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The Potential Role of Sympathetic Nerve Activity in the Development of Diabetic Nephropathy

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Diabetic nephropathy is one of the direst complications of diabetes. Progress in medical science has led to introduction of adequate therapeutic methods that can significantly reduce the incidence of this complication, but cannot entirely prevent it. In the recent period much attention was dedicated to the role of excessive activation of the sympathetic nervous system (SNS) in pathogenesis of kidney diseases. The results of experimental and clinical studies reveal that renal affect is associated with increased activity of the SNS, which may lead to progressive multiorgan injury. However, application of drugs inhibiting the activity of the SNS results in lowering of the rate of development of systemic lesions and progression of the glomerulopathy. Preliminary clinical data show that application of moxonidine, SNS inhibitor, in non-hypotensive doses in normotensive patients with type 1 diabetes and microalbuminuria results in decrease of urinary albumin excretion. Non-hypotensive effect of moxonidine, leading to decrease in the progression of diabetic nephropathy, should be confirmed in large clinical trials. Administration of SNS-inhibiting drugs may then become a new therapeutic option in prevention of microangiopathic diabetic complications. *J Clin Basic Cardiol* 2001; 4: 183–184.

Key words: diabetes, nephropathy, sympathetic activity

Application of insulin for the treatment of diabetes mellitus resulted in life extension of diabetic patients. However, it did not prevent them from the development of late complications, which often result in disability, decrease in comfort of life and shortening of life expectancy. Diabetic nephropathy is one of the microangiopathic complications. According to epidemiological data it develops in over 30 % of patients with type 1 diabetes [1]. Recent analyses reveal the decrease in incidence of nephropathy below 10 % in cases of patients treated for over 15 years [2]. Reduction of incidence of diabetic nephropathy is associated with improvement of metabolic control, obtained by the result of widespread administration of intensive insulin therapy [3]. Nevertheless, diabetic nephropathy can develop in a significant number of patients, eventually leading to end-stage renal disease.

Microalbuminuria is the earliest symptom of incipient nephropathy in patients with type 1 diabetes [4]. This term is defined as persistently increased urinary excretion of albumins over a level of 30 mg/24 hours [5]. In accordance with natural history of the nephropathy, microalbuminuria is accompanied by increased arterial pressure [6]. Aggressive antihypertensive treatment of patients with early diabetic renal injury is fundamental in prevention of development of the more advanced stages of nephropathy [7]. It has been confirmed in numerous studies that ACE inhibitors have additional protective impact on the kidneys. There is a consensus placing these drugs in first-line treatment of hypertension in diabetic patients [8, 9]. In spite of ever more perfect methods of pharmacotherapy the progression of renal damage is observed in a significant number of patients. Search for additional pharmacological methods of preventing this progression seems to be of great value.

In recent years increasing attention was paid to the role of activation of the sympathetic nervous system. Hypertension accompanying chronic renal failure CRF may be associated with intensified activation of the SNS. Ye et al. demonstrated in an experiment conducted on 5/6 nephrectomised rats – being the experimental model of renal affect – that noradrenaline turnover and secretion is elevated in posterior nuclei of the hypothalamus in comparison to control animals

[10]. The kidneys are equipped with a rich network of baro- and chemoreceptors [11, 12], while efferent renal nerves are connected with the central nervous system (CNS), responsible for the regulation of the arterial pressure [13]. Activation of the hypothalamic nuclei may thus be related to kidney-generated impulses. Campese et al. [10, 14, 15] demonstrated that in chronic renal ablation model, activation of baro- and chemoreceptors generates stimulating signals, which are next transmitted to the hypothalamus, causing increased local turnover of catecholamines and induction of the intensified efferent sympathetic traffic. This sympathetic system activation series in the experimental model may explain the increase in arterial pressure associated with renal affect. This theory is confirmed by observed normalisation of arterial pressure in animal model after bilateral nephrectomy resulting in elimination of efferent stimuli in the CNS [16].

Thus arises the question whether pharmacological inhibition of the sympathetic nervous system activity could not decrease the progression of glomerulopathy.

Moxonidine, an agonist of I1-imidazole receptors, is one of the drugs that inhibit sympathetic activity. It causes the inhibition of sympathetic activity both in the experimental and clinical model [17] and it acts predominantly on the central level [18]. Main clinical effect of moxonidine is decrease in arterial pressure [19]. The question is whether inhibition of the sympathetic system can result in additional, other than hypotensive, clinical effects. Preliminary data from experimental studies point to such a possibility. Aman et al. measured the progression of renal damage in a group of subtotally nephrectomized rats [20]. In the group of rats receiving low doses of moxonidine the progression of lesions was significantly decreased, with lower glomerulosclerosis index and vascular injury index, in comparison to rats receiving placebo. The protective effect of moxonidine in this experimental model was independent from its hypotensive action. The values of arterial pressure measured telemetrically in animals both on moxonidine and placebo were comparable. Glomerulosclerosis-inhibiting effect is not unique for moxonidine. In the experimental model similar results were obtained with metoprolol [21]. Such data confirm the signifi-

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cant role of the sympathetic nervous system in the progression of organ injury and point to potentially new options of pharmacotherapy [22].

Preliminary clinical data on the role of sympathetic nervous system blockade in prevention of diabetic nephropathy were also obtained [23]. The study we performed comprised 15 patients with type I diabetes, with microalbuminuria and normal arterial pressure. The patients received alternately either moxonidine 0.2 mg bid or placebo for 3 weeks. After every observation period 24 hour ABPM and albumin secretion were measured. The dose applied in our study, carried out on normotensive patients, did not modify the values of arterial pressure. Significant decrease of urinary albumin excretion was observed in patients on moxonidine versus placebo. This short 3-week observation does not definitely confirm the protective effect of sympathetic nervous system blockade in progression of nephropathy. However, it has been demonstrated for the first time that administration of drugs inhibiting the SNS may be a novel therapeutic option in prevention of nephropathy.

In summary it should be stressed that in spite of significant progress in medical sciences observed in recent years the development of nephropathy in diabetic patients cannot be prevented. Aggressive therapy aimed at maintenance of normoglycaemia and normotension slows down the development of ESRD in the course of nephropathy. However, additional therapeutic methods that can altogether stop the progression of nephropathy should be developed. Recently growing attention is dedicated to the role of sympathetic nervous system activation in pathogenesis of organ damage induction. Data from experimental studies and preliminary clinical reports suggest that application of moxonidine may be beneficial in treatment of diabetic patients with early stages of nephropathy. Further studies on larger groups of patients with diabetic renal damage are necessary for complete confirmation of preventive effect of sympathetic nervous system blockade.

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