuria develops (albumin > 300 mg/dU), GFR decreases below 60 mL/min/1.73 m², and blood pressure increases above normal values.

Stage V: Terminal kidney failure (TKF) (GFR < 15 mL/min/1.73 m²). Approximately 50% of the patients with TKF require kidney replacement therapy (peritoneal dialysis, hemodialysis, kidney transplantation) [5].

In the initial stages of diabetic nephropathy, increased kidney size and changed Doppler indicators may be the early morphological signs of renal damage, while proteinuria and GFR are the best indicators of the degree of the damage [6].

2. Epidemiology

The prognostic value of a small amount of albumin in urine for the development of kidney damage in patients with type 1 or 2 DM was confirmed in the early 1980's. This stage of kidney damage was called the microalbuminuria stage or initial nephropathy [7]. Approximately 20-30% of the patients develop microalbuminuria after 15 years of disease duration and less than half develop renal nephropathy [8]. The European Diabetes (EURODIAB) Prospective Complications Study Group [9] and 18-year Danish study [10] showed that the overall occurrence of microalbuminuria in patients with type 1 and 2 DM is 12.6% (after 7.3 years) and 33%, respectively. According to the United Kingdom Prospective Diabetes Study (UKPDS), the annual incidence of microalbuminuria in patients with type 2 DM in Great Britain is 2% and the prevalence is 25% ten years after the diagnosis [2]. Proteinuria develops in approximately 15-40% patients with type 1 DM, usually after 15-20 years of DM duration [11]. In patients with type 2 DM, the prevalence varies between 5% and 20% on average [2]. Diabetic nephropathy is more frequent in African Americans, Asian Americans, and Native Americans [12]. In Caucasians, the progressive kidney disease is more frequent in patients with type 1 than type 2 DM, although its overall prevalence in the diabetic population is higher in patients with type 2 DM because this type of DM is more prevalent [13]. The occurrence of diabetic nephropathy in Pima Indians is very interesting, indeed. According to a study published in 1990, around 50% of Pima Indians with type 2 DM developed nephropathy after 20 years of the disease, and 15% of them were already in the terminal stage of kidney failure [14].

In the United States, the occurrence of diabetic nephropathy in patients beginning kidney replacement therapy doubled in the 1991-2001 period [12]. Fortunately, the trend has been decreasing, most likely due to the better prevention and earlier diagnosis and treatment of DM [15].

3. Pathology

Glomerular filtration barrier functions as a complex biological sieve. As opposed to other capillaries in the body, glomerular capillaries are highly permeable to water (hydraulic conductivity) and relatively impermeable to large molecules. Such permeability is possible because of the unique three-layer structure of glomerular filtration membrane consisting of endothelial glycocalyx, glomerular basement membrane, and podocytes (glomerular visceral epithelial cells). Pathological changes develop in the glomeruli of patients with long-duration DM before the appearance of microalbuminuria.

The severity of glomerular damage is proportional to GFR value, DM duration, and blood glucose regulation [16,17]. The main pathohistological changes in diabetic nephropathy include the thickening of the glomerular basement membrane (GBM), mesangial expansion, nodular sclerosis – Kimmelstiel-Wilson change, diffuse glomerular sclerosis, tubular interstitial fibrosis, and arteriosclerosis and hyalinosis of kidney blood vessels (Figures 1-3).

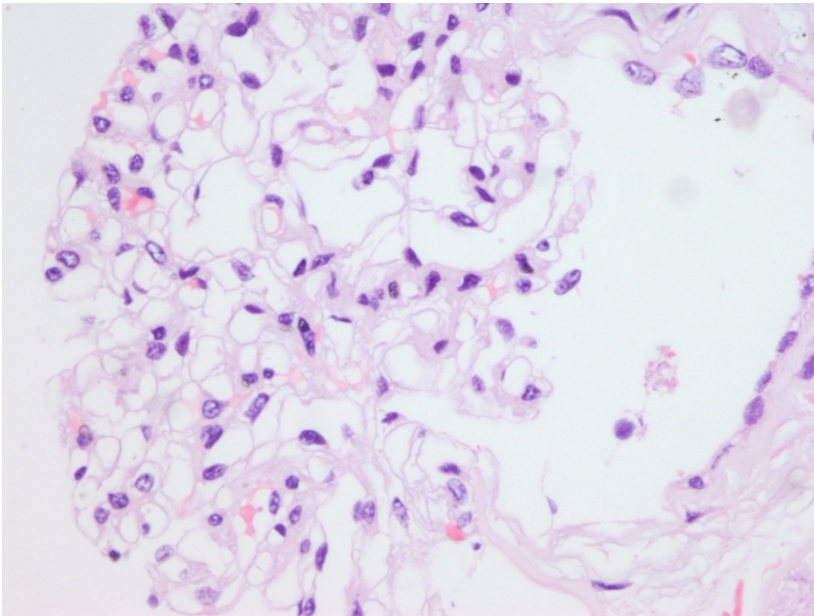


Figure 1. Photography shows delicate structure of normal glomerulus with thin glomerular basement membrane and unrecognizable mesangium. HE stain, X 400.

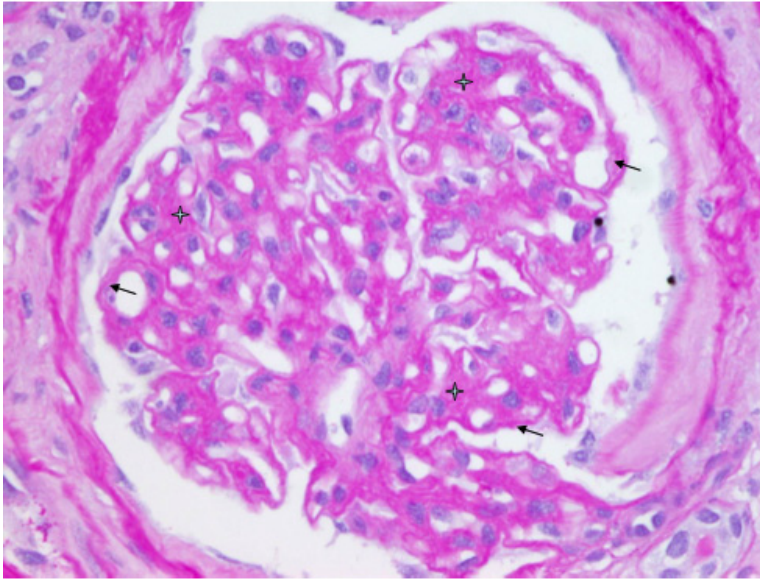


Figure 2. Class II b diabetic nephropathy. Diffuse expansion of mesangium (star) and diffuse thickening of the glomerular basement membrane (arrow). PAS stain, X400.

