

THE NOVELLA ABOUT DIABETIC NEPHROPATHY

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SUMMARY – Diabetic nephropathy is a common complication in patients with diabetes mellitus and one of the major reasons for renal replacement therapy in Croatia, Europe and the United States. It is characterized by proteinuria, decline in glomerular filtration, hypertension, and high risk of cardiovascular morbidity and mortality. Deterioration of renal function in diabetic nephropathy develops through five clinical stages characterized by the respective histologic description. Genetic susceptibility, hyperglycemia, high blood pressure and duration of diabetes mellitus definitely play a role in the pathogenetic sequence. Early diagnosis, appropriate patient follow up and treatment are essential to improve the outcomes. Interdisciplinary approach and close collaboration of nephrologists and diabetologists are essential for timely detection of disease progression. Tight glycemic control under the supervision of diabetologists, screening of patients, and once a year report of albuminuria and glomerular filtration allow for detection of renal damage in the early stages and timely referral to a nephrologist. The points of interest given in this overview are description of clinical staging in relation to pathologic classification, repetition of basic causal features, and brief analysis of treatment.

Key words: *Diabetic nephropathy – diagnosis; Diabetic nephropathy – therapy; Albuminuria; Kidney transplantation; Review*

Introduction

Diabetic nephropathy (DN) is the most common chronic complication in patients with type 1 and type 2 diabetes mellitus, as well as in other, secondary forms of diabetes mellitus^{1,2}. It is a major cause of end-stage renal disease (ESRD) in Europe³ and the United States⁴. According to the Registry of Renal Replacement Therapy in 2012, Croatia follows global trends, so that DN was the primary renal disease in 29% of patients starting renal replacement therapy⁵. The reason for the increased number of patients affected by DN with consequent ESRD lies in the growing world

prevalence of diabetes mellitus among adults. Global estimates based on numerous studies predict an increase from 6.4% and 285 million adults with diabetes mellitus in 2010 to 7.7% and 439 million in 2030, especially in developing countries⁶, despite the progress in diagnosis and treatment. Diabetic nephropathy is one of the major risk factors for cardiovascular disease^{7,8} marked with albuminuria, decline in glomerular filtration rate (GFR) and hypertension⁹.

Clinical Characteristics

Diabetic nephropathy is a slowly progressive and long time asymptomatic glomerulopathy¹⁰ characterized by structural changes in the form of glomerular basement membrane thickening, mesangial expansion, or finally glomerular sclerosis^{11,12}. Functional characteristics are based on hyperfiltration at the early stage,

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moderately increased albuminuria (previously called microalbuminuria) with urine albumin excretion of 30–300 mg/day, and severely increased albuminuria (previously called macroalbuminuria) with urine albumin excretion above 300 mg/day. Albuminuria is still the only noninvasive marker of early DN development. Data have shown that the level of albuminuria need not be always associated with progression of the disease¹³, and low GFR without albuminuria was observed in approximately 10% of patients with type 2 diabetes mellitus¹⁴. There is still no convincing evidence for such development of the disease.

Pathogenesis

The pathogenesis of DN is multifactorial. Most frequently described factors that contribute to the development and simultaneously influence the pathogenesis of DN are hyperglycemia, genetic susceptibility, high blood pressure and duration of diabetes mellitus. The advanced glycosylation end products (AGEs) are formed by nonenzymatic process in excess of chronic hyperglycemia and thus accelerate the development of microvascular complications. Hyperglycemia also activates protein kinase C, which enhances permeability of the glomerular membrane for albumin and increases the expression of transforming growth factor- β (TGF- β), which is one of the crucial elements of tubulointerstitial damage and glomerulosclerosis in DN¹⁵. Hemodynamic changes in the kidney are mediated by several factors such as the renin-angiotensin system, vascular endothelial growth factor (VEGF), TGF- β , prostanoids and nitric oxide. Thereby impaired autoregulation of blood flow through the kidney leads to elevated hydraulic pressure in the glomerular capillaries, and consequently to afferent arteriolar vasodilatation, accompanied by vasoconstriction of efferent arterioles, resulting in hyperfiltration, hypoperfusion and glomerular hypertension¹⁵. Data from several studies on the pathogenetic sequence also point to the role of the transmembrane protein nephrin and its decreased expression, which leads to increased permeability of the glomerular membrane and ultimately to leakage of albumin^{16,17}. However, a number of factors, as well as potential new markers are being investigated, which could help in the early detection and treatment of DN. Recent data have confirmed that bone morphogenic protein-7 (BMP-

