PATHOPHYSIOLOGY OF DIABETIC POLYNEUROPATHY - METABOLIC THEORIES

ADINA STOIAN[1], M. STOIAN[2], OLGA BRUSNIC[3], CARMEN DUICU[4], CRISTINA GÎRBOVAN[5], C. NEAGU[6], F. BUICU[7]

[1,4,5,6,7]University of Medicine and Pharmacy, Tg-Mureş, [2]County Clinical Hospital, Mureş, [3]Regional Emergency Clinical Hospital, Mureş

Keywords: *diabetic polyneuropathy, risk factors, metabolic theories*

Abstract: *The aim of this article is to bring into light the current metabolic theories underlying the pathophysiological changes that lead ultimately to the development of diabetic polyneuropathy. The factors that contribute to the development of diabetic polyneuropathy are not fully understood, so that multiple hypotheses were advanced. It is generally accepted as a multifactorial process. The development of clinical symptoms depends on many factors such as prolonged hyperglycaemia and other risk factors such as dyslipidaemia, hypertension, smoking, overweight, exposure to other toxic agents like alcohol. Genetic factors also play an important part.*

Cuvinte cheie: *polineuropatie diabetica, factori de risc, teorii metabolice*

Rezumat: *Scopul acestui articol este de a readuce în discuție teorii metabolice recente care stau la baza modificărilor fiziopatologice care conduc în final la dezvoltarea polineuropatiei diabetice. Factorii care contribuie la dezvoltarea polineuropatiei diabetice nu sunt pe deplin înțeleși, motiv pentru care au fost avansate multiple ipoteze. În general se acceptă că este un proces multifactorial. Dezvoltarea simptomelor depinde de o multitudine de factori precum hiperglicemia prelungită și alți factori de risc cum sunt dislipidemia, hipertensiunea arterială, fumatul, supraponderabilitatea, expunerea și la alți agenți toxici precum alcoolul etilic. Factorii genetici joacă de asemenea un rol important.*

The factors that contribute to the development of diabetic polyneuropathy are not fully understood, so that multiple hypotheses were advanced. It is generally accepted as a multifactorial process.

1. Hyperglycaemia

The pathogenesis is complex but hyperglycaemia is the primary factor. Numerous clinical studies, including Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) that analyzed the relationship between glycaemia control on one hand and the onset and progression of microvascular complications on the other hand, have confirmed this.(6) The risk of microvascular and macrovascular complications in the patients with type 2 diabetes in the UKPD study is closely associated with hyperglycaemia, including the level of HbA1c. There is no evidence of a threshold value but the risk is three-fold from HbA1c values of <6% at values ≥10%.(7)

In Oxford, Stockholm (8) and DCCT (9), clinical trials intensive treatment of hyperglycaemia was clearly associated with a reduction in the progression of polyneuropathy.

The Kumamoto Study that randomized 110 Japanese patients with type 2 diabetes, 55 of them having background diabetic retinopathy at baseline, showed 8 years later that in the group with multiple daily injections of insulin and tight glycaemia control, there was a reduced progression of retinopathy and an improvement rather than a worsening in nerve conduction velocities compared with the group treated less intensively.(10)

Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed a reduction in microvascular complications in the kidney, eyes and peripheral nerves in the group of patients with type 2 diabetes and intensive glycaemia control with a value of HbA1c<6% compared with the group of standard therapy and a value of HbA1c between 7-7,9%. These benefits at microvascular level must be weighed against the risk of severe hypoglycaemia, weight gain and an increase in cardiovascular mortality and total mortality that occurred in the group with intensive glycaemia control.(11)

Although some authors contest the presence of suggestive neurophysiological evidence in patients with impaired glucose tolerance (IGT), recent studies demonstrate the role of glycemic imbalance and the development of polyneuropathy.(12)

Children with type 1 diabetes present a reduction in nerve conduction velocities suggesting that neural dysfunction starts relatively early but in spite of advanced nerve dysfunction, there is a degree o reversibility in the patients with pancreatic transplant (after the transplant, there was found an improvement in the neurophysiological results in these patients).(13)

An intensive insulin therapy or pancreatic transplant that improves hyperglycaemia is followed by an improvement in electrophysiology tests in the patients with type 1 diabetes.(14).