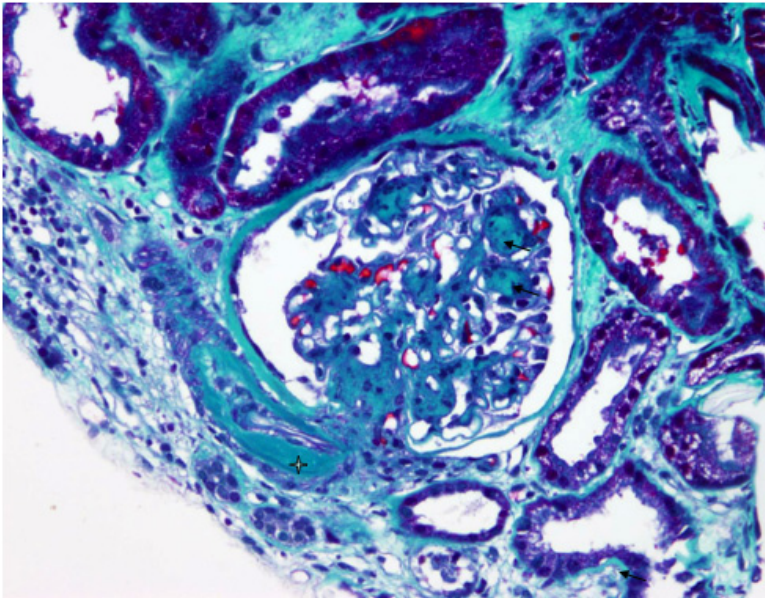


Figure 3. Class III diabetic nephropathy. Sclerotic nodule (Kimmelstiel–Wilson) in nodular diabetic nephropathy (arrow). Afferent and efferent arteriolar hyalinosis is characteristic for diabetic nephropathy (star). The arrow in the lower right corner indicates thickening of the tubular basement membrane. Mallory stain, X 100.

Among other pathological lesions, we should mention hyalinosis, the so-called fibrin cap, which consists of accumulated hyaline material between endothelial cells and glomerular basement membrane (Figure 4) [18]. Fibrin cap is present in approximately 60% of the cases and is believed to be associated with chronic ischemia [19].

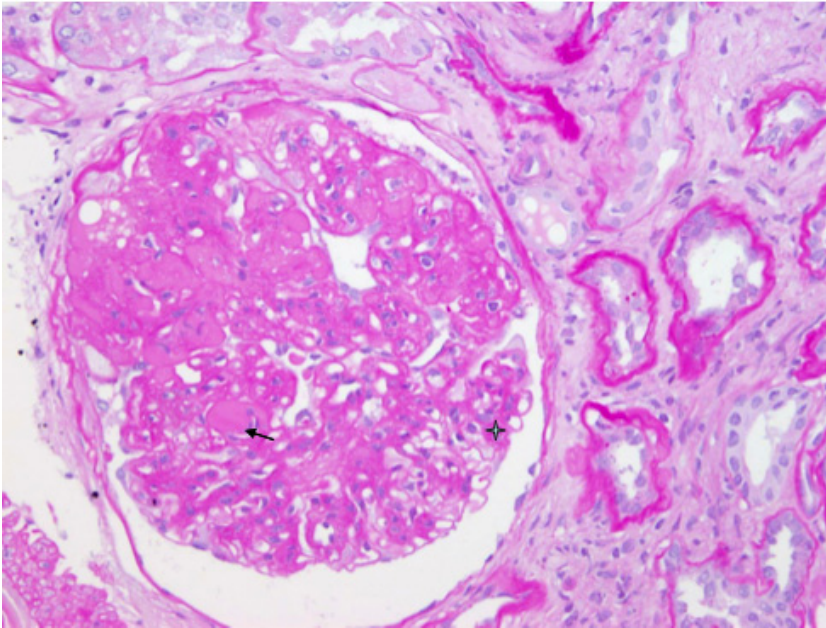


Figure 4. Fibrin cap (arrow) is characteristic for diabetic nephropathy. It is caused by insudation and accumulation of glycosylated plasma proteins between the glomerular endothelium and the glomerular basement membrane. Diffuse expansion of mesangium is designated by four point star. PAS stain, X 200.

There is a significant overlap between the described changes in patients in different stages of albuminuria, independent of their type of DM [16]. All histological patterns have identical prognostic significance (Figures 5,6). However, the fact that the expansion of mesangium and glomerular sclerosis do not occur simultaneously indicates their different pathogenesis within diabetic nephropathy [20]. Under light microscopy, the reduction in the podocyte number is easily noticed in patients with type 1 DM and 2 [21].

Since histological changes in both types of DM overlap to a great extent, the Scientific Committee of the Society for Pathological Anatomy established the Pathologic Classification of Diabetic Nephropathy, where diabetic nephropathy is histologically divided into four stages of glomerular damage (Table 2).

| Class | Description | Inclusion criteria |
|-------|---|---|
| I | Mild or nonspecific LM changes and EM-proven GBM thickening | Biopsy does not meet any of the criteria mentioned below for class II, III, or IV GBM 395 nm in female and 430 nm in male individuals 9 years of age and older ^a |
| II a | Mild mesangial expansion | Biopsy does not meet criteria for class III or IV Mild mesangial expansion in 25% of the observed mesangium |
| II b | Severe mesangial expansion | Biopsy does not meet criteria for class III or IV Severe mesangial expansion in 25% of the observed mesangium |
| III | Nodular sclerosis (Kimmelstiel – Wilson lesion) | Biopsy does not meet criteria for class IV At least one convincing Kimmelstiel –Wilson lesion |
| IV | Advanced diabetic glomerulosclerosis | Global glomerular sclerosis in 50% of Glomeruli Lesions from classes I through III |

Table 2. Four classes of glomerular lesions in diabetic nephropathy. Adapted from [22].