7) expression and podocyte number are decreased in DN¹⁸. In DN, tubular cells produce a large amount of extracellular matrix proteins, which leads to interstitial fibrosis. BMP-7 can reduce increased expression of interstitial extracellular matrix proteins¹⁹, so further investigations are required to determine the right position of such findings and direction of next researches. Some authors are also focused on redefining the role and potential therapeutic strategies of antioxidative stress in DN^{20,21}, whereas conventional antioxidants did not provide the expected benefits.

In the majority of patients, diagnosis is based on typical clinical presentation. In the situation of unusually rapid progression of renal disease in less than 10-year duration of type 1 diabetes mellitus or rapid deterioration of GFR that cannot be explained by DN, presence of nephrotic range proteinuria at the time of diabetes diagnosis despite optimal blood pressure regulation, elevated serum creatinine without abnormalities in urine, hematuria, active urinary sediment, and presence of other systemic disease including autoimmune disease²², renal biopsy should be performed as the gold standard, and therefore therapeutic approach is essentially different²³.

Retinopathy is easy to diagnose by fundus examination, and it is part of routine screening in diabetic patients. According to the KDOQI guidelines from 2007, diabetic patients with proteinuria, retinopathy and renal impairment are considered to have DN, otherwise the causes of nondiabetic kidney disease should be examined²².

Screening for nephropathy in patients with type 1 diabetes, where the onset of disease is known, should be done about 5 years of diagnosis, while in patients with type 2 screening should be done immediately upon detection of the disease and then once a year by determining the rate of estimated GFR and albuminuria²².

A uniform classification of DN proposed by the Renal Pathology Society has since recently been used in clinical practice. It is based on grading glomerular lesions from basement membrane thickening through mesangial expansion, the appearance Kimmelstiel-Wilson lesions to ultimately advanced diabetic sclerosis. Interstitial and vascular lesions are described separately¹².

Stages and Progression of Diabetic Nephropathy

Deterioration of renal function in DN develops through 5 clinical stages²⁴, which are characterized by histologic description below.

Stage 1 – hyperfiltration

First stage is characterized by supranormal GFR of 125 to 140 mL min⁻¹ 1.73 m², thus being called hyperfiltration. The prevalence ranging is variable; 40%-60% in type 1 diabetes and lower, mainly 0%-40% in type 2 diabetes²⁵. It commonly develops 3-5 years from the onset of type 1 diabetes mellitus, whereas in type 2 diabetes it can already be found at the time of diagnosis because the onset of disease is usually difficult to determine. To investigate the effect of hyperfiltration on future development of nephropathy, Magee *et al.* have presented data from a meta-analysis in 780 diabetic 1 patients, 130 of which developed nephropathy; the median follow up in the studies was 11.2 years. These results support the hypothesis that patients with hyperfiltration have an increased risk of further disease progression to nephropathy²⁶. Hyperfiltration is also closely related to the increased kidney size, predominantly seen in type 1 diabetes mellitus, due to hypertrophy of the tubules and interstitial expansion¹⁵. However, it is believed that changes occurring at this point are brief and reversible.

Stage 2 – ‘silent’ stage

This stage develops silently for up to 20 years. GFR is high or regular, albumin excretion and blood pressure are normal. In these patients, failure of blood pressure to decrease at night predicts further development of albuminuria^{1,27}.

Some patients remain in this stage for lifetime. In addition, a study on fifteen adolescents with type 1 diabetes, duration of more than 5 years, was aimed to investigate the relationship of specific factors in the development of morphological changes five years before kidney biopsy. Data showed that basement membrane thickness was predicted by 5-year mean HbA_{1c}, diabetes duration and earlier GFR²⁸. Thus, ultrastructural glomerular changes at this stage appear as a result of advancement during previous hyperfiltration.

