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Clinical aspects of protein glycation

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ABSTRACT

Introduction. Glycation is a post-translational modification of proteins that depends on the non-enzymatic linkage of a ketone or aldehyde group of sugar with a free amino group of protein. Pathological effects of this process are observed in many disease states under conditions of hyperglycemia, in diabetic complications, and neurodegenerative diseases such as multiple sclerosis.

Aim. In this paper we present the characteristics of the glycation process, its consequences, as well as a review of current knowledge about the role of glycation in multiple sclerosis.

Material and methods. The databases EBSCO, PubMed, ScienceDirect and SpringerLink were used to search the literature.

Analysis of the literature. Intermediate glycation products form a number of derivatives that contribute to oxidative stress and structural changes in the proteins, including induction of aggregation or reduction of affinity for drug proteins. Glucose products may contribute to neurodegenerative changes in patients with multiple sclerosis. Determination of protein glycation products can be successfully used to evaluate the course of multiple sclerosis as a diagnostic marker.

Keywords. AGEs, glycation, advanced glycation end products, multiple sclerosis.
ments are stable AGEs, which can accumulate in tissues (Fig. 1).1-3

Aim
The aim of this paper is to review the consequences of glycation of proteins and to determine the contribution of glycation in multiple sclerosis.

Material and methods
The following databases were searched: EBSCO, PubMed, ScienceDirect, SpringerLink (from 2003 to 2017) using the keywords: glycation, glycoxidation, advanced glycation end products, AGEs, multiple sclerosis.

Analysis of the literature
Advanced glycation end products
During the course of non-enzymatic glycation, reactive oxygen species (ROS) are generated and for this reason the reaction is often called glycoxidation.4 The most important glycoxidation products of the AGEs group are pentosidine and carboxymethyllysine.5 Peroxides generated by the mitochondria play an important role in the formation and accumulation of AGEs in tissues, resulting in oxidative stress and inflammation.6 The reactive oxygen species generated during glycation are able to oxidize the amino acid residues of the proteins to form carbonyl derivatives and disulfide bridges between the various protein molecules that result from the oxidation of thiol groups.7 Glucose is also affected by highly reactive sugar derivatives such as 1-oxoaldehydes, including glyoxal and methylglyoxal. These aldehydes are important precursors of AGEs and can develop in the body as a result of glucose degradation and early glycation product formation. Glyoxal is synthesized by lipid peroxidation, monosaccharide degradation and glycated proteins. In turn, methylglyoxal under physiological conditions is generated by non-enzymatic dephosphorylation of phosphodihydroxyacetone and 3-phosphoglycerol aldehyde as well as DNA degradation.8 Elevated concentrations of methylglyoxal is observed in the plasma of patients with diabetes and may be a marker for predicting progression of diabetic microangiopathy.10 Methylglyoxal is an inducer of glycation on arginine residues, resulting in formation of adducts of hydroimidazolone while glucose reacts with lysine residues or with N-terminal amino acid residues resulting in the formation of fructosamine adducts. In this reaction, glycated hemoglobin is formed.11 AGEs are formed under physiological conditions, although pathological formation occurs under hyperglycaemia, diabetic complications, and progresses with age and in various disease such as Alzheimer’s disease, Parkinson’s disease, cataract, cystic fibrosis or multiple sclerosis.12-18

Consequences of protein glycation
Glycation induces a number of structural changes in proteins, including increase in molecular weight, resistance to proteolytic enzymes, reduction in microbial polarity, hydrophobicity, protein affinity for many drugs, and induction of protein aggregation.19,20 The literature indicates that AGEs gradually accumulate in the lens and retina resulting in the formation of high molecular weight protein aggregates that diffuse light and restrict the field of vision. Accumulation of AGEs causes diabetic retinopathy and age-related macular degeneration and progression of cataracts is exacerbated in patients with diabetes mellitus.21 Proteins such as collagen, lens crystalline, ferritin, apolipoprotein and albumin are glycated in vivo. The amino acid residues that are most susceptible to glycation are lysine, arginine and cysteine due to strong nucleophilic properties. Lysine at position 525. in human albumin and lysine at position 524. in bovine albumin are considered to be the most reactive glycation sites of albumin in native conformation.22,23 Cysteine thiol is a potent nucleophile that can be glycated to S-carboxymethylcystine, suggesting involvement of cysteine at position 34. in this process.24 Glycation of plasma proteins, including albumin, fibrinogen and globulin can cause adverse effects including changes in

Figure 1. The steps of the formation of advanced glycation end products
platelet activation, ROS formation, fibrinolysis or immune system dysfunction.42

Glycated albumin has significant clinical effects as it has been confirmed participation glycated albumin in diabetic retinopathy and coronary diseases related to diabetes.25,26 It was shown a correlation between the level of glycated albumin and renal failure and diabetic microangiopathy.27 The results of studies indicate that glycated albumin, due to a shorter half-life than hemoglobin, can be used as an alternative marker for glycemic control.28 Moreover, the marker more accurately reflects plasma glucose changes even in patients with hematological disorders.29 Some researchers hypothesize that with age or in various pathological conditions, there is an imbalance between generation and removal of AGEs. Increased endogenous formation of AGEs and the provision of AGEs in the diet leads to a deterioration of renal function. Accumulation of AGEs in tissues results in organ dysfunction.