LM, light microscopy. EM, electronic microscopy. GBM, glomerular basement membrane.

^a On the basis of direct measurement of GBM width by EM, these individual cutoff levels may be considered indicative when other GBM measurements are used.

The same group of international experts established the histological scoring system for the changes in the interstitium and relevant blood vessels (Table 3) [22].

| Lesion | Criteria | Score |
|---------------------------------------|--|--------|
| Interstitial lesions | | |
| IFTA | No IFTA | 0 |
| | < 25% | 1 |
| | 25% - 50% | 2 |
| | > 50% | 3 |
| interstitial inflammation | Absent | 0 |
| | Infiltration only in relation to IFTA | 1 |
| | Infiltration in areas without IFTA | 2 |
| Vascular lesions | | |
| arteriolar hyalinosis | Absent | 0 |
| | At least one area of arteriolar hyalinosis | 1 |
| | More than one area of arteriolar hyalinosis | 2 |
| presence of large vessels | | Yes/No |
| arteriosclerosis (score worst artery) | No intimal thickening | 0 |
| | Intimal thickening less than thickness of media | 1 |
| | Intimal thickening greater than thickness of media | 2 |

Table 3. Interstitial and vascular lesions of diabetic nephropathy. Adapted from [22].

IFTA, interstitial fibrosis and tubular atrophy.

In addition to diabetic nephropathy, glomerular sclerosis can also develop in other pathological conditions in patients with DM. These are:

- a. dysproteinemia (amyloidosis and other deposit diseases)
- b. conditions with chronic ischemia (cyanotic congenital heart disease)
- c. chronic membranoproliferative glomerulonephritis
- d. Idiopathic diseases mostly associated with smoking and increased blood pressure [23].

It means that pathological findings in the urine of patients with DM (proteinuria and erythrocyturia) are not necessarily the result of diabetic nephropathy and should not be considered as such. This finding is a diagnostic challenge for a clinician as well as pathologist [24]. Therefore, in case of hematuria, more severe nephrotic syndrome, and/or rapidly advancing deterioration of renal function without concomitant diabetic nephropathy in patients with DM, we should consider an underlying non-diabetic kidney disease. Kidney biopsy with a complete analysis of the sample (light, immunofluorescent, and electron microscopy) represents the gold standard in the diagnostic workup of patients with non-diabetic renal disease. Always correlate the biopsy findings with the clinical history. If the patient is not diabetic, consider the diagnosis of idiopathic nodular glomerulosclerosis

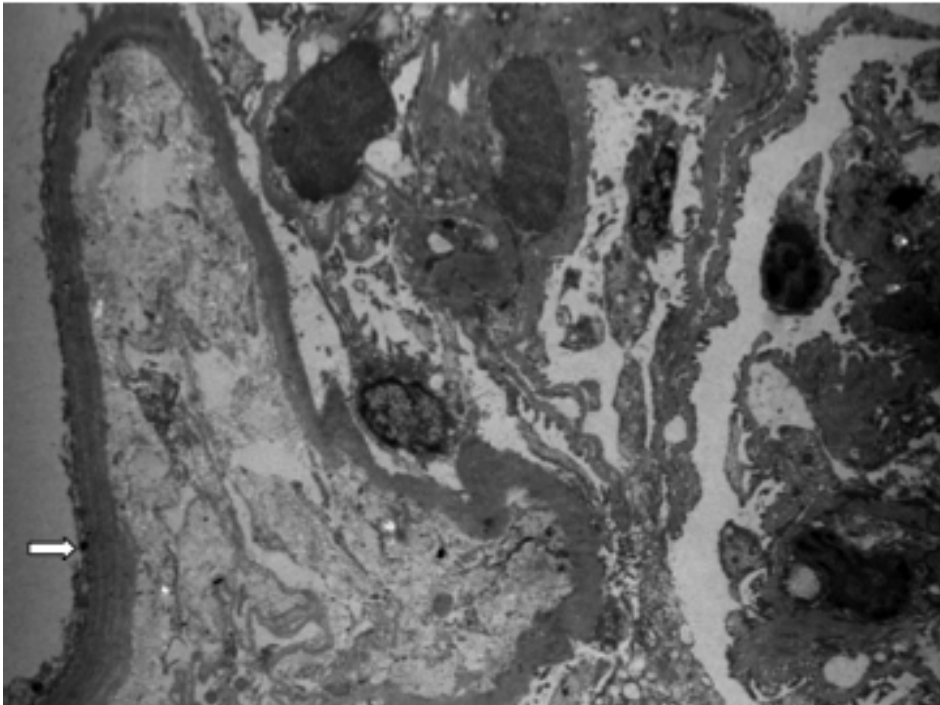


Figure 5. There was marked thickening, irregularity of the basement membrane of the capillary wall with lamellation (electron microscopy, arrow, 2.8 k)

