

## REVIEW

# Risk factors in diabetic nephropathy progression at present

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**Abstract:** Diabetic nephropathy is becoming an increasingly important cause of morbidity and mortality worldwide as a consequence of increasing prevalence of type 2 diabetes and obesity. The glomeruli of patients with diabetes are characterized by glomerular hypertrophy, widening of the glomerular basement membrane, mesangial expansion, podocytopenia leading to nodular (Kimmelstiel-Wilson) glomerulosclerosis. Many studies have reported the initiation and progression of incipient nephropathy in type 1 diabetes patients, but only limited data are available in type 2 diabetes patients. The information on the risk factors and conversion rate of normal renal function to proteinuria in type 2 diabetes patients is sparse. In this report, we review risk factors of diabetic nephropathy progression in type 2 diabetes patients (*Ref. 50*). Text in PDF [www.elis.sk](http://www.elis.sk).

**Key words:** diabetic nephropathy, nephropathy progression, diabetic patients, risk factors.

**Abbreviations:** ACE – inhibitor-angiotensin-converting enzyme inhibitor, BMI – body mass index, CKD – chronic kidney disease, CRF – chronic renal failure, DCCT – Diabetes Control and Complications Trial, eGFR – estimated glomerular filtration rate, FGF23 – Fibroblast growth factor 23, GFR – glomerular filtration rate, HbA<sub>1c</sub> – glycolysed hemoglobin, HDL – high-density lipoprotein, IDL – intermediate-density lipoprotein, LDL – low-density lipoprotein, VLDL – very low-density lipoprotein

Diabetic nephropathy represents a major concern for public health worldwide affecting 25 % to 40 % patients with diabetes mellitus. Diabetic nephropathy may progress to end-stage chronic kidney disease with need of hemodialysis and even kidney transplantation (1, 2). Diabetic nephropathy is a glomerular disease with five different stages: glomerular hyperfiltration, incipient nephropathy, microalbuminuria, overt proteinuria and end-stage renal disease (3). Many environmental factors have been established as contributing to the development of diabetic nephropathy while the role of others has yet to be clearly understood (4). It is known that factors such as hyperglycemia, arterial hypertension and dyslipidemia play a role in the development of diabetic nephropathy in only genetically predisposed individuals. Those who do not develop diabetic nephropathy in the first 15 years after the disease onset seem to be genetically protected (5).

## Hyperglycaemia, duration of diabetes and diabetic nephropathy

Chronic hyperglycemia associated with diabetes mellitus is considered to be a state of increased oxidative stress related to

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the excess generation of reactive oxygen species and an impaired antioxidant response (6). Diabetic hyperglycaemia induces cell cycle arrest and cellular hypertrophy of podocytes, and the expression of nephrin is reduced. As a result, the permselectivity of glomerular capillaries is impaired and this induces proteinuria and subsequent focal and global sclerosis (7). Type 2 diabetes patients with uncontrolled diabetes and increase in blood pressure are at high risk of developing nephropathy. In the same study, long duration of diabetes, elevated blood pressure, poor glycaemic control and presence of retinopathy are significantly associated with the progression of diabetic nephropathy. Glucose levels, glycosylated hemoglobin (HbA<sub>1c</sub>), systolic blood pressure, triglycerides, and urea levels were significantly higher at baseline among progressors compared to non-progressors. Averaged risk factors such as HbA<sub>1c</sub>, triglycerides and systolic blood pressure showed a significant association with the development of macroalbuminuria (8). Collaborative study in 2009 found out that intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or microvascular complications, with the exception of progression of albuminuria ( $p = 0.01$ ) (9).

## Obesity and diabetic nephropathy

Until recently a limited number of epidemiologic studies have examined the association between obesity and chronic kidney disease (CKD). A retrospective cohort study that evaluated the impact of obesity on the rate of non-diabetic CKD progression was performed by Othman. Baseline body mass index (BMI) and young age were strongly and independently associated with faster CKD progression based on the annual rate of eGFR (estimated glomerular filtration) fall. However, association between obesity and CKD needs to be further explored (10). Brown et al (11) examined the association between BMI and kidney disease progression among 499 adults with established stage 3–5 CKD in the absence of dia-

betes. Neither BMI as a continuous variable nor obesity (BMI  $\geq 30$ ) as a categorical variable was associated with an increased rate of progression of existing CKD in this predominantly white population. Raised BMI did not influence the rate of progression of chronic kidney disease in patients with type 2 diabetes mellitus (11). In another study with type 2 diabetes patients, metabolic syndrome treatment and its control were independently associated with a lesser progression of diabetic nephropathy (12). In type 1 diabetic patients, central obesity measured by waist circumference, is an independent risk factor for incident microalbuminuria. This association suggests that metabolic abnormalities that are associated with central obesity may contribute to the pathogenesis of microalbuminuria in type 1 diabetes (13).

