

Peripheral diabetic neuropathy: better prevent than cure

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Diabetes and its chronic complications are associated with significant morbidity and mortality, have a significant impact on the quality of life of patients, and are still a great challenge for medicine. Neurovascular complications are specific to patients with diabetes and include retinopathy, diabetic kidney disease, and neuropathy. The specificity means that hyperglycemia plays a crucial role in the development of neurovascular complications in diabetes. There is strong evidence that chronic hyperglycemia, as well as considerable fluctuations in blood glucose levels (glycemic variability), leads to functional and structural destruction of tissue. Glucotoxicity is primarily manifested in the cells that assimilate glucose in the insulin-independent mechanisms, such as endothelial and nervous cells. Neurodegeneration is regarded as a phenomenon that links pathology of the eye with the nervous system. Its pathogenesis in diabetes is multifactorial, complex, and not fully understood. Various mechanisms that lead to neurovascular complications have been reported, such as protein glycosylation, low-grade inflammatory process, oxidative stress, mitochondrial dysfunction, activation of polymorphonuclear neutrophils, glutamate excitotoxicity, and imbalance in neuroprotective factors.¹

In hyperglycemia, glucose metabolism is intensified both by the main and alternative pathways. It results in enhanced glycolysis and mitochondrial overproduction of superoxide anions (O_2^-) that are the main substrate for other reactive oxygen species (ROS). Mitochondria are a source of endogenous ROS in all cell types including endothelial and nervous cells. This reduces mitochondrial energy production and leads to the onset and progression of neurodegeneration. Moreover, hyperglycemia activates polyol pathway flux, leading to accumulation of sorbitol, a decrease in the ratio of a reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) to nicotinamide adenine dinucleotide phosphate, and an increase

in the ratio of a reduced form of nicotinamide adenine dinucleotide to nicotinamide adenine dinucleotide (NADH to NAD ratio). The decline in cellular NADPH may decrease the generation of nitric oxide in cells and alter the cellular redox balance.² The elevation in the NADH to NAD ratio induced by hyperglycemia is characteristic of hypoxia and termed “metabolic pseudohypoxia.” Both endothelial and nervous cells are sensitive to oxygen deficiency. Under conditions of hypoxia, the production of a transcription factor, hypoxia-inducible factor 1 (HIF-1), has been elevated. In diabetes, augmented levels of neuronal HIF-1 have been observed to be associated with an increased inflammatory process.

Moreover, HIF-1 has been found to contribute to impaired regeneration of axons in diabetes. HIF-1 derived from hypoxia can also lead to an increase of NADPH oxidase, which is a major source of ROS in endothelium.³ In diabetic neuropathy, ROS can lead to vascular endothelium dysfunction with reduced nerve perfusion and endoneurial hypoxia.

Physiologically, there is a balance between ROS production and antioxidant defense system. However, in poor glycemic control of diabetes, endogenous antioxidants including superoxide dismutase, catalase, and glutathione enzymatic complex are not efficient enough.⁴ Hyperglycemia boosts glycation of proteins. In the first stage of this phenomenon, poorly reversible early glycation products arise, and in the next stage completely irreversible advanced glycation end products (AGEs) are formed. Intra- and extracellular proteins are modified by AGEs.

AGEs activate inflammatory cells such as mononuclear and polymorphonuclear leukocytes through specific receptors.¹ Metabolic disturbances such as pseudohypoxia, glucose auto-oxidation, and increased production of AGEs generate a peculiar cascade of phenomena leading to activation of protein kinase C and nuclear factor κ B.⁵ This leads to increased production of proinflammatory

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cytokines, chemokines and growth factors, causing other damage of tissues. Thus, protein glycation and AGE formation trigger a chain reaction, creating a vicious circle that leads to the development and progression of chronic complications of diabetes.