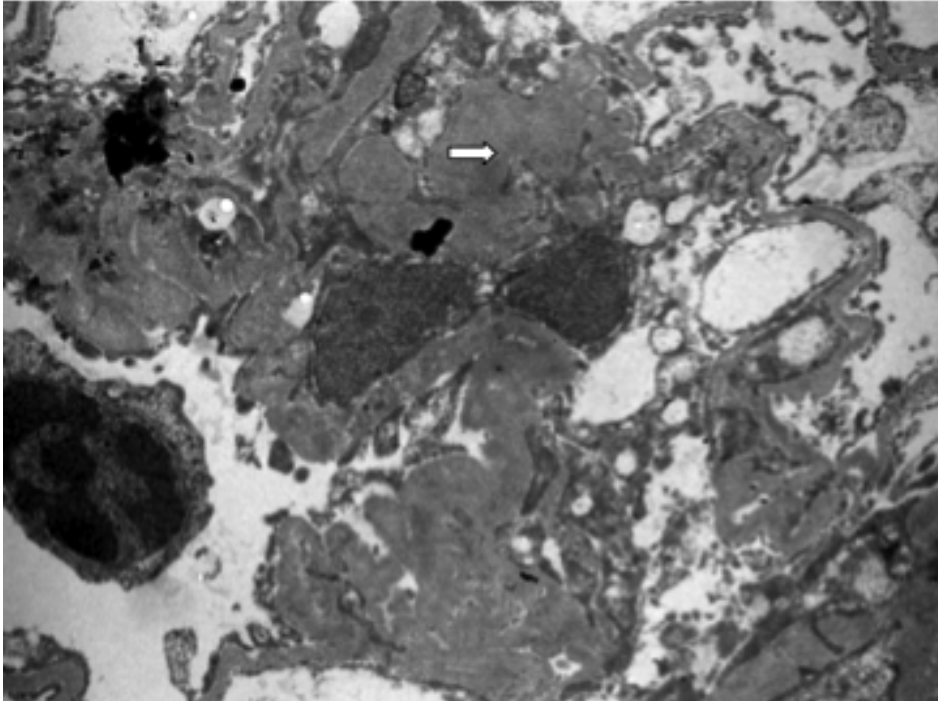


Figure 6. Mesangial regions are also expanded by excess mesangial matrix-like material (electron microscopy, arrow, 7.1 k)

If primary glomerular disease is found in a patient with DM, with or without diabetic nephropathy, the therapeutic approach changes as well as the course and outcome of the renal disease [25].

4. Pathogenesis

Pathogenesis of diabetic nephropathy is very complicated and results from the interaction of hemodynamic and metabolic factors.

Glomerular hyper filtration

Increased intraglomerular pressure and hyper filtration as early changes in the development of diabetic nephropathy were described by Stadler and Schmidt in 1959 [26]. In the 1970's, Mogensen emphasized that as many as 40% newly found DM cases had increased glomerular filtration [27].

Although the mechanism of development of hyper filtration is not completely understood, several factors have been found to play a role in its development.

Hormones

The role of hormones was experimentally demonstrated in the study by Serri et al, who showed that the infusion of somatostatin analogues (octreotide) partly led to the decrease in hyperfiltration and kidney size. In their study, glycemic regulation, plasma glucagon, and growth hormone levels remained unchanged, but the concentration of insulin-like growth factor-1 (IGF-1) decreased [28]. Pathogenetic role of IGF-1 has not been completely elucidated, but it is known that exogenous administration of his hormone in non-DM patients leads to afferent arteriolar dilation and GFR increase, which are the changes also observed in initial diabetic nephropathy [29]. The identical hemodynamic changes, along with the increase in kidney size, occur in experimental animal models after the infusion of IGF-1 [30]. Sex hormones may also influence hyperfiltration. Cherney et al. [31] observed a decrease in kidney blood flow and vascular resistance in response to hyperglycemia in women, but not in men. The same study showed that the addition of angiotensin-converting enzyme inhibitor (ACEI) resulted in a decrease in blood pressure in both men and women, but GFR decreased only in women [31].

Sorbitol

The enzyme aldose reductase converts intracellular glucose to sorbitol, which remains in the cell. Although research in patients with type 1 DM and known hyperfiltration has shown that the infusion of aldose reductase inhibitor (tolrestat) decreases GFR to normal values, a possible therapeutic use of this agent should be confirmed in more studies [32].

Increased sodium reabsorption and tubuloglomerular feedback

Increased renal tubular sodium reabsorption due to increased sodium-glucose co-transport leads to the increase in extracellular fluid volume, which then increases GFR [33]. In an experimental DM model, it was shown that hyperinsulinemia and mild hyperglycemia stimulate reabsorption of sodium in the proximal tubules, resulting in the decreased fluid flow to distal tubules, which then activates the so-called tubuloglomerular feedback mechanism in the macula densa [34]. This causes the afferent arteriole dilation and leads to an increase in the GFR. In this case, the renal hyper filtration response to the imbalance caused by increased sodium reabsorption in the proximal tubules consequently increases fluid retention. Although the role of glomerular hyperfiltration in the pathogenesis of diabetic nephropathy is unquestionable, it itself is not sufficient to cause kidney damage.

Poor control of metabolic factors

Glycation end-products

Part of the excess glucose in chronic hyperglycemia binds to free amino acids of circulating or tissue proteins. This non-enzymatic process produces reversible early glycation products, and later, irreversible advanced glycation end products (AGEs), which accumulate in the tissues and contribute to the development of microvascular complications of DM [35].

AGEs modulate the cell activation, signal transduction, and cytokine and growth factor expression through the activation of R-dependent and R-independent signal pathways. Bonding to their podocyte receptors, AGEs may induce expression of some factors considered to play the key role in the pathogenesis of diabetic nephropathy, such as transforming growth factor-beta (TGF-beta) and connective tissue growth factor (CTGF) [36]. In non-diabetic mice, the infusion of early products of glycation up to the concentration seen in diabetic mice increases the kidneys blood flow, GFR, and intraglomerular pressure, which are characteristic of untreated DM [37].

Hyperglycemia

The evidence from *in vitro* studies shows that hyperglycemia has a direct effect on mesangial cell proliferation, matrix expansion, and glycosylation of glomerular proteins [38,39].

Protein kinase C

The activation of protein kinase C (PKC) is one of the main mediators of hyperglycemia-induced tissue injury. PKC activation leads to increased vascular permeability, increased synthesis of extracellular matrix components, and increased production of reactive oxygen species (ROS), which are important mediators of kidney injury [40].

Heparanase Expression

The regulation of heparanase expression plays an important role in the pathogenesis of diabetic nephropathy. The reduction in heparin sulfate on the surface of endothelial cell changes the negative charge of glycocalyx and consequently increases albumin permeability of the glomerular filtration membrane [41].

