Introduction

Approximately 425 million people in the world have diabetes mellitus (DM), out of which around 1.3 million cases of DM were registered in Ukraine. The global prevalence of DM in individuals over the age of 18 years has risen from 4.7% in 1980 to 8.5% in 2014 [1]. According to the WHO, diabetes was the seventh leading cause of death in 2016.

DM is characterized by hyperglycemia-induced tissue damage as established in the Diabetes Control and Complications Trial and the U.K. Prospective Diabetes Study. Generally, the damaging effects of hyperglycemia are differentiated into microvascular complications (diabetic retinopathy, neuropathy and nephropathy) and macrovascular complications (coronary artery disease, peripheral artery disease and stroke). The effects of hyperglycemia are not seen in all cells of the body, but are distinct only in certain types of cells: neurons and Schwann cells in peripheral nerves, capillary endothelial cells, mesangial cells in the renal glomerulus due to their inability to effectively maintain a constant level of glucose, in contrast most cells are able to reduce the transport of glucose when exposed to hyperglycemia [2, 3].

Diabetic sensory polyneuropathy (DSPN) is amongst the most common long-term complications of diabetes [7]. It has been estimated that 50% of diabetic patients will have neuropathy within 25 years of their disease history [8]. The increased risk of non-traumatic foot amputations and lower extremity disease in diabetic patients has been attributed to DSPN [9, 10]. An early diagnosis helps identify patients at risk before the onset of disabling
complications. Despite its common occurrence, DSPN shows considerable variability in prevalence. This can be attributed to the differences in definitions of neuropathy and the tests used for the evaluation [11].

Information on existing mechanisms

The exact mechanism of damage to the peripheral nerves due to hyperglycemia is not understood fully but is likely to be related to sorbitol accumulation, advanced glycation end products (AGE) and oxidative stress [5]. Peripheral neuropathy may manifest in various forms: sensory, focal, multifocal, autonomic. Although neurological signs and symptoms are recommended diagnostic tools [12], subjectivity, lack of reproducibility and proficiency of the examiner leads to inaccuracies [13]. Moreover, asymptomatic neuropathy is common, present in up to 30% of cases, and clinical features do not always correlate with the severity of pathological changes [14]. Other forms of neuropathy may replicate the picture in diabetic sensory neuropathy and mononeuropathy [5]. Chronic inflammatory polyneuropathy, vitamin B₁ deficiency, hypothyroidism, and uremia should be considered while evaluating diabetic polyneuropathy in patients [15].

Diabetic autonomous neuropathy is also one of the important factors leading to morbidity and mortality in diabetic patients. Neuropathic changes may manifest as gastroparesis, constipation, erectile dysfunction, bladder dysfunction, resting tachycardia, silent ischemia, and even cardiac arrest [15].

The pathobiology of diabetic complications as a unifying mechanism has been explained in the Banting lecture in 2004. Hyperglycemia-induced mitochondrial superoxide production activates the four damaging pathways by inhibiting GAPDH that leads to microvascular diabetic complications.

The polyol pathway activation resulted from the increase of glucose flux causes sorbitol accumulation in cells. Increased sorbitol is considered as the underlying mechanism in the development of diabetic microvascular complications [4, 5].

Advanced glycation end products pathway leads to the increase of the major intracellular AGE precursor methylglyoxal [4]. These substances have been linked with the formation of microaneurysms and pericyte loss [5].

Protein kinase C pathway is activated due to the inhibition of GAPDH activity that leads to the increase in intracellular glucose, thereby protecting endothelial cells from glucose-induced damage [21]; benfotiamine corrects glucose-induced endothelial cell damage by normalizing cell replication rates and decreasing apoptosis [21].

Prophylaxis and treatment

According to the generally approved guidelines and practices, the primary goal of the therapy in DM patients is to control symptoms and prevent worsening of microvascular diabetic complications. Although some studies suggest that tight glycemic control and avoidance of glycemic excursions may improve symptoms in diabetic peripheral neuropathy [5].

One of the novel approaches for the prevention and treatment of diabetic complications based upon the unifying mechanism for the pathogenesis of diabetic complications is using the transketolase activators [4]. Fructose-6-phosphate and glyceraldehyde-3-phosphate are also final products of transketolase reaction in the pentose phosphate shunt [16]. As glycolytic intermediates can flow to the pentose phosphate pathway depending on the concentration of substrate presented to transketolase and as in the case of diabetic patients with hyperglycemia, activation of transketolase diverts the flux of glycolytic intermediates away from the damaging pathways [5]. The enzyme transketolase requires a co-factor thiamine for activation.

