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The role of haemodynamic and metabolic factors in the development of diabetic nephropathy

Rola czynników hemodynamicznych i metabolicznych w powstawaniu nefropatii cukrzycowej

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S u m m a r y

Diabetic nephropathy results from the interaction of various factors (metabolic, hemodynamic, neurogenic, and toxic ones) in a genetically predisposed diabetic patient. Up to 50% of diabetics are affected. This manuscript reviews the role of hemodynamic and metabolic factors in the development of diabetic nephropathy. First, the role of glomerular blood pressure changes is described, together with different factors that may influence it in different mechanisms. Then, metabolic factors like hyperglycemia, dyslipidaemia and excess dietary protein intake are addressed. Special attention was paid to hyperglycemia. Four mechanisms associated with it are described, Glucotoxicity, non-enzymatic glycosylation, polyol pathway activation and oxidative stress, all may contribute to development of nephropathy in patients with diabetes. Therefore it seems that also treatment of this complication should be multifactorial.

Key words: diabetes, diabetic nephropathy, intraglomerular blood pressure, hyperglycemia, dyslipidaemia

S t r e s z c z e n i e

Nefropatia cukrzycowa jest wynikiem interakcji wielu różnych czynników patofizjologicznych (metabolicznych, hemodynamicznych, neurogennych i toksycznych) u chorego predysponowanego genetycznie. Występuje ona nawet u 50% chorych. Praca niniejsza opisuje rolę czynników hemodynamicznych i metabolicznych w powstawaniu nefropatii cukrzycowej. Najpierw omówiono rolę zmian ciśnienia tętniczego wewnątrz kłębuszka nerkowego i czynniki mogące je w wielu mechanizmach patogenetycznych modyfikować. Następnie opisano czynniki metaboliczne, takie jak hiperglikemia, dyslipidemia i nadmiar białka w diecie. Szczególną uwagę poświęcono hiperglikemii. Opisano cztery mechanizmy, w których może ona przyczyniać się do rozwoju nefropatii u chorych na cukrzycę: glukotoksyczność, nieenzymatyczną glikację, aktywację szlaku poliolowego oraz stres oksydacyjny. Wydaje się zatem, że leczenie nefropatii cukrzycowej powinno być także wieloczynnikowe.

Słowa kluczowe: cukrzyca, nefropatia cukrzycowa, ciśnienie tętnicze wewnątrzkłębuszkowe, hiperglikemia, dyslipidemia

Overt diabetic nephropathy develops in 20-40% of diabetic patients (1-4). Although pathogenesis of diabetic nephropathy is not entirely elucidated, it is evident from numerous studies that hemodynamic as well as metabolic factors play an important role in its development. Diabetic nephropathy is thus a result of an interplay between those patophysiologic factors, although the basal pathogenetic factor is of course hyperglycemia.

HAEMODYNAMIC FACTORS

Glomerular hyperfiltration is an independent risk factor of diabetic nephropathy both in type 1 and type 2 diabetes (5, 6). It seems that it depends directly upon haemodynamic factors active in the kidneys. Blood pressure and haemodynamics in the glomeruli are under control of and results from an interplay of contracting or dilating afferent and efferent arterioles. Changes in that interplay can be evoked by various factors. In patients with

diabetes, all these factors (tab. 1), as well as variation in systemic blood pressure, result in high blood pressure in glomerular capillaries. This may lead, especially in genetically predisposed patients, to stiffening of glomerular vessels (in a process similar to that that occurs in diabetic retinopathy) and results in transmission of blood pressure onto mesangium with later damage of the latter structure, and in glomerular hyperfiltration. Glomerular hypertension contributes also to damage, apoptosis and separation of podocytes, resulting in proteinuria (7).

Table 1. Chosen factors influencing intracapillary blood pressure (according to 13).