Reactive Oxygen Species

Increasing evidence shows the importance of reactive oxygen species (ROS) in the pathogenesis of diabetic nephropathy. Although the ROS production may be influenced by numerous mechanisms, the most important role in their production is played by superoxide produced by glycolysis and oxidative phosphorylation in the mitochondria. ROS activate all important pathogenetic mechanisms, such as increased production of AGEs, increased glucose entry into the polyol pathway, and PKC activation [42]. In addition, ROS directly damage endothelial glycocalyx, which leads to albuminuria without the concurrent damage to the GBM itself.

Prorenin

Increased serum prorenin plays a role in the development of diabetic nephropathy in children and adolescents [43]. Prorenin binds to a specific tissue receptor, leading to the activation of the signal pathway of mitogen-activating protein kinases (MAPK), which potentiate the development of kidney damage [44]. Using an experimental model of diabetic nephropathy, Ichihara et al. [45] indicated a possible role of prorenin in the development of diabetic nephropathy. In their study, a prolonged prorenin receptor blockade cancelled the activation of MAPK, which prevented the development of diabetic nephropathy despite the increased activity of angiotensin II.

Cytokines and Growth Factors

Hyperglycemia stimulates increased expression of different growth factors and activation of cytokines, which overall contributes to further kidney damage [46,47].

In the kidney biopsy samples from patients with type 2 DM, a significant increase in platelet derived growth factor (PDGF) expression was found. Moreover, the site of expression of this factor is adjacent to the areas of interstitial fibrosis, which is important in the pathogenesis of fibrosis in kidney injury [48].

Hyperglycemia also increases the glomerular expression of TGF-beta; matrix proteins are specifically stimulated by this growth factor [49]. Furthermore, the expression of bone morphogenic protein 7 (BMP-7) in DM is decreased, and the expression of profibrogenic TGF-beta is increased [50,51].

Nephrine Expression

Nephrine is a transmembrane protein, the main structural element in *slit* diaphragm and as such, it is important for the maintenance of filtration membrane integrity. More recent studies have shown the association between the decreased expression of nephrine and albuminuria progression in the model of human diabetic nephropathy [52,53].

5. Risk factors

There are several risk factors for the development of diabetic nephropathy. They can be divided into those that cannot be altered (genetic factors, age, and race) and those that can and must be changed (hyperglycemia, hypertension, dyslipidemia, and GFR) [53].

Genetic Predisposition

Genetic predisposition substantially determines the occurrence and severity of diabetic nephropathy [18,40]. The likeliness of diabetic nephropathy is higher in siblings and children of parents with diabetic nephropathy, independently of the type of DM [54]. There is a 14% probability for a child of the parents without proteinuria to develop clinical proteinuria, 23% probabilities in cases where one of the parents has proteinuria, and 46% probability in case that both parents have proteinuria. This increased risk cannot be explained by the duration of DM, increased blood pressure or glycemic regulation. However, genetic predisposition for excessive salt intake and arterial hypertension could play a role. Although likeliness of chromosomes 3, 7, 18, and 20 to be associated with diabetic nephropathy is relatively high, we still cannot confirm the role of particular predisposing genetic determinants due to inconsistent results of the studies of genetic factors important in the development of this disease.

Race

The incidence of diabetic nephropathy is increased in African American, Mexican American, and Asian Indian ethnic groups. Occurrence and severity of the disease are higher in Blacks

(3- to 6-fold in comparison with Caucasians), American Mexicans, and especially in Pima Indians in the North West part of the United States [55]. This observation in genetically incongruent populations suggests that socioeconomic factors, such as nutrition and poor control of glycemia, blood pressure, and body weight, play the key role.

Age

In patients with type 2 DM, age and duration of DM increase the risk for albuminuria [53]. In the population study of 1586 Pima Indians with type 2 DM, subjects diagnosed with DM before age 20 had a higher risk of developing terminal kidney failure (25 vs. 5 patients in 1000 incident patients). According to Svensson et al. [56] the risk of terminal kidney failure in patients with type 1 DM was low if the disease was diagnosed by the age of 5.

Increased Blood Pressure

There is a high prevalence rate of hypertension in patients with type 1 DM (40%) and type 2 DM (70%), even before albuminuria can be found.

Evidence from several large clinical studies (UKPDS, ADVANCE) indicates a causal relationship between the increased arterial pressure and diabetic nephropathy [57]. Moreover, at least three factors have been shown to contribute to the development of increased arterial pressure in this metabolic disorder including hyperinsulinemia, excessive extracellular fluid volume, and increased arterial rigidity. Hyperinsulinemia contributes to the development of increased arterial pressure via insulin resistance in type 2 DM or via administration of insulin *per se*. Randeree et al. study in 80 patients with type 2 DM who started treatment with exogenous insulin showed an increase in their blood pressure from 132/81 mm Hg to 149/89 mm Hg [58]. This hypertensive response, although not reported in all clinical studies, is most likely mediated by weight gain combined with pro-hypertensive effect of insulin. Hyperinsulinemia could be the link between overweight and increased blood pressure in patients with or without DM, since it increases sympathetic activity and retention of sodium in the kidneys.

Sodium and water retention are induced by insulin itself, while the increased filtration of glucose is induced by hyperglycemia. The excess filtered glucose is reabsorbed (as long as there is a moderate hyperglycemia) in the proximal tubule via sodium-glucose co-transport, which concurrently leads to the increase in sodium reabsorption [59]. Sodium reabsorption increases blood pressure, which may be prevented and regulated by salt-free diet.

Patients with DM have increased arterial stiffness, which develops due to the increased glycation of proteins and consequent development of arteriosclerosis. Decreased arterial elasticity in patients with glucose intolerance or DM contributes to the increased systolic pressure as an independent mortality risk factor [60].

Glomerular Filtration Rate

Increased GFR at diagnosis is a risk factor for the development of diabetic nephropathy. In approximately half of the patients with type 1 DM lasting up to five years, GFR value is

approximately 25-50% above normal range. These patients have a higher risk of developing diabetic nephropathy [61].