About 70% of consumed AGEs remain in the body and accumulate in tissues, while the remaining 30% is excreted within three days after ingestion.30 Diets of populations from developed countries is particularly rich in advanced glycation end products, and products especially rich in AGEs are processed products and food of animal origin.31

It is known that consumption of foods rich in AGEs in patients with diabetes mellitus type I and II contribute to the generation of proinflammatory cytokines which leads to tissue damage, and insulin resistance.32,33 Moreover, studies carried out in vitro on cell lines and in vivo indicate that exogenous AGEs cause damage to pancreatic β-cells.34 Currently, many studies focus on finding effective glycation inhibitors that could be used in future diabetes therapy. Effective glycation inhibitors include aminoguanidine and pyridoxine, polyphenols and nitroxides, i.e. synthetic organic radicals that have an unpaired electron located on the nitroxyl group.35-37 Increasingly, the attention of researchers are turning to natural products or even natural ingredients of food due to the high availability and effectiveness of inhibiting the generation of AGEs. Effective inhibitors of glycation with plant origin include rutin, quercetin, genistein, kaempferol, naringin, caffeic acid and ferulic acid.38

It is known that antioxidants can quench free radicals generated by glycation, and also prevent autooxidation of monosaccharides and Amadori products. It is also claimed that these compounds may prevent cross-linking of proteins by AGEs.38

Multiple sclerosis and glycation
Multiple sclerosis (MS) is a chronic, autoimmune, inflammatory disease of the central nervous system which causes demyelination and destruction of axons. The immune response mainly involving autoreactive T lymphocytes, is directed against myelin, which is recognized as a foreign substance. In addition, microglial cells and macrophages release inflammatory mediators and leukocyte stimulating activity in support of damage within the central nervous system.39

The course of the disease is very diverse and unpredictable. In most patients, the disease initially causes reversible neurological deficits often accompanied by progressive deterioration of the neurological state over time.40 About 85% of patients suffer from the relapsing-remitting form of MS characterized by the appearance of relapses, which are emergency signs of damage to the nervous system including periods of relative stability.41

It is estimated that about 2.5 million people suffer from multiple sclerosis in the world.42 MS is a complex disease that is caused by the interaction of environmental factors and genetic predisposition. In recent years, factors involved in the etiology of the disease include oxidative stress, which is defined as the imbalance between the generation of ROS and the mechanisms that are responsible for their elimination. It has been suggested that enhanced generation of ROS as well as reactive nitrogen forms leads to oxidative and nitrosative stress that damages mitochondria, myelin, causes oligodendrocyte apoptosis and astrocyte dysfunction.43 It seems that increased oxidative stress in patients can promote the progress of glycoxidative damage proteins, and determination of glycation end products can be a marker for assessment of the clinical status of patients with MS. In patients with multiple sclerosis, elevated plasma pentosidine levels as well as carboxymethyllysine were detected by immunohistochemical techniques in posthumous hippocampal preparations.44,45 On the other hand, no significant difference in the concentrations of AGEs and pentosidine was observed in the cerebrospinal fluid and serum of patients with MS as compared to the control group in a study carried by Kalousová et al.46 Studies conducted by Sternberg indicate that the determination of AGEs, especially the glycation product – carboxethyl lysine, may be useful for assessing the severity of the disease. Moreover, in these studies it was demonstrated that the use of disease-modifying drugs (interferon β, glatiramer acetate, and natalizumab) reduces glycation end products in the plasma of patients.17

Studies conducted by Sadowska-Bartosz indicate that despite elevated blood glucose levels, elevated AGEs levels in serum were detected in newly diagnosed and previously untreated patients compared with healthy subjects. The level of AGEs in cerebrospinal fluid did not significantly differ between patients with MS and the control group.19 Many studies have shown that in MS patients, increased glycolysis and lipid peroxidation occurs which causes an increased synthesis of AGEs derived from methylglyoxal.57,48 Literature data suggest that in MS patients, astrocytes and oligodendrocytes
are the main source of reactive dicarbonyl compounds which are precursors of AGEs.49

In patients with MS, decreased levels of reduced glutathione, which is a co-factor of glyoxalase involved in the detoxification of methylglyoxal, was observed. In turn, it was noted that the enzyme activity of glyoxalase is reduced which leads to accumulation of aldehyde in the cells, which promotes increased production of AGEs.26,51 Studies conducted by Andersson show that the expression of receptors for advanced glycation end products changes in animal models of MS.52 Similarly, overexpression of these receptors was observed in phagocytes and CD4+ T cells in samples from the brains of experimental animal model of MS.53 The impact of methylglyoxal on endothelial cells of the blood-brain barrier leads to the glycation of proteins of the basal membrane and intercellular structural proteins, leading to a loss of a tight junction between cells and promotes increased permeability of immune system cells.54 It seems that treatment with glycation inhibitors can be included in therapeutic methods for MS for prevention of AGEs formation, which may be a new and improved therapeutic tool for patients with multiple sclerosis.

Conclusions
— Glycation of proteins causes many structural and functional changes in proteins.
— The process of glycation increases with age, as well as in a number of disease states.
— In MS patients, increased generation of AGEs is observed.
— Determination of glycation products can be used to assess the course of MS and the effectiveness of therapy.

References
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