Atherosclerosis and atherothrombosis
Hyperglycemia
Glucagon
Hyperinsulinemia
Hyperketonemia
Insulin-like growth factor-1
Intracellular sorbitol abundance and myo-inositol deficiency
Neurogenic factors
Prostaglandins and bradykinin

In many studies it was shown that glomerular filtration may be affected by following factors: renal blood flow, transcapillary hydrostatic pressure, oncotic pressure and ultrafiltration coefficient (8). These factors are also responsible for hyperfiltration developing in diabetic kidney, in which decrease in the tonus of afferent glomerular arterioles and increase (even if only relative) of it in the efferent arterioles results in increase of intracapillary pressure (9). As angiotensin receptor blockers and angiotensin converting enzyme inhibitors exert a beneficial effect in diabetic nephropathy, and it is known that in diabetic animals and patients the systemic activity of renin-angiotensin-aldosterone system (RAAS) is rather decreased (10), it is believed that it is overactivity of the local renin-angiotensin system that is responsible for these abnormalities.

Similarly, as RAAS inhibiting agents seem to be effective in decreasing of proteinuria also in doses not lowering systemic blood pressure (11), their effectiveness must be dependent upon improvement of local hemodynamic, but also improvement of neural (decrease of adrenergic system activation) and other local factors (decrease of oxidative stress and of local proinflammatory and profibrotic factors) (12).

METABOLIC FACTORS

Hyperglycemia

Hyperglycemia leads to structural and functional disturbances in all diabetic patients (14, 15). In 20-30% of patients who are genetically predisposed renal injury happens faster and is more abundant. Numerous studies revealed an increased risk of glomerular filtration (GFR) decline and albuminuria with elevated HbA_{1c} levels (16-19). Improved glycemic control reduces the risk of micro- or macroalbuminuria, although does not eliminate it. For example, in the Diabetes Control and Complications Trial (DCCT) it has been shown that in type 1 diabetes a more intensive hypoglycemic treatment diminishes the risk of nephropathy by 34-56%, depending on the stage of the disease at baseline (20). In type 2 diabetes intensive glucose-lowering therapy decreases the risk of nephropathy by 33-72% (17, 21). Among newer studies, the ADVANCE trial has shown that an improved glycemic control with the use of gliclazide (as well as a better blood pressure control with perindopril and indapamide) was associated with a 33% reduction of the risk of a new-onset or progression of a previously present nephropathy (22). It is not clear whether a threshold level of HbA_{1c} exists, below which advance of nephropathy is significantly slower. Some studies suggested that this level is at ~8% (21, 23).

It should be added that hyperglycemia is also a risk factor of chronic kidney disease, and a good glycemic control can delay end-stage renal disease (24-26).

Among metabolic mediators of kidney injury due to hyperglycemia, glucotoxicity, non-enzymatic glycosylation, activation of polyol pathway of glucose metabolism, and oxidative stress can be named.

Glucotoxicity

This term describes a direct toxic effect of high glucose concentrations on cells and organs. In kidneys high glucose levels increase extracellular matrix production, number of mesangial cells, and influences expression of different proteins, and cytokines and enzymes. Among them collagen, laminin and fibronectin (27), transforming growth factor β (TGF-β) (28) and matrix metaloproteinases (29) seem to be most important.

Non-enzymatic glycosylation of proteins

Persistent hyperglycemia leads to irreversible glycosylation (glycation) of proteins, forming at the end of this process so called advanced glycation end products (AGEs), with half-life time, that cumulate and exert toxic effects in different tissues, with kidney tissue among them. The result of this process is between others a rise in the number of collagen cross-links and less effective degradation in the extracellular matrix. Cross-linked collagen and other proteins are resistant against degrading enzymes, like metalloproteinases. Additionally AGEs may enhance synthesis of various cytokines, in that way influencing mechanism leading to diabetic nephropathy (30).

Administration of inhibitors of the formation of AGEs (e.g. aminoguanidine) reduces renal accumulation of AGEs and resulting mesangial hypertrophy and albuminuria in experimental animals (31). In humans, a similar nephroprotective effect may be exerted by vitamins B1 and B6 (32, 33). It also seems that beneficial influence of irbesartane in diabetic nephropathy can be attributed to its interaction with AGE receptor and subsequent inhibition of free radicals generation (34).