Dynamics of structural and hemodynamic changes is influenced by increased intraglomerular pressure, with the resulting glomerular hyperfiltration and hypertrophy and damage to the endothelial wall. Strict glyceamic control, limited protein intake, and blood pressure control may slow down the progress of renal disease in type 1 DM [62]. The situation with type 2 DM is somewhat different. More than 45% of patients with type 2 DM at diagnosis have GFR that is two standard deviations higher than that in their age-matched no-DM or overweight controls [63]. Granted, the hyper filtration rate (117-133 mL/min on average) is lower than that in type 1 DM. Patients with type 2 DM are older and, therefore, have greater likelihood of developing atherosclerotic vascular changes that influence GFR and glomerular size [64]. The role of intraglomerular hypertension in the pathogenesis of diabetic nephropathy explains why systemic hypertension is such an important risk factor for the development of this kidney disease [65]. Studies on animal models showed that DM is associated with damage of renal autoregulation. As a result, increased blood pressure does not induce the expected vasoconstriction in the afferent arteriole, which would reduce the influence of systemic hypertension on intraglomerular pressure [66].

Glyceamic Regulation

Diabetic nephropathy often develops in patients with poor glyceamic control. The degree of glyceamic control is an important predictor of terminal kidney failure [67]. In Krolewski et al's [68] study, the prevalence of terminal kidney failure was 36% in patients with the worst glyceamic control in comparison with 9% in the group with well-controlled glycaemia.

It is generally accepted that the degree of glyceamic control is a very important risk factor for the development diabetic nephropathy.

Overweight

High body mass index (BMI) increases the risk of development of chronic kidney disease in patients with DM [53]. Furthermore, adequate diet and reduction in body weight decrease proteinuria and improve kidney function in these patients [69]. The role of overweight as a risk factor for diabetic nephropathy (independent of DM and glyceamic control) has not been clearly confirmed.

Smoking

Although recent studies have shown the association between smoking and progression of diabetic nephropathy, a large prospective study by Hovind et al. [70] did not confirm the association between smoking and decreased GFR rate in patients with DM with or without ACEI therapy.

Oral Contraception

Ahmed et al. [71] showed the association between the use of oral contraceptives and development of diabetic nephropathy.

Each of the above-described factors increases the risk of diabetic nephropathy, but none is predictive enough for the development of diabetic nephropathy in an individual patient.

6. Association between diabetic nephropathy and retinopathy

Patients with type 1 DM and nephropathy almost always have other complications related to the underlying disease, such as retinopathy and neuropathy [9]. Retinopathy has easily recognizable clinical manifestations and always precedes the clinically manifest signs of nephropathy in the same patient. The vice versa is not the case. A small number of patients with advanced retinopathy have glomerular histological changes and microalbuminuria, but most have no biopsy evidence of kidney disease [72]. The association between diabetic nephropathy and retinopathy is weaker in patients with type 2 DM. In a study carried out by Parving et al. [73] in 35 patients with type 2 DM and proteinuria (> 300 mg/day), 27 of these patients had biopsy evidence of nephropathy. Diabetic retinopathy was present in 15 of these 27 patients and in none of the eight patients without diabetic nephropathy. Further analysis showed that approximately one-third of patients without retinopathy had no biopsy evidence of diabetic nephropathy [74].

Thus, patients with type 2 DM and significant proteinuria and retinopathy were most likely to develop diabetic nephropathy, whereas those with proteinuria but without retinopathy had a greater likelihood of having an underlying non-diabetic kidney disease [75]. In the study by Schwartz et al, biopsy was performed in 36 patients with type 2 DM and nephropathy. In 17 of them, biopsy showed visible glomerulosclerosis with Kimmelstiel-Wilson nodules, whereas in the remaining 15 patients, biopsy showed changes characteristic of diabetic nephropathy (mesangial sclerosis), but with no classical nodules present. There was no difference in the duration of disease and glycemic regulation between patients with and those without nodules. A strong association was found between severe retinopathy and presence of Kimmelstiel-Wilson nodules. The reason is still unknown [76].

According to the K/DOQI 2007 Guidelines, etiology of kidney disease in most patients with DM should be ascribed to DM if pathologic proteinuria and retinopathy are present [77]. In case that no retinopathy is present, non-diabetic causes of kidney disease should be investigated.

7. Biomarkers of diabetic nephropathy

Albuminuria remains the only biomarker acceptable for diagnostic purposes, although some growth factors are expected to replace albuminuria in future. It is known that values of TGF beta, vascular endothelial growth factor (VEGF), and CTGF are increased in the plasma and urine of patients with diabetic nephropathy [78-80].

8. Non-diabetic kidney disease

Proteinuria is sometimes present in DM because of the primary glomerular disease rather than diabetic nephropathy. In that case, possible causes of kidney damage may include

membrane nephropathy, minimal change disease, IgA nephropathy, focal glomerulosclerosis, Henoch-Schönlein purpura, proliferative glomerulonephritis, and so on. The main clinical signs of primary glomerular disease are as follows:

- a. Proteinuria, which started in the first five years after the diagnosis of type 1 DM. Latent nephropathy, is present between 10 and 15 years after the onset of type 1 DM. This period is probably the same in type 2 DM, but the exact time of the onset of the disease is difficult to determine.
- b. Acute onset of kidney disease. Diabetic nephropathy is a slowly developing disease.
- c. The presence of erythrocytes (mostly acanthocytes) and rouleaux formations in urine sediment. Patients with microscopic hematuria may have a benign familial hematuria, which is present in approximately 9% of population with or without diabetic nephropathy [81]
- d. The absence of diabetic retinopathy or neuropathy in patients with type 1 DM. As opposed to that, the absence of retinopathy in patients with type 2 DM does not exclude the presence of diabetic retinopathy.
- e. Signs and/or symptoms of other systemic disease.
- f. A significant decrease in GFR (>30%) within two to three months after the introduction of ACEI or angiotensin II receptor blockers (ARB) therapy.

