Horizon | Journal of Humanity and Artificial Intelligence

EVALUATION OF THE EFFECTIVENESS OF ANTIOXIDANTS ON THE FUNCTIONAL STATE OF THE KIDNEYS IN PATIENTS WITH DIABETIC NEPHROPATHY

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Abstract

Diabetic nephropathy (DN) is a specific kidney damage in diabetes mellitus (DM) accompanied by the formation of nodular or diffuse glomerulosclerosis, the terminal stage of which is characterized by the development of chronic kidney disease (CKD). Diabetic nephropathy is a serious and frequent complication of diabetes mellitus, leading to end-stage renal failure in 30% of diabetic patients. The first manifestation of DN is microalbuminuria, which occurs as a result of decreased barrier function of glomerular filtration for albumin. Reactive oxygen species, inflammatory cytokines and growth factors play key roles in the impairment of this function. Worldwide, DN and resulting CKD is the leading cause of death in type 1 DM patients. In patients with type 2 diabetes, DN is the second leading cause of death after cardiovascular disease. Diabetology has accumulated experience in the use of all antioxidants. In principle, the prescription of antioxidant therapy in DM can pursue two goals: prevention (slowing down the development) of the disease; prevention (slowing down the development) of its complications.

Keywords: Diabetes mellitus, diabetic nephropathy, chronic kidney disease, oxidative stress, antioxidants.

Diabetes mellitus is a metabolic disease defined by a relative or absolute deficiency in insulin secretion. Today, diabetes is known to be one of the leading causes of mortality and morbidity in the world.

Complications of disease progression include retinopathy, nephropathy, cardiomyopathy, hepatopathy, and neuropathy. Diabetes generally consists of several subcategories, such as type 1 diabetes mellitus, which is manifested by absolute insulin deficiency caused by cell-specific autoimmune destruction of the insulin-producing beta cells of the pancreas. Type 2 diabetes mellitus resulting from inability of beta cells to balance insulin release or selective loss of pancreatic beta cells due to vivo infections or toxic damage leading to insulin insufficiency. Diabetic nephropathy is one of the critical problems of diabetes mellitus, the prevalence of which is increasing worldwide.

The high prevalence of type 2 diabetes mellitus (DM2) worldwide has led to a dramatic increase in the number of patients with chronic diabetic complications, among which diabetic nephropathy (DN) is one of the most dangerous. Its prevalence in patients with DM2 is estimated at about 40%.

The term “diabetic nephropathy” refers to specific kidney damage in diabetes, accompanied by the formation of nodular or diffuse glomerulosclerosis, leading to the development of terminal renal failure (TRF), requiring renal replacement therapy (RRT) or kidney transplantation. The diagnosis of DN is based on the presence of albuminuria (AU) and/or decreased glomerular filtration rate (GFR). Urinary albumin excretion reflects systemic endothelial dysfunction, glomerular barrier permeability, proximal tubule reabsorption capacity and is an important indicator of renal function.

The first descriptions of kidney pathology in diabetes were casuistic, because life expectancy in diabetes was extremely short due to the high mortality rate from ketoacidotic coma. Rarely did patients with "sugar disease" survive to the pronounced clinical manifestations of diabetic nephropathy.

Worldwide, diabetic nephropathy (DN) and the resulting renal failure are the leading cause of death in patients with diabetes mellitus (DM) type 1. In patients with type 2 diabetes, DN is the second leading cause of death after cardiovascular disease.

The World Health Organization has officially recognized diabetes as an incurable disease at the current level of medical science and clinical practice, placing the onus on the patient himself to take responsibility for his health. It can be assumed that the global transition of mankind to a dramatically disconnected from nature lifestyle, which inevitably generates diabetes, is paid for by such a powerful biological shake-up of the entire planetary population.

The situation changed dramatically 80 years ago when Canadian surgeons F.G. Banting and S.N. Best, together with biochemist J.B. Collip made a breakthrough in the treatment of DM by isolating insulin from the pancreas of animals, suitable for the treatment of DM in humans. Since that time the structure of DM complications gradually began to change: acute ketoacidotic states, the frequency of which was up to 90% in the early 20th century, gave way to late vascular complications - micro- and macroangiopathies, the frequency of which now reaches 50-70%.

Today, the term “diabetic nephropathy” is more commonly used, since the term “diabetic glomerulosclerosis” reflects already far advanced morphological changes.

DN is one of the most serious complications of DM, leading to early disability and death of patients from terminal renal failure.

DN as a form of pathology in DM is characterized by a complex of lesions of arteries, arterioles, glomeruli and tubules of kidneys resulting from disorders of carbohydrate and lipid metabolism.