Thiamine diphosphate, also known as thiamine pyrophosphate or cocarboxylase is a water-soluble vitamin. Thiamine diphosphate is the coenzyme for five key metabolic enzymes: mitochondrial pyruvate dehydrogenase complexes, oxoglutarate dehydrogenase complexes, branched-chain 2-oxo acid dehydrogenase complexes, 2-hydroxycyt-CoA lyase 1 as well as the cytosolic transketolase.

Allithiamine (benfotiamine) is a member of the class of lipophilic thiamine derivatives. The unique properties of the allithiamines result from the opening of the thiazole ring of thiamine upon reaction with sulphur compounds. Upon dephosphorylation of benfotiamine in the intestinal tract [17, 18] a lipophilic molecule is produced, which readily diffuses across cell membranes and is absorbed much better than water-soluble thiamine salts. This property allows for greater absorption both in the intestines and in target tissues as compared with thiamine itself. Following penetrating into the cell, the molecule undergoes catalytic reduction by intracellular sulfhydryl compounds and/or enzymatic debenzoylation [17], closing the thiazole ring and releasing the active thiamine into the cell and circulation [17].

In one study, thiamine activated transketolase by 25% in arterial endothelial cells, benfotiamine activated transketolase by 250% [5]. The properties of benfotiamine and its role in cell metabolism have been described in various fundamental research papers, to name a few: Hammes H.P. et al. described that benfotiamine prevents the increase in UDP-N-acetylglucosamine, and normalizes protein kinase C activity and prevents nuclear factor kappa B activation in retina of diabetic patients [20]. Berrone E., Beltramo E. et al. demonstrated that benfotiamine corrects imbalances in the polyol pathway by decreasing aldose reductase activity, sorbitol concentrations and intracellular glucose, thereby protecting endothelial cells from glucose-induced damage [21]; benfotiamine corrects glucose-induced endothelial cell damage by normalizing cell replication rates and decreasing apoptosis [21].

The significance of benfotiamine in clinical practice has also been demonstrated in many clinical trials with
variable trial designs, patient groups and history of diabetes, e.g. the BEDIP study and BENDIP study.

Conclusions

As allithiamines activate transketolase more significantly, further investigation is needed to verify the effect of allithiamines in comparison to thiamine diphosphate in terms of their affinity to THTR-1 receptor and THTR-2 receptor, which are encoded by the reduced folate carrier family.

In the Ukrainian Research and Practical Centre for Endocrine Surgery, Transplantation of Endocrine Organs and Tissues, we have also been studying the role of benfotiamine. A fundamental study regarding the efficacy of benfotiamine in treating patients with diabetic polyneuropathy in its various stages of manifestation and its effect on the expression of genes of the reduced folate carrier is being carried out.

The detailed description of the study is out of the scope of this article and will be presented in consequent articles.

Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

References

1. Emerging Risk Factors Collaboration, N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Emerging Risk Factors Collaboration. Lancet. 2010 Jun 26;375(9733):2215-22. doi:10.1016/S0140-6736(10)60484-9.

2. Kaiser N, Sasson S, Feener EP, et al. Differential regulation of glucose transport and transporters by glucose in vascular endothelial and smooth muscle cells. Diabetes. 1993;42(1):80-89. doi: 10.2337/diab.42.1.80.

3. Heilig CW, Concepcion LA, Riser BL, Freytag SO, Zhu M, Cortes P. Overexpression of glucose transporters in rat mesangial cells cultured in a normal glucose milieu mimics the diabetic phenotype. J Clin Invest. 1995 Oct;96(4):1802-14. doi: 10.1172/JCI118226.

4. Brownlee M. The pathobiology of diabetic complications, a unifying mechanism. Diabetes. 2005 Jun;54(6):1615-25. doi: 10.2337/diabetes.54.6.1615.

5. Fowler MJ. Microvascular and Macrovacular Complications of Diabetes. Clinical Diabetes. 2008;26(2):77-82. doi:10.2337/diabetics.54.6.1615.

6. Du XL, Edelstein D, Rossetti L, et al. Hyperglycemia-induced mitochondrial superoxide overproduction activates the hexosamine pathway and induces plasminogen activator inhibitor-1 expression by increasing Sp1 glycosylation. Proc Natl Acad Sci U S A. 2000 Oct 24;97(22):12222-6. doi:10.1073/pnas.97.22.12222.