Nephrosclerosis

Proteinuria and kidney failure in patients with DM may also be caused by other diseases apart from primary glomerular diseases. The most frequent cause is atherosclerotic vascular disease (nephrosclerosis) in older patients with type 2 DM [82]. This disease cannot be clinically discerned from diabetic nephropathy without kidney biopsy. However, kidney biopsy is not necessary in most cases, because the correct diagnosis in this patient group is not clinically important. What speaks in favor of nephrosclerosis is the significant increase in serum creatinine after the introduction of ACEI or ARB for the treatment of hypertension or slowing down the progress of chronic kidney disease. The same occurs when there is a bilateral renal artery stenosis.

9. Treatment

Strict Glycemic Control

The effect of strict glycemic control depends on the DM stage in which it was started and consequent normalization of glucose metabolism. Intensified insulin therapy has the following effects on the kidney:

- a. It partly decreases glomerular hypertrophy and hyperfiltration (in fasting state and after protein-rich meal), both of which are important risk factors for permanent glomerular damage.
- b. It postpones the development of albuminuria [83]. Intensified insulin therapy that keeps glucose values within normal ranges decreases the development or progress of diabetic nephropathy.

- c. It stabilizes or decreases the elimination of proteins in patients with pronounced proteinuria. This effect is not apparent in patients who are not relatively normoglycemic during two years. Furthermore, re-established normoglycemia after combined kidney and pancreas transplantation in patients with type 1 DM has preventive effects on recurrence of nephropathy in kidney transplant [84].
- d. It slows down the progress of kidney disease in case of already developed proteinuria confirmed by semiquantitative method (test strip).
- e. It reduces mesangial cell number and mesangial matrix.
- f. In some patients, the thickness of glomerular and tubular basement membranes and mesangial cell number become normal and glomerular nodules disappear.
- g. The progress of tubular atrophy is slowed down.

Strict Blood Pressure Control

Strict blood pressure control is important in the prevention of progress of diabetic nephropathy and other complications in patients with type 2 DM. The optimum lower range of systolic blood pressure is not clearly defined. According to the UKPDS study, a reduction in systolic blood pressure by 10 mm Hg decreases the risk of development of diabetic complications by 12%; the risk is the lowest where systolic blood pressure values are below 120 mm Hg [85]. The Irbesartan Diabetic Nephropathy Trial showed that decreasing systolic blood pressure to the lower limit value of 120 mm Hg reduces the risk of cardiovascular mortality and heart failure (but not of myocardial infarction) and the risk of double increase in serum creatinine or progress to terminal kidney failure [86].

According to the current Guidelines on Arterial Hypertension Treatment [87], the target blood pressure in patients with DM should be <130/80 mm Hg. Antihypertensive therapy may be started even when blood pressure values are in the upper normal range.

Inhibition of Renin-Angiotensin-Aldosterone System

Angiotensin II is the most effective factor of renin-angiotensin-aldosterone system (RAAS), resulting from a range of proteolytic reactions that begin with the conversion of angiotensinogen to angiotensin I through the catalytic action of renin (Figure 7).

RAAS is directly associated with blood pressure regulation, body fluid volume, and vascular response to injury and inflammation. Inappropriate activation of this system increases the blood pressure and has anti-inflammatory, prothrombotic, and proatherogenic effects, which in the long run lead to irreversible damage of target organs. Although aldosterone, renin, and end-products of angiotensin degradation are also involved in this process, majority of the RAAS effects on target organs are mediated by angiotensin II, which is present in the bloodstream and tissues. Angiotensin II, which is produced in the heart, brain, and kidneys through alternative pathways by kinase and endopeptidase activity, is more effective than angiotensin II produced in the bloodstream [88]. Angiotensin II binds to AT1 and AT2 receptors. AT1 receptor activation is responsible for vasoconstriction, release of aldosterone, vascular remodeling, oxidative stress, and has anti-inflammatory, proatherogenic, and prothrombotic effects [89]. The activation of AT2 receptors leads not

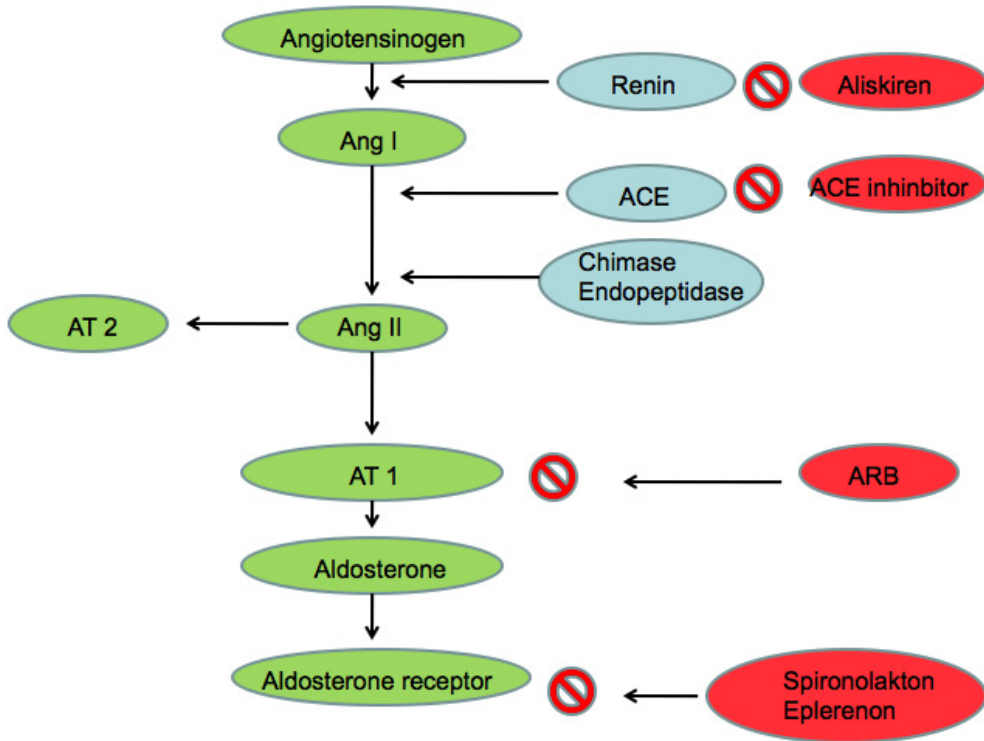


Figure 7. The RAAS and examples of RAAS inhibitors that are available for oral treatment.