Histologically presented thickening of the basement membrane, as well as some clinical characteristics overlap in the first and second stages.

Stage 3 – moderately increased albuminuria/microalbuminuria/incipient nephropathy

According to the available data, in some patients there is genetic predisposition that determines development of albuminuria and DN progression²⁹. At this stage, albumin excretion of 30-300 mg over 24 h is expressed as hypertension in type 1 diabetes mellitus. In type 2 diabetes mellitus, hypertension may already be seen at the time of diagnosis. This stage develops after 6-15 years. Observational data from a recent Japanese study on type 2 diabetes patients suggest that microalbuminuria and diabetic retinopathy are associated with fastest GRF decline³⁰, which is consistent with earlier findings on gradual deterioration of renal function at this stage³¹. Although timely detection of the disease, in particular albuminuria, and appropriate treatment are inevitable goals, there is evidence in support of the thesis that microalbuminuria may regress to normoalbuminuria in type 1 diabetes mellitus, regardless of angiotensin-converting enzyme (ACE) inhibitors in therapy³². The changes found on biopsy specimens correspond to basement membrane thickening and mesangial matrix expansion³³.

Stage 4 – severely increased albuminuria/overt nephropathy

Fourth stage usually develops after 10-25 years of the disease onset and is characterized by urinary albumin excretion rate above 300 mg/day, an increased incidence of hypertension and further GFR reduction. Advanced histologic changes at renal biopsy with at least one Kimmelstiel-Wilson lesion can be seen. A higher mortality rate has been reported in a group of patients with developed albuminuria³⁴, as well as progression to ESRD. However, recognition and influence on modifiable risk factors and aggressive treatment approach may reduce mortality by 30%³⁵. In spite of all efforts, satisfactory pathogenetic explanation of particular stages is not yet sufficiently known.

Stage 5 – end-stage renal disease

After 10-30 years of diabetes mellitus diagnosis, progression to ESRD, with GFR <15 mL/min/1.73 m² may be expected. Histologically, these changes correspond to class IV and advanced glomerulosclerosis¹². There is no significant difference in disease progression between type 1 and type 2 diabetes mellitus, as most patients die from cardiovascular complications before the onset of ESRD. In a subset of patients, deterioration of kidney disease occurs as a result of late disease detection on the one hand and diagnosis delay due to temporary disappearance of hyperglycemia because of anorexia on the other hand¹⁵. In addition to conservative measures, treatment is carried out by hemodialysis, peritoneal dialysis, or kidney transplantation.

Kidney transplantation is the best option for suitable patients since it provides better survival than dialysis³⁶ because of a decreased risk of fatal and non-fatal cardiovascular complications³⁷. Atypical presentation of cardiovascular incidents should also be considered³⁸.

In order to improve post-transplant graft and patient outcome, transplantation should be done as soon as possible and prior to initiating dialysis if possible, since interdependence has been observed between the increased mortality risk and graft loss and time spent on dialysis³⁹; living donor kidney should be preferred to cadaveric kidney.

The simultaneous kidney-pancreas transplantation is still debated because of more complications associated with the increased morbidity and mortality, especially in type 2 diabetes mellitus, where properly selected patients with low cardiac risk can benefit, as opposed to type 1 where excellent results are reported^{40,41}. Therefore, diabetic patients have to undergo detailed assessment of coronary disease, which in symptomatic subjects implies cardiac catheterization, while others are advised to undergo dobutamine-induced stress echocardiography. Attenuated physical condition is a limiting factor because of which exercise electrocardiography and exercise echocardiography are not suitable in dialysis patients⁴². If there is clinical suspicion of associated peripheral occlusive disease, it requires extensive diagnostic workup in consultation with vascular specialist.

In order to achieve the best results and bearing in mind the complexity of the problem, the transplantation team must have sufficient time to assess which is the best option for patients.

Generally, after transplantation, urinary tract infections are more often in these patients, while evidence for other complications such as allograft rejection, malignancies or viral infection is still insufficient. Graft failure due to DN rarely occurs.