It is accepted to distinguish three stages of DN:

1. stage of microalbuminuria (MAU);
2. stage of proteinuria with preserved kidney function
3. stage of chronic kidney disease (CKD)

At the same time, it has been established that only at the MAU stage (the so-called silent stage) it is possible to prevent the progression of renal pathology and to prevent the development of CKD.

Oxidative stress caused by hyperglycemia has been identified as one of the main links between diabetes and diabetic complications. Consequently, hyperglycemia causes auto-oxidation of glucose and glycosylation of proteins by generating free radicals, thus increasing the amount of reactive oxygen species (ROS), accompanied by a decrease in antioxidant activity, resulting in oxidative stress. They can cause endothelial dysfunction, insulin resistance and changes in the proportion and function of pancreatic betta cells and ultimately lead to diabetic microvascular and macrovascular complications.

To date, oxidative stress has been defined as a state of imbalance between the presence of antioxidants and oxidants in the biological system towards the predominance of the latter, which leads to cell damage.

Levels of reactive oxygen species that exceed the cell’s defenses cause serious cellular damage by damaging DNA, proteins, carbohydrates, and lipids.

Fibrogenic responses induced by reactive oxygen species include various cellular functions such as hypertrophy, migration, proliferation, apoptosis, and regulation of the extracellular matrix. It has been shown that active oxygen species are directly related to the diffusion of fibroblasts to a smooth muscle actin expressed by myofibroblasts.

Reactive oxygen species are generated by one-electron reduction of oxygen, usually by non-enzymatic and enzymatic (xanthine oxidase, myeloperoxidase, mitochondrial oxidases, lipoxygenase and nicotinamide adenine dinucleotide phosphate oxidase - NADPH oxidase) pathways. NADPH oxidase is a major source of enzymes for the generation of reactive oxygen species in fibrotic disease and is now recognized as a key mediator of cell proliferation and extracellular matrix accumulation in renal disease. This enzyme is multicomponent. NADPH oxidase was originally found in neutrophils, where it plays an important role in defense against bacteria by producing superoxidanion via electron transport, enabling oxygen-mediated phagocytosis.

Antioxidants (AO) are substances that have the ability to interact with various reactive oxidants, reactive oxygen species (ROS), other free radicals and lead to their partial or complete inactivation.

Drugs with antioxidant activity are widely used in medicine to correct free-radical oxidation (FRO) processes in various diseases. ARs can effectively correct energy metabolism by normalizing the functions of the respiratory chain of mitochondria that carry out oxidative phosphorylation, and other metabolic pathways that supply energy substrates. There is a physiological antioxidant system (AOS) in the body that maintains the oxidant-antioxidant balance in all organs and systems.

All ARs are classified into drugs of indirect and direct action. In addition, according to the origin ARs are divided into two groups: enzymatic superoxide dismutase (SOD), katalase, glutathione peroxidase (GP), glutathione reductase and non-enzymatic nature. The latter are subdivided into substances of endogenous (coenzyme Q10, glutathione, a-lipoic acid, etc.) and exogenous origin - vitamins A, C, E, carotenoids, polyphenols (flavonoids) and their synthetic analogues - low molecular weight compounds (ubiquinone, glutathione), microelements (selenium).

Derivatives of the 3-oxypyridine series have a wide range of biological effects. Among them, compounds that have antihypoxic, antioxidant activity, the original spectrum of neurotropic drug action at the neuronal level (antioxidant, antihypoxic, cerebroprotective, anti-amnestic and anti-alcoholic), improve cerebral blood flow, inhibit platelet aggregation, increase antithrombogenic potential of blood, reduce total cholesterol levels, have cardioprotective and anti-atherosclerotic effects. Thus, it is reasonable to search for potential cardio- and neuroprotective agents among the oxypyridine derivatives. In recent years, the drugs ethylmethylhydroxypyridine succinate and tiotriazolin are being actively studied.

Ethylmethylmercaptopyridine succinate inhibits free-radical processes of lipid oxidation and has a modulating effect on the activity of membrane-bound enzymes and ion channels. It was found that ethylmethylhydroxypyridine succinate has no effect on the activity of trypsin-like, cysteine proteinases and their endogenous inhibitors in the rat brain tissue extract in vitro. However, the ability of ethylmethylhydroxypyridine succinate to affect the activity of proteolytic enzymes and their endogenous inhibitors in the brain tissue and serum has not been sufficiently studied.

Ethylmethylhydroxypyridine succinate has antioxidant, membrane stabilizing and nootropic effects. It inhibits lipid peroxidation, increases the activity of the antioxidant system, activates energy-synthesizing functions of mitochondria, improves energy metabolism in the cell. Improves metabolism, blood rheological properties and microcirculation, inhibits platelet aggregation. Lowers total cholesterol and low-density lipoprotein levels and causes regression of atherosclerotic changes in arteries.

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