ACE, angiotensin-converting enzyme; Ang I, angiotensin I; Ang II, angiotensin II; ARB, angiotensin-II-receptor blocker; AT 1, angiotensin II type 1 receptor; AT2, angiotensin II type 2 receptor; RAAS, renin-angiotensin-aldosterone system.

only to vasodilatation, growth inhibition, and antiatherogenic effects, but also to heart hypertrophy and poorer revascularization after the obstruction of coronary or peripheral artery [90]. In 1977, Ondetti et al. [91] started a new era in the research of pathophysiological role of the RAAS in kidney disease by developing the first ACEI (captopril) for the treatment of renovascular hypertension. In 1986, Zatz et al. [92] provided evidence that RAAS plays a role in the pathogenesis and progress of diabetic nephropathy by proving that enalapril decreases glomerular capillary hypertension, structural glomerular damage, and proteinuria in diabetic rats. Later studies have confirmed that angiotensin II plays the key role in the functional and structural changes linking proteinuria with the development of diabetic nephropathy. Along with pleiotropic effects, angiotensin II has effects on the structure of glomerular filtration membrane, inducing the remodeling of the podocytic cytoskeleton and causing their apoptosis, which contributes to easier ultrafiltration of plasma proteins [93]. Renoprotective effect of ACEI and ARB has been confirmed in a meta-analysis showing that ACEI and ARB decrease albuminuria in patients with DM more effectively than antihypertensive medications whose mechanism of action excludes RAAS

[94]. Early treatment with ACEI may prevent microalbuminuria, which is the early sign of glomerular damage and marker of cardiovascular risk in patients with DM. Delayed treatment with ACEI or ARB in patients with type 2 DM, diabetic nephropathy, and proteinuria is not effective enough. Increasing ACEI and ARB dosages above the recommended values for the treatment of hypertension or their combination is very effective in reducing albuminuria [95]. Aldosterone receptor antagonists and renin inhibitors also decrease albuminuria in patients with DM, but large randomized trial are needed to determine their possible advantage over ACEI and ARB either as monotherapy or combined therapy [96].

Dyslipidemia

Dyslipidemia occurs in all patients with DM, and its occurrence increases with the development of diabetic nephropathy. Aggressive plasma lipid reduction is an important therapeutic intervention, because patients with DM have an increased risk of coronary disease. In addition, dyslipidemia contributes to the development of diabetic nephropathy. Treating dyslipidemia with statins slows down the progression of diabetic nephropathy [97]. In addition to statins, fenofibrate also decreases the progression of albuminuria in patients with DM [98]. In addition to anti-inflammatory effect, it decreases the production of collagen type 1 in mesangial cells via nuclear peroxisome proliferator-activated receptors (PPAR) alpha [99]. Intensive glycemic control, blood pressure control by RAAS inhibitors, and decreasing serum lipid concentration is an optimal therapeutic approach in patients with DM and diabetic nephropathy (including the microalbuminuria stage).

The Role of Other Factors

Transforming growth factor beta (TGF-beta) has effects on cell hypertrophy and increased collagen synthesis. Inhibition of TGF-beta in experimental DM model prevented the development and progression of diabetic nephropathy [100]. Experimental studies have shown that non-dihydropyridine calcium channel blocker (diltiazem) slows down the progression of most morphological changes in diabetic nephropathy [101]. On the other hand, diltiazem monotherapy leads to the increased tubulointerstitial fibrosis and global, but not segmental, glomerulosclerosis. This negative effect of diltiazem can be corrected by ACEI therapy.

Peroxisome proliferator-activated receptors (PPAR) play a significant role in the regulation of adipogenesis, lipid metabolism, insulin sensitivity, inflammation, and blood pressure control; however, they also seem to play a significant role in the development of diabetic nephropathy in type 2 DM patients [102]. In an experimental animal model of diabetic nephropathy, PPAR gamma agonists, such as thiazolidinediones (oral hypoglycemic agents), were shown to reduce fibrosis, mesangial proliferation, and inflammation [103]. In addition, these agents reduce albuminuria in different stages of diabetic nephropathy and decrease blood pressure [104]. Their possible renoprotective effects still need to be confirmed in randomized clinical trials including a large number of patients.

New Treatment Strategies

Current treatment has not always been effective in all patients. Therefore, new treatment options are being investigated.

High doses of thiamine and its derivative benfotiamine (S-benzoylthiamine O-monophosphate) were shown to slow down the development of microalbuminuria in animal models, most likely by decreasing the activation of PKC, protein glycation, and oxidative stress [105]. In experimental animals treated with ALT-711, which metabolizes AGEs, a decrease in blood pressure and kidney damage was observed [106]. PKC-beta inhibitor (ruboxistaurin) normalizes GFR, reduces or decreases albuminuria, and improves kidney function in experimental animals [107]. Pimagedin (second generation AGE inhibitor) reduces albuminuria and GFR decrease in patients with type 1 DM and proteinuria [108].

Smaller clinical trials have produced contradictory results, while the results of large randomized clinical trials are still not available.

In an experimental model of induced glomerulosclerosis, modified heparin glycosaminoglycan prevented albuminuria, accumulation of extracellular matrix proteins, and increased expression of TGF-beta [109]. Although animal models held promise, the administration of sulodexid in a large multicentric SUN-Micro-Trial did not achieve the primary outcome, i.e., there were no significant differences in the reduction of albuminuria between the treatment and control groups [110].

10. Conclusion

In the last several years, we have witnessed an enormous progress made not only in our understanding of the risk factors and mechanism of the development of diabetic nephropathy, but also in the treatment possibilities aimed at preventing the progression of diabetic nephropathy.

Early detection of this chronic DM complication along with the treatment of main risk factors (hyperglycemia, hypertension, and dyslipidemia) and use of renoprotective drugs (ACEI and ARB) may decrease the progression of this kidney disease. The treatment of increased blood pressure is a priority. All listed measures lead to a decrease in the overall and cardiovascular mortality in patients with DM.

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