### Blood pressure control and diabetic nephropathy

Numerous studies confirmed arterial hypertension to be a risk factor for progression of diabetic nephropathy (14, 8). Blood pressure reduction and angiotensin-converting enzyme (ACE) inhibitors slow but do not stop progressive decline of renal function in established diabetic nephropathy. Chuahirun et al showed, that smoking significantly predicted renal function decline. Renal function declined is faster in smokers than in nonsmokers with type 2 diabetic nephropathy and arterial hypertension despite adequate antihypertensive therapy including ACE inhibitors (15). Fixed combination of perindopril and indapamide reduces the risks of major vascular events, including death to patients with type 2 diabetes. (16).

### Dyslipidemia and diabetic nephropathy

Chang et al demonstrated for the first time, that type 2 diabetic patients under a standard disease management program who have a stable and a higher mean high-density lipoprotein (HDL) level were associated with a lower risk of developing diabetic nephropathy (17). In another study high triglyceride-to-HDL cholesterol ratio was found to be an important risk factor for nephropathy in type 2 diabetic patients (18). Thomas et al showed, that the relationship between lipid variables and progression of diabetic kidney disease is not the same at all stages. In patients with normoalbuminuria, progression was associated with male sex ( $p < 0.05$ ) and low-density lipoprotein (LDL) ( $p = 0.02$ ). In patients with microalbuminuria, progression was independently associated with triglyceride content of very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) (both  $p < 0.05$ ). In patients with macroalbuminuria, a significant decline in renal function ( $> 3 \text{ ml min}^{-1} \text{ year}^{-1}$ ) was independently associated with poor glycemic control, hypertension, and LDL size ( $p < 0.05$ ) (19).

### Smoking and diabetic nephropathy

In general population smoking is associated with an increased risk for chronic renal failure (CRF). The risk of CRF increases with high daily doses (among smokers of  $> 20$  cigarettes/d), long duration (among smokers for  $> 40$  yr) and a high cumulative dose

(among smokers with  $> 30$  pack-years). Heavy cigarette smoking increases the risk of CRF for both men and women (20). In type 1 diabetic patients with diabetic nephropathy smoking is not associated with decline in kidney function (21). On the contrary, de Boer et al (13) reported important data from an observational extension of the randomized prospective Diabetes Control and Complications Trial (DCCT). Among 1105 patients with type 1 diabetes and normal urine albumin excretion at baseline, a 4.3-fold greater rate of GFR decline was observed in active versus nonactive smokers (13). Sawicki referred that cigarette smoking represents an important factor associated with progression of nephropathy in treated hypertensive type 1 diabetic patients (22). In type 2 diabetic patients cigarette smoking is a predictive factor of nephropathy progression despite improved blood pressure control and ACE inhibition. Cigarette smoking increases urine albumin excretion in these patients despite improved blood pressure control and ACE inhibition (23). Baggio et al observed an effect of smoking habit on abnormal albumin excretion rate in 96 patients with type 2 diabetes. Cigarette smoking affects glomerular structure and function in type 2 diabetes and may be an important factor for the onset and progression of diabetic nephropathy (24).

### Other life style factors and diabetic nephropathy

Physical inactivity contributes to the risk of CKD (25). In type 2 diabetic patients, the high intake of protein and the low intake of polyunsaturated fatty acids particularly from plant oils, is associated with the presence of microalbuminuria. Reducing protein intake from animal sources and increasing the intake of lipids from vegetable origin might reduce the risk of microalbuminuria (26). Deji et al confirmed that feeding mice with a high-fat diet induces major systemic alterations compatible to human metabolic syndrome, including obesity, hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and hypertension. After the onset of metabolic syndrome, mice on a high-fat diet developed increased urinary albumin excretion and glomerular lesions with the accumulation of extracellular matrix protein. Increase in body weight, rather than high-fat diet per se, contributes to the development of these abnormalities (27).

### Oxidative stress and diabetic nephropathy

Insulin has a vasodilatory effect on the skeletal muscle vasculature, as it promotes synthesis and/or release of nitric oxide from the endothelial cell (28). Absolute insulin deficiency in type 1 diabetes mellitus and functional insulin deficiency or insulin resistance in type 2 diabetes mellitus can thus contribute to endothelial cell dysfunction. Oxidant injury as a result of excessive oxidative stress has been implicated in the etiology of endothelial cell dysfunction in the glomerulus and tubules, before the manifestation of microalbuminuria (29).

### Genetics and diabetic nephropathy

Factors determining the occurrence and progression of diabetic nephropathy include hyperglycemia, hypertension, hyperlipidemia

and also genetic factors. Especially those that are reversible or treatable such as hypertension, hyperlipidemia and hyperglycemia are important for clinicians as they can be influenced by treatment. At present genetic factors may be important only for theoretical discussion but with the rapidly advancing field of gene therapy, it is probably a question of time when the genetic risk factors for diabetic nephropathy will be favourably modified. Genes involved in the genetic predisposition to diabetic nephropathy are likely to be those involved in renin-angiotensin system, nitric oxide pathway, aldose reductase pathway and lipoproteins metabolism (30).