Polyol pathway of glucose metabolism

The main enzyme of polyol pathway is aldose reductaze (AR), which is intensively expressed in kidneys. This results in higher metabolism of glucose and higher sorbitol synthesis (especially in hyperglycemic

subjects) with accompanying decrease in myoinositol in glomerular cells (35), similarly as in neurons. The mechanism of sorbitol contribution to nephropathy (and neuropathy) is not fully elucidated. It may damage renal cells as an osmotic factor, directly or changing concentration of other osmotic compounds, e.g. sodium. Another possible mechanism is increase of diacylglycerol synthesis, with resulting hyperfiltration.

In few animal and human studies aldose reductase inhibitors (polrestat, fidarestat, tolrestat) reductions of hyperfiltration and albuminuria were noted (36).

Oxidative stress

In the last years the meaning of an oxidative stress in the pathogenesis of diabetic nephropathy is increasing. It appears most likely that oxidative stress and free radicals take part in the pathogenesis of diabetic nephropathy. It is known that high glycemia may cause mesangial cell proliferation also by activation of metabolic pathways leading to free radicals formation. Oxidative stress can be induced by a variety of factors taking part in the pathogenesis of diabetic nephropathy, like AGEs or renin-angiotensin-aldosterone system elements. The latter ones can both stimulate (by AT1 angiotensin receptor induction) or hinder (by activating AT2 angiotensin receptor) formation of free radicals and development of nephropathy (37).

These findings can be of a therapeutic potential, as these pathways can be blocked with resveratrol contained in red wine. It has to be noted, though, that various studies assessing outcomes of inhibition of free radicals formation failed to reveal any clinically significant impact on the progression of nephropathy (38).

Insulin resistance

Insulin resistance can occur independently of hyperglycemia. It is observed that already before the onset of diabetes, overweight, and more precisely visceral obesity, is associated with peripheral insulin resistance. It seems that insulin resistance can also contribute to the development of diabetic nephropathy (39), especially when accompanied by high blood pressure and dyslipidemia. Metabolic syndrome occurrs in almost one third of normoalbuminuric type 1 diabetic patients, almost half of those with microalbuminuria, and in more than 60% of patients with macroalbuminuria or those end-stage renal disease. Metabolic syndrome augments significantly the risk of diabetic nephropathy in the course of type 1 diabetes.

Dyslipidaemia

Diabetic dyslipidaemia is commonly described as atherogenic cluster of elevated serum concentrations of VLDL-, with low HDL-cholesterol levels, and high LDL-cholesterol concentration with formation of so called little dense LDL particles and glycoxydated LDL-cholesterol particles (40).

Disorders of lipid metabolism in diabetic nephropathy are partially due to increased proteinuria (40). On the other hand, and probly most importantly, it is believed, that diabetic dyslipidemia aggravates diabetic nephropathy (41). Glycoxidated LDL may for example increase permeability of the glomerular basement membrane, inducing proteinuria, increase oxidative stress or stimulate mesangial cells proliferation (42). Dyslipidemia may also accelerate diabetic nephropathy as a result of haemodynamic changes following atherosclerosis of renal vessels.

In patients with diabetes high serum cholesterol concentration is associated with faster progression of diabetic kidney disease. It has been also shown that statins can normalize proteinuria and slow down evolution of diabetic kidney disease even independently of lipid-lowering effect, when used adjunctively with the blockade of renin-angiotensin-aldosterone system (43). Statins were found to interfere with prenylation of small GTP-binding proteins of the Ras and Rho families, thereby inhibiting genes encoding proinflammatory and profibrotic mediators, to reduce oxidative stress and to decrease cytokines' synthesis (44).

Excess of dietary protein intake

High protein intake increases albumin excretion. Nevertheless, it should be noted that a good long-term compliance of patients with dietary protein restrictions is hardly achievable, even in the settings of controlled clinical trials. This issue may lie behind the results of a recent study showing no nephroprotective effect of a low-protein diet, in which no statistically significant differences in protein ingestion between the studied groups were observed (45).

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