Treatment

Correction of dietary habits, lifestyle modification including smoking cessation, and maintaining optimal body weight, and use of hypoglycemic agents to ensure HbA_{1c} ~7.0% and renin-angiotensin system blockers constitute the framework for treatment of DN, all in order to reduce albuminuria and delay disease progression to ESRD.

Glycemic control

The benefits of glycemic control in normalizing hyperfiltration and preservation of renal function have been previously described^{1,43,44}. Results of large studies, UKPDS, DCCT and ADVANCE, confirm the role of tight glycemic control in the development of microalbuminuria and progression of chronic kidney disease⁴⁵⁻⁴⁷. In the UKPDS study, this is achieved by reducing HbA_{1c} from 7.9% to 7.0% with intensified form of treatment, thus a target of near 7% HbA_{1c} value has been implemented in the recommendations of the majority of professional societies because there is evidence that lower HbA_{1c} values (below 6%) are associated with an increased patient mortality^{45,48}. Therapeutic options should be adjusted individually to each patient depending on the estimated glomerular filtration, in order to avoid hypoglycemia, which develops mainly due to impaired clearance of insulin and oral antidiabetic agents, as well as diminished kidney gluconeogenesis²².

The effect of strict glycemic control on renal outcomes was exemplified on functional graft after pancreas transplantation during ten-year follow up. In eight patients with functional pancreas transplant, of which three patients had normal albumin excretion, three had moderately increased albuminuria and two had severely increased albuminuria before transplantation, at five-year follow up renal function was stable

but without significant impact on histologic changes in the kidneys. However, after 10 years, changes in the glomeruli were retreated and renal function recovered⁴⁹. Optimal glycemic control, except for the effects on DN, is also particularly important to prevent worsening of associated diabetic retinopathy and development of blindness⁵⁰.

Blood pressure control

Several studies confirmed the importance of good blood pressure control and benefits of renin-angiotensin blockers. Evidence from the UKPDS shows the beneficial effect of lowering blood pressure on the incidence of complications due to diabetes, as well as on the reduced risk of death due to diabetes⁵¹. In the Irbesartan Diabetic Nephropathy trial, hypertensive diabetic 2 patients with nephropathy were randomized into irbesartan, amlodipine or placebo group; study data suggested that gradual lowering of systolic blood pressure to 120 mm Hg was associated with improved renal outcomes⁵².

The latest AHA/ESC guidelines for the management of arterial hypertension recommend lowering of systolic blood pressure to <130 mm Hg (grade 2B), especially in the presence of overt proteinuria⁵³, and in this respect renin-angiotensin blockers are better option than other antihypertensives (grade 1a)^{53,54}.

The protective effect of these drugs on the kidney is a result of interaction of multiple factors⁵⁵. Deterioration of the autoregulatory mechanism decreases resistance of afferent arterioles, resulting in enhanced total blood flow through the glomeruli and increased structural glomerular injury. Simultaneously with lowering of systemic hypertension, ACE inhibitors normalize glomerular capillary hydraulic pressure by dilatation of efferent arterioles^{52,56}, achieve further reduction in proteinuria independent of blood pressure^{55,57}, and reduce production of collagen⁵⁸, possibly due to the opposed effect of angiotensin II and decreased stimulation of TGF- β ^{55,59}.

Other antihypertensive drugs should be added when indicated, with control of the relevant laboratory test results and regular blood pressure measurement. Preferred is a combination with diuretics (thiazide or loop diuretic depending on GFR), calcium channel blocker or beta-blocker, and drugs from other groups as necessary.

Correction of anemia

Treatment of anemia can delay the progression of ESRD and improve the quality of life of patients. Treatment with drugs that stimulate erythropoiesis should be started when other causes of anemia are excluded and hemoglobin value is less than 110 g/L, with target values of 110-120 g/L. Hemoglobin values above 120 g/L are not desirable because of the increased rate of cardiovascular complications. Simultaneously, iron preparations and B vitamins should be administered⁶⁰⁻⁶².

