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Editorial

Current Approach in Diagnosis and Management of Chronic Diabetic Complications

Vojtková Jarmila*

Department of Pediatrics, Comenius University, Slovakia

***Corresponding author:** Vojtková Jarmila, Department of Pediatrics, Jessenius Faculty of Medicine Comenius University and University Hospital in Martin, Kollárova 2, 036 01 Martin, Slovakia, Tel: 421 43 4203 254; Fax: 421 43 4222 678; Email: jarmilavojtkova@gmail.com

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Editorial

Diabetes mellitus, as a heterogeneous group of metabolic diseases characterized by hyperglycemia, becomes a pandemy nowadays considering its dramatically increasing incidence. Hyperglycemia can trigger the variety of processes like non-enzymatic glycation of proteins, polyole pathway, oxidative stress, activation of protein kinase C, proinflammatory cytokines, activation of nuclear factor kappa B or lack of neural growth factor. These processes act in mutual interactions and harm target compounds (proteins, DNA, lipids), cell organelles and membranes, tissues and organ systems. Thus chronic diabetic complications arise (microvascular - diabetic neuropathy, retinopathy, nephropathy and macrovascular – coronary artery disease, cerebrovascular disease and peripheral artery disease), which negatively determine the quality of life in patients with diabetes. The main risk factor for development of chronic complications is long lasting hyperglycemia, the impact of which is highlighted by poor compensation and duration of diabetes, however also other factors are notable – genetic predisposition, immune, environmental or epigenetic influences. By these factors can be explained common clinical experience that some patients despite poor compensation and long diabetes duration do not suffer from any chronic complications and on the other hand, some patients with adequate compensation and just few years after the diagnosis of diabetes have some signs of chronic complications. Dysregulation of autonomic nervous system, that belongs among the first microvascular complications [1], has been described even at the time of diagnosis of type 1 diabetes. Thus, current medical effort is made on the early diagnosis and prompt management of diabetic complications.

In diagnosis, actual trend is to detect the microvascular changes in their earliest stage without visible clinical symptoms. Examination of heart rate variability is regarded as the gold standard in the diagnosis of cardiovascular autonomic neuropathy as it can detect subtle disorders in parasympathetic and sympathetic regulation of heart beat [2]. Decrease of heart rate variability can be found early even when the patient has no symptoms like rest tachycardia or orthostatic hypotension. As the cornea is the most dense innervated part of human body, corneal confocal microscopy enables to analyze the density of corneal nerves, their morphology and branching where by detecting diabetic neuropathy. Other valuable methods are examination of electrodermal activity, electrophysiologic examinations, quantitative examination of sensitive function, electrogastrography, cough reflex sensitivity [3] or spirometry. Possible indicator of tubulopathy is N-Acetyl-Beta-D-Glucoseaminidase (NAG) which positivity in urine precedes the positivity of microalbuminuria and other biomarkers involved in renal tubule-interstitial damage, changes of extracellular matrix or in micro inflammation are searched. New approach in diagnosis is establishment of gene polymorphisms of various genes encoding enzymes that play role in etiopathogenesis of chronic diabetic complications [4]. Gene polymorphisms of aldose reductase, glutathione-S-transpherase M1/T1, superoxide dismutase, catalase, glutathione peroxidase, uncoupling proteins, paraoxonase or angiotensin-converting enzyme have been described to be associated with development of diabetic neuropathy, retinopathy, nephropathy or macrovascular complications. The identification of concrete gene polymorphisms in concrete patient gives base for „customized“ or „individually tailored“ therapy in future.