2. The polyol pathway

Hyperglycaemia increases the intracellular levels of glucose in the nerve cells, leading to the saturation of the normal glycolytic pathway. The activity of hexokinase /glucokinase is insufficient to counter the effect of increased glucose influx, while the excessive glucose is metabolised by alternative pathways, primarily on the polyol pathway and converted to sorbitol and fructose by the enzymes aldose reductase and sorbitol dehydrogenase.(15) Aldose reductase reduces glucose to

[1] Corresponding author: Florin Buicu, Str. Maramureş Nr. 10, cod postal: 540552, Tg-Mureș, e-mail: gabrielabuicu@yahoo.com
Article received on 05.04.2012 and accepted for publication on 18.05.2012
ACTA MEDICA TRANSILVANICA June 2012;2(2):218-221

sorbitol by using Nicotinamide adenine dinucleotide phosphate (NADPH) and sorbitol is reduced to fructose by using Nicotinamide adenine dinucleotide (NAD^+). The excessive consumption of NADPH reduces the level of nitric oxide in the vasculature (16) and an increased NADH/NAD^+ ratio leads to the amplification of the oxidative stress and decreases the activity of Na^+/K^+-ATP-ase.(17)

The consequences of these metabolic alterations are: Sorbitol and fructose cover poorly the cell membrane and being thus accumulated intracellularly with an osmotic imbalance and hyperosmolarity development with an increased water influx and efflux of other osmo-effectors like myoinositol and taurine.(18,19) Myoinositol depletion was held responsible for the secondary worsening of the membranary phosphoinositides with the reduction of the activity of Na^+/K^+-ATP-ase with intra-axonal Na^+ accumulation and further increase of intracellular hyperosmolarity leading to altered axonal transport, structural lesions of the nerves with abnormal propagation of the action potential and decreased nerve conduction velocity. The oxidative stress is accentuated and there is "pseudo hypoxia" through NADH/NAD complex imbalance. There is an increased formation of advanced glycation and products (fructose is ten times more susceptible to glycation process than glucose).

Studies performed on animal models have convincingly demonstrated the association between the increased flux through polyol pathway and a reduction in nerve conduction velocity, both of them being improved after the administration of aldose reductase inhibitors.(20)

Zenarestat, a potent inhibitor of aldose reductase showed a reduction in the levels of sorbitol with over 80% in sural nerve biopsy, an improvement in nerve conduction velocities and in morphological changes in the patients with diabetic polyneuropathy.(21)

Another study on 279 patients with diabetes showed an increase in nerve conduction velocity in median nerve accompanied by a reduction of pain, paraesthesia and hyperaesthesia after the administration of fidarestat, a potent inhibitor of aldose reductase.(22)

3. Activation of hexosamine pathway

This pathway has been proposed as a self-regulating mechanism for the adjustment of cell's acquisition and use of glucose.(23) The excess of glucose-6-phosphate instead of being metabolized to fructose-1,6-bisphosphate through glycolysis pathway is converted to glucosamine-6-phosphate, a process catalyzed by the enzyme fructose-6-phosphate aminotransferase and further is converted to the synthesis of UDP (uridine-diphosphate)-N-acetyl-glucosamine which in turn induces: alterations in proteins phosphorylation with decreased activity of Endothelial Nitric Oxide Synthase (eNOS); activations of nuclear transcription factors and increased synthesis of TGF-β1 (transforming growth factor-β1), TGF-α, plasminogen activator inhibitor (PAI-1) which are involved in vascular regulation and development of vascular complications.(24)

4. Protein glycosylation

Hyperglycaemia in diabetes may induce irreversible glycation of intracellular and extracellular proteins, resulting in Advanced Glycation End-products (AGEs) which play an important part in the ageing processes and diabetic vascular complications development.(25)

The initial phase of this process consisting in Schiff base formation is reversible.