Treatment of dyslipidemia

Since dyslipidemia with diabetes and chronic kidney disease are risk factors for coronary heart disease, in case of failing to achieve target lipid values by changing the habits, statin therapy should be introduced²². In addition, Tonolo *et al.* in their study demonstrated that lipid lowering may slow progression of chronic kidney disease, as well as of DN, probably *via* increased expression of nephrin, podocin, CD2AP, and FAT, alpha-actin proteins which are associated into lipid rafts. Disabling the synthesis of cholesterol with statin plays an important role in modifying these lipid rafts⁶³⁻⁶⁸.

Novel agents

In order to improve treatment of DN and delay progression to ESRD, new therapeutic options are being investigated. One of the studies showed that, if combined with conventional therapy with renin-angiotensin system blockers, vitamin D at a dose of 2 mg/day successfully lowered residual albuminuria in patients with DN⁶⁹; however, prior to its implementation in everyday practice, it will be necessary to wait for the results of further research.

An interesting approach to the treatment of DN is the one focused on the mechanisms of oxidative stress and inflammation due to hyperglycemia. Bardoxolone methyl is a synthetic triterpenoid that significantly improves GFR, but raises blood pressure, encourages fluid retention and increases the incidence of adverse cardiovascular events. Hence, it is necessary to determine safety of these substances⁷⁰. Sulodexide is an antifibrotic agent, which has the ability to decrease the production of TGF- β and thus

reduce the basement membrane permeability, but a larger study had to be terminated earlier as there was no difference compared to placebo^{71,72}.

There have also been attempts to show the benefit of inhibition of AGE formation by pyridoxamine⁷³ and inhibition of protein kinase by ruboxistaurine⁷⁴, and some recent studies have pointed to the use of baking soda in slowing the progression of renal function and improve the patient nutritional status⁷⁵.

Conclusion

In the last decade, DN has been the leading cause of ESRD, identified as an important risk factor for high cardiovascular morbidity and mortality. Although the understanding of DN pathogenesis has improved, it has not yet been fully clarified. Early diagnosis, through close collaboration of nephrologists and diabetologists, correction of variable risk factors such as rigorous glycemia and blood pressure control, lifestyle modification, administration of statins and anemia rectification, along with proper monitoring of patient are still the core of each approach that increases the chances of survival in our patients. Kidney transplantation is an optimal renal replacement therapy in well selected diabetic patients with DN and ESRD because it significantly improves the quality of life and reduces cardiovascular morbidity and mortality. Further investigation of the novel agents are required to upgrade the treatment of patients with DN.

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Sažetak

NOVELA O DIJABETIČKOJ NEFROPATIJU

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Dijabetička nefropatija je najčešća komplikacija u bolesnika sa šećernom bolešću tip 2 i jedan je od najčešćih razloga za nadomještavanje bubrežne funkcije u Hrvatskoj, Europi i Sjedinjenim Američkim Državama. Obilježena je proteinurijom, smanjenjem glomerularne filtracije te visokim srčano-žilnim pobolom i smrtnošću. Oštećenje bubrežne funkcije u dijabetičkoj se nefropatiji razvija kroz pet kliničkih stadija s pripadajućim patohistološkim značajkama. U patogenetskom slijedu neosporna je uloga genetske predispozicije, hiperglikemije, arterijske hipertenzije i trajanja šećerne bolesti. Interdisciplinarni pristup i bliska suradnja nefrologa i dijabetologa neophodni su za pravodobno otkrivanje i napredovanje bolesti, a time i za poboljšanje ishoda bolesnika. Kontrola glikemije, probir bolesnika te jedanput godišnje određivanje albuminurije i glomerularne filtracije omogućava otkrivanje bubrežnog oštećenja u ranoj fazi i pravodobno upućivanje nefrologu. U ovome su radu prikazani klinički stadiji bolesti u korelaciji s patohistološkom klasifikacijom, ponovljene su osnove patogeneze i pristupa liječenju.

Ključne riječi: Dijabetička nefropatija – dijagnostika; Dijabetička nefropatija – terapija; Albuminurija; Transplantacija bubrega; Pregledni rad