According to Diabetes Control and Complication Trial [5] patients with better compensation had lower prevalence of diabetic complications and each period of worsened compensation can negatively influence the prognosis of diabetic patient („the effect of metabolic memory“). As important risk factors for micro vascular complications are considered cigarette smoking and genetic susceptibility to hypertension at early stages of diabetes and poorer glycemic control, higher blood pressure and unfavorable lipid profile at later stages. Thus, management of chronic complications is complex and especially involves the improvement of metabolic control of diabetes (tight control of glycemia, lipid profile and blood pressure). Patients with type 1 diabetes are treated by intensified insulin regimen and in patients with type 2 diabetes, administration of selected per oral anti diabetics or insulin therapy is considered. Sufficient physical activity, life style modification (quit smoking, adequate sleep) and dietary management (carbohydrate counting, enough vegetables and fruit, correct food preparation) also contribute to adequate compensation and to delay of the onset of chronic complications. Actually used management of diabetic neuropathy includes supportive (thioctic acid, vitamins group B, antioxidants – vitamin C, E, polyunsaturated fatty acids, L-carnitine) and symptomatic treatment (e.g. magneto therapy, painkillers, beta blockers). Proliferative retinopathy (and also macular edema) can be effectively treated by laser photocoagulation of retina; vitrectomy may be used in the case of severe bleeding or retinal detachment. In diabetic nephropathy, restriction of protein and salt intake and normalization of blood pressure is recommended (angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists or others). Use of ant platelet agents is effective for secondary prevention of diabetic macroangiopathic complications; HMG-CoA reductase inhibitors are effective for primary and secondary prevention of coronary artery

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disease and cerebral infarction. Possibilities in the management of limb ischemia depend on the stage of disease and include muscle training, medications (anti platelet therapy, infusion of prostaglandins), percutaneous transluminar angioplasty, dermoepidermal grafts [6] infection treatment, local therapy of ulceration which is to prevent limb amputation. Other therapeutic possibilities are experimental, till now. In clinical studies, inhibitors of al dose reductase, the key enzyme in polyole pathway, significantly improved the peripheral and cardiovascular autonomic neuropathy [7] and inhibited the progression of diabetic retinopathy and nephropathy [8]. Selective inhibitor of protein kinase C – β, ruboxistaurin, can improve circulatory parameters of retina, decrease macular edema [9], reduce albumin-creatinine ratio [10] and improve the objective measures of diabetic neuropathy [11]. Aminoguanidin is able to prevent the formation of products of advanced glycation and alagebrium chloride helps to eliminate them. Some studies in animal models confirmed their beneficial effect on diabetic micro vascular complications [12,13]. Possibilities of medicament treatment of diabetic retinopathy include intravitreal injections of anti-VEGF (vascular endothelial growth factor) - bevacizumab, that inhibits angiogenesis. On the other hand, combined autologous intramuscular bone marrow mononuclear cell and VEGF gene therapy seems to be effective and safe for patients with diabetes and critical limb ischemia [14]. In the study of Swedish authors, substitution of C-peptide together with insulin in patients with type 1diabetes led to improved functions of peripheral nervous system [15]. As oxidative stress is one of the pathomechanisms of chronic diabetic complications, several studies have reported beneficial effects of a therapy with trace elements able to modulate red ox status or with antioxidants that can eitherreduce the generation of Reactive Oxygen Species (ROS), scavenge them or interfere with alterations induced by ROS. Most of the studies have been done in animal models, e.g. cardio protective effect of sodium ferulate, ROS scavenger, has been shown in streptozocin-induced diabetic rats [16]. Antioxidant mime tics with selen-manganese complexes can possess superoxide dismutase, catalase and glutathione peroxidase activity and decrease the level of lipid peroxidation products [17]. Seleno-organic glutathione peroxidase mimetic, M-hydroxy ebselen, attenuated diabetic nephropathy and diabetes-associated atherosclerosis in mice [18] and superoxide dismutase mimetic, tempol, ameliorated the early retinal changes in diabetic rats [19]. Novel copper-zinc superoxide dismutase mimetic D34 seems to have ant hyperglycemic and neuroprotective effects [20].

To sum up, current research in possible management of chronic complications requires deep knowledge about the pathogenesis as the hope in the therapy represents drugs interfering with certain pathways or molecules involved in the pathogenesis of chronic complications. Identification of concrete gene in concrete patient enables the individual approach and customized therapy in future.

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