There are several methods to assess AGEs. One of them is the measurement of skin autofluorescence. It is well proven that this easy and noninvasive method reflects the accumulation of AGEs in the skin and provides insight into long and very long-term glycemic exposure. Skin autofluorescence measurement has been validated using the assessment of AGE accumulation in skin biopsies.⁵ It has been shown that skin autofluorescence is higher in diabetic patients than in healthy controls. Additionally, there is good evidence that higher skin autofluorescence is associated with a higher risk of chronic diabetic complications including peripheral and small-fiber neuropathy.⁷

AGE accumulation in the corneal epithelial basement membrane and stroma in patients with diabetes may be responsible for clinically observed increased autofluorescence of the lens.⁸ Cahn et al⁹ showed using the ClearPath DS-120 lens fluorescence biomicroscope (Freedom Meditech, San Diego, California, United States) progressively higher fluorescence values in healthy people, patients with prediabetes, type 2 diabetes, and type 1 diabetes. At a fluorescence deviation of 2500, a sensitivity of 67% and a specificity of 94% was observed for the detection of type 2 diabetes. The authors proposed that lens autofluorescence might serve as an additional screening for undiagnosed diabetes. The assessment is fast, noninvasive, and highly specific. The results are corrected for the effect of age. In this issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Sertbas et al¹⁰ presented their findings on the usefulness of lens fluorescence assessment for the diagnosis of diabetic peripheral neuropathy (DPN).

Accumulation of AGEs in the lens is associated with persistent hyperglycemia, thus being an accelerator of aging and a key factor of neurodegeneration. Therefore, the assessment of lens fluorescence might serve as a biomarker of a long-term glycemic exposure. It would be interesting to compare both measurement methods of skin and lens autofluorescence and their usefulness in the early diagnosis of DPN.

The survival, growth, and function of nervous cells depend on the local availability of neurotrophic and growth factors. Dysregulation of neurotrophic factors is considered a major feature of neurodegeneration in the course of diabetes. Several factors have neuroprotective properties; such factors include, for example, somatostatin, brain-derived neurotrophic factor and nerve growth factor, vascular endothelial growth factor, insulin growth factor 1, pigment epithelium-derived factor, and interstitial retinol-binding protein. In diabetes,

the efficacy and reduced concentrations of the above neuroprotective factors have been observed.¹¹ There is emerging evidence that imbalance in the synthesis of neuroprotective factors is an early and crucial phenomenon in diabetic neurodegeneration. These findings are interesting and have clinical implications, but require further research for better understanding.

Diabetic peripheral neuropathy arises as a consequence of damage to the sensory, motor, and autonomic nerves and presents with diverse symptoms and deficits. The development of diabetic peripheral neuropathy affects approximately 50% of patients with diabetes.^{12,13} The most common presentations are somatic and autonomic neuropathies, and an early diagnosis of these subtypes is recommended. Small-fiber neuropathy can develop in patients with prediabetes and patients with newly diagnosed type 2 diabetes. It is possible that insulin resistance and metabolic disturbances associated with these conditions participate in the pathomechanism of neurodegeneration.

The methods currently used in clinical practice to diagnose DPN include obtaining the history of symptoms, a neurologic examination with the assessment of sensation of touch, vibration, temperature, and pain, and evaluation of tendon reflexes. These methods allow a detection of moderate and severe large-fiber neuropathy, but are not sufficient to detect early small-fiber neuropathy. The small-fiber damage in diabetes is typically manifested as painful neuropathy.¹² The risk factors for painful diabetic neuropathy include older age, duration of diabetes, poor glycemic control, obesity, smoking, low high-density lipoprotein cholesterol levels, elevated low-density lipoprotein cholesterol and triglyceride levels, and renal failure. Thus, small-fiber damage seems to be associated with insulin resistance and aging. The gold standard for diagnosis of small-fiber neuropathy is skin biopsy and the assessment of intraepidermal nerve fiber density. This invasive method is not easy and not useful in the clinical practice. It was shown previously that intraepidermal nerve fiber density in skin biopsy is associated with a higher accumulation of AGEs in the skin.¹³ Measuring skin and lens autofluorescence is a noninvasive assessment of the accumulation of AGEs with fluorescent properties in tissues, and it might confirm that symptoms and signs of neuropathy are a result of glucotoxicity.¹⁴

Diabetic neuropathy has a significant impact on morbidity and mortality in diabetes and yet remains a vastly underdiagnosed and inadequately managed complication. There is evidence that improvement in vascular risk factors alongside glycemia may have a beneficial effect on the prevention and treatment of DPN.¹⁵ Moderate relief of symptomatic, painful, and autonomic neuropathy seems to be possible, but the key is early recognition and tailored treatment. Therefore,

a better understanding of the risk factors and mechanisms underlying the pathogenesis of neuropathy increases the chance of greater efficacy in the prevention and treatment of this particular complication of diabetes.

ARTICLE INFORMATION

DISCLAIMER The opinions expressed by the author are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

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