7. Dyck PJ, Kratz KM, Karmes JL, et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. Neurology. 1993;43(4):817-24. doi: 10.1212/wnl.43.4.817.

8. Tesfaye S, Boulton AJ, Dyck PJ, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care. 2010;33(10):2285-93. doi: 10.2337/dc10-1303.

9. Vamos EP, Bottle A, Edmonds ME, Valabhi J, Majeed A, Millett C. Trends in lower extremity amputations in people with and without diabetes in England. 1996-2005. Diabetes Res Clin Pract. 2010;87(2):275-82. doi: 10.1016/j.diabres.2009.11.016.

10. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA. 2005 Jan 12;293(2):217-28. doi: 10.1001/jama.293.2.217.

11. Llewellyn JG, Tomlinson DR, Thomas PK. Diabetic Neuropathies. In: Dyck PJ, Thomas, PK, editors. Peripheral Neuropathy. 4th Edition. Philadelphia: Elsevier; 2005. 1951-1992 pp.

12. Dyck PJ. Severity and staging of diabetic polyneuropathy. In: Gries FA, Cameron NE, Low PA, Ziegler D, editors. Textbook of Diabetic Neuropathy. Stuttgart, Thieme; 2003. 170-175 pp.

13. Dyck PJ, Overland CJ, Low PA, et al. Signs and symptoms versus nerve conduction studies to diagnose diabetic sensorimotor polyneuropathy: CI vs. NPhy trial. Muscle Nerve. 2011;42(2):157-64. doi: 10.1002/mus.21661.

14. Boulton AJM, Malik RA, Arezzo JC, Saxenska JM. Diabetic Somatic neuropathies. Diabetes Care. 2004;27(6):1458-78. doi: 10.2337/diabetes.27.6.1458.

15. Boulton AJ, Vinik AI, Arezzo JC, et al. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care. 2005;28(4):956-962. doi: 10.2337/diabetes.28.4.956.

16. Hammers HP, Du X, Edelstein D, et al. Benfotiamine blocks three major pathways of hyperglycemic damage and prevents experimental diabetic retinopathy. Nat Med. 2003;9:294-299. doi:10.1038/nm834.

17. Rote Liste, 2008. Fachinfo-Service, Fach informationsverzeichnis Deutschland (einschließlich EU-Zulassungen), Verlag Rote Liste Service GmbH, Frankfurt/Main.

18. Volpert ML, Seyen S, Piette M, et al. Benfotiamine, a synthetic S-acetyl thiamine derivative, has different mechanisms of action and a different pharmacological profile than lipid-soluble thiamine disulfide derivatives. BMC Pharmacol. 2008 Jun 12;8:10. doi: 10.1186/1471-2210-8-10.

19. Loew D. Pharmacokinetics of thiamine derivatives especially of benfotiamine. Int J Clin Pharmacol Ther. 1996 Feb;34(2):47-50. doi:10.1186/1471-2210-8-10.

20. Hammers HP, Du X, Edelstein D, et al. Benfotiamine blocks three major pathways of hyperglycemic damage and prevents experimental diabetes. Nat Med. 2003 Mar;9(3):294-9. doi: 10.1038/nm834.

21. Beltramo E, Berrome E, Buttiglieri S, Porta M. Thiamine and benfotiamine prevent increased apoptosis in endothelial cells and pericytes cultured in high glucose. Diabetes Metab Res Rev. 2004 Jul-Aug;20(4):330-6. doi: 10.1002/dmr4.470.

Received 11.08.2019
Revised 29.08.2019
Accepted 15.09.2019
Активатори транскетолази як новий підхід до лікування: їх значення в патогенезі та лікуванні діабетичних мікросудинних ускладнень

Резюме. В оглядовій статті наведено аналіз літературних даних про вплив тіаміну і його похідних на метаболізм у клітинах і його роль у патогенезі ускладнень цукрового діабету. Розглянуто особливості перетворення неактивної форми, яка потрапляє в організм людини з продуктами харчування та препаратами, в активну форму тіаміну. Також розглянуто особливості метаболічних шляхів тіаміну і його похідних. Описані особливості аллітіаміну і прикладне значення його метаболізму в клітинах для лікування ускладнень цукрового діабету, зокрема діабетичної полінейропатії. Дані, наведені в цій статті, допоможуть клініцистам зрозуміти важливість та необхідність використання препаратів, що містять тіамін.

Ключові слова: сахарный диабет; мікросудинні осложнення; транскетолаза; діабетична полінейропатія; тіамін; аллітіамін; огляд