### Age, gender, race and diabetic nephropathy

There is an evidence of familial clustering of diabetic nephropathy in type 2 diabetes and the affected sib-pair linkage analysis has identified loci associated with diabetic nephropathy in type 2 diabetes (31,32). Interestingly, in Pima Indians blood pressure levels before the onset of diabetes, predict the future risk of developing nephropathy (33). Blacks who are at a greater risk of renal failure than whites also experience a greater prevalence of diabetic nephropathy (34). Diabetic nephropathy progression occurs more frequently in male sex (19). Age is associated with progressive decline in renal function in type 2 diabetic patients (35, 8).

### Hyperuricemia and diabetic nephropathy

Chronic hyperuricemia would stimulate the renin-angiotensin system and inhibit release of endothelial nitric oxide, contributing to renal vasoconstriction and increasing blood pressure, at the same time. Thus high levels of uric acid may have a pathogenetic role in interstitial inflammation and progression of renal disease (36, 37). In another study, hyperuricemia/gout is a predictor of diabetic nephropathy (14). Allopurinol decreases serum uric acid level by inhibiting the enzyme xanthine oxidase and slows down the progression of renal disease in patients with chronic kidney disease. In addition, allopurinol reduces cardiovascular and hospitalization risk in these subjects (35).

### Bone metabolism and diabetic nephropathy

Schwarz et al examined the association of baseline levels of serum phosphorus, calcium, and calcium-phosphorus product with renal functional outcomes in patients with CKD stages 1 through 5 and who have not undergone dialysis yet. Lower serum calcium showed a trend toward higher risk for progressive CKD but without statistical significance. Higher serum phosphorus and higher calcium-phosphorus product are associated with progression of CKD (38).

### Predictors of diabetic nephropathy progression

*Waist circumference* – predicts the subsequent development of microalbuminuria in type 1 diabetes (13).

*Microalbuminuria* – elevated levels of microalbuminuria strongly predict the development of clinical diabetic nephropathy

(39) and is a risk factor for premature death from cardiovascular disease in type 2 diabetes patients (40).

*Glomerular filtration rate* – Early decline in GFR may reflect progressive kidney disease in type 1 diabetes, but its predictive value in type 2 diabetes is uncertain. In type 2 diabetes, loss of GFR often occurs before the onset of macroalbuminuria, but a decline predictive of an end stage renal disease is strongly dependent on progression to macroalbuminuria (41). Both albuminuria and reduced e-GFR are significant and independent risk factors for further deterioration of diabetic nephropathy (42).

*Adiponectin* – Galovičová et al studied the relationship between renal functions and serum adiponectin in patients suffering from diabetic nephropathy. The beginning and progress of diabetic nephropathy play probably one of the most important roles in increased synthesis and excretion of adiponectin to blood circulation in patients with overt diabetic nephropathy (43).

*Fibroblast growth factor 23 (FGF23)* is a novel independent predictor of progression of renal disease in patients with non-diabetic CKD (44). FGF23, „phosphatonin”, is implicated in the systemic balance of phosphate maintained by the interaction of intestine, bone, and kidneys (45).

*Leptin* – The first longitudinal study focusing on the association between leptin and diabetic kidney disease was performed by Hanai et al in 2011. Both low and high serum leptin levels were proved to be risk factors for kidney function decline. Patients with low leptin levels had a significantly elevated risk of progression of albuminuria compared to those with high leptin levels (46).

*Helicobacter pylori* – Tanriverdi et al demonstrated the relationship between *Helicobacter pylori* infection and diabetic microalbuminuria. The presence of *Helicobacter pylori* infection was detected in 53 of 93 diabetic patients. Diabetic patients infected by *Helicobacter pylori* showed significantly higher microalbuminuria than non-infected patients. Diabetics infected with *Helicobacter pylori* had significantly higher inflammation marker levels than non-infected patients. The relationship between *Helicobacter pylori* infection and diabetic microalbuminuria is, however, due to small number of patients inadequate. Therefore, clinical and molecular studies involving more patients should be supported (47).

### Conclusion

The development of diabetic nephropathy is commonly thought to result from the cumulative interactions between multiple metabolic and hemodynamic factors which activate common intracellular signaling pathways that in turn trigger the production of cytokines and growth factors, leading to renal disease (48). Type 2 diabetes patients with uncontrolled diabetes and increase in blood pressure are at high risk of developing nephropathy. Age, long duration of diabetes, elevated blood pressure and poor glycaemic control are significantly associated with the progression of diabetic nephropathy (23). Early identification of patients at high risk for diabetic nephropathy is therefore important in order to intensify the treatment and modify associated risk factors (49). From the treatment point, tight control of blood glucose, blood pressure, and using drugs affecting renin-angiotensin system, cy-

tokine production and anti-oxidants, may all help to salvage the renal damage. At present, there is sparse information on the risk factors and conversion rate of normal renal function to proteinuria among type 2 diabetes patients. Therefore, further studies are necessary to explore the role of this and other risk factors in diabetic nephropathy. Prevention or slowing the progression of diabetic nephropathy will significantly improve both the patient's quality of life and reduce the public health expenditure (50).

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