The appearance of early glycations products reflects irreversible changes. These early products of glycosilation are subsequently transformed in AGEs in the presence of oxygen.

Excessive formation of AGEs induces cell injury through several mechanisms including modification of extracellular proteins such as collagen type I and IV with secondary alterations of their functions.(26) AGEs act on specific receptors (RAGEs), some of them being identified in endothelial cells, pericytes, smooth vascular muscle cells, mesangial cells, monocytes/macrophages and lymphocytes all of them being involved in the development of diabetic vascular complications.(27)

In experimental diabetes, these changes can be prevented by administration of AGE inhibitors.(28,29). Early glication products act themselves as catalysts in reactions involving the formation of free radicals and play a part in tissue damage caused by lipid peroxidation.

The interaction between myelin and AGE on one hand and macrophages on the other hand is considered by some authors as the first stage of segmental demyelination.(30)

AGEs have been identified in patients with diabetic polyneuropathy in the endonerium, capillary endothelial cells within the endonerium and perinerium.(31)

5. Myoinositol

Although myoinositol deficiency was suspected to have a role in the pathogenesis of diabetic polyneuropathy, there are many conflicting data showing that a number of issues remain unsolved despite the application of recent technology methods and intensive efforts made by researchers. Impaired axonal transport of certain enzymes such as acetylcolinestherase and dopamine β-hydroxylase was demonstrated in patients with diabetic polyneuropathy.(32) It is assumed that certain stages of slow anterograde transport are related to changes in myoinositol metabolism. These assumptions are suggested by the observation that both administrations of myoinositol and aldose reductase inhibitors normalize delayed transport of acetylcolin transferase in diabetes induced by streptozocin.(33) In paranodal region of the node of Ranvier in the peripheral nerves, the increased intracellular Na^+ leads to axonal swelling and axoglial disjunction with detachment of the myelin layer from the axon. According to some authors, the primary cause of these lesions is Na^+/K^+-ATP-ase dysfunction because they could not prove a causal relationship between myoinositol depletion and reduced activity of Na^+/K^+-ATP-ase. Another study conducted in 2000, shows that the level of myoinositol in sural nerve does not differ in the patients with normal glucose tolerance, IGT or type 2 diabetes.(34)

6. Oxidative stress

Physiologically, tissue concentrations of reactive oxygen species (ROS) is set by the balance between pro-oxidant and antioxidant actions. Increased oxidative stress is due to the formation of excessive ROS (superoxide and hydroxyl radicals) and by reducing ROS scavengers (glutathione, catalase and superoxide dismutase).(35)

Hyperglycaemia can induce oxidative stress through several mechanisms.(36) AGEs accumulation and AGEs-RAGE interaction causes vascular oxidative stress, action that is probably mediated by the activation of NADH oxidase and protein kinase C. A major source of ROS formation in diabetic patients is an increased flow through mitochondrial respiratory chain producing increased quantities of protons with reducing role resulting in superoxide generation increase.(17)

ROS formation and increased oxidative stress may contribute to multiple vascular lesions in diabetic patients such as endothelial dysfunction, vascular permeability changes, induction of leukocyte adhesion, altered vasomotor tone.

The role of oxidative stress in the development of diabetic vascular complications is supported by several clinical studies demonstrating the beneficial effect of antioxidants. The administration, on animal studies, of antioxidants such as vitamin C, vitamin E and α-lipoic acid partially prevents

vascular pathological changes, positive effects regarding diabetic neuropathy being reported.(37)

Aladin II study reported benefits after α-lipoic acid administration, a powerful antioxidant that neutralizes hydroxyl, superoxide and peroxyl radicals and produces glutathione regeneration.(38)

There is evidence that genes polymorphisms for mitochondrial superoxide dismutase (SOD2) and extracellular superoxide dismutase (SOD3) may confer an increased risk for developing polyneuropathy. This may partly explain the lack of effect of some antioxidants.(39)

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