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Biochemical mechanisms of metabolic disorders in diabetes mellitus from the perspective of Yolqin Kholmatovich Turaqulov's scientific heritage in the field of biochemistry and endocrinology

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Abstract: This article analyzes the biochemical mechanisms of metabolic disorders in diabetes mellitus. The study is based on the scientific school of the Uzbek biochemist and endocrinologist, Professor Yolqin Kholmatovich Turaqulov and his conceptual approaches to metabolic pathology. The extent of carbohydrate, lipid and protein metabolism disorders in conditions of insulin deficiency and insulin resistance, the consequences of oxidative stress and mitochondrial dysfunction at the cellular level, as well as regulatory defects in gluconeogenesis and gluconeogenesis are considered. The article highlights such important biochemical chains as the effect of hyperglycemia on tissues through the formation of advanced glycation end-products (AGE), activation of the sorbitol pathway, and increased production of reactive oxygen species (ROS). According to the tradition of Turaqulov, the need to analyze metabolic disorders not as separate syndromes, but within a single pathogenetic continuum is substantiated. This approach serves as a theoretical basis for early diagnosis of clinical manifestations of diabetes, development of new biomarkers, and formulation of pathogenetically based therapeutic strategies.
Keywords : diabetes, metabolic disorders, biochemical mechanisms, insulin resistance, oxidative stress, gluconeogenesis, AGE, mitochondrial dysfunction, YX Turaqulov, endocrinology.

Login: Diabetes mellitus (DM) is recognized as one of the most common endocrine-metabolic diseases threatening global health today . According to the International Diabetes Federation (IDF), more than 537 million people aged 20-79 years worldwide are diagnosed with diabetes, and this figure is predicted to reach 783 million by 2045. The economic burden of the disease on the national economy and healthcare system is also increasing year by year, as diabetes-related complications - nephropathy, retinopathy, neuropathy, cardiovascular diseases and diabetic foot syndrome - lead to a sharp decrease in the working capacity of patients. This situation makes the in-depth study of the pathogenesis of diabetes mellitus at the molecular level a crucial issue not only from a theoretical but also from a practical point of view.

The contribution of Professor Yolqin Kholmatovich Turaqulov to the development of the National School of Biochemistry and Endocrinology of Uzbekistan occupies a special place. His scientific research is mainly focused on the biochemical foundations of hormonal regulation, disruption of cell-to-cell signaling in endocrine pathologies, and the mechanisms of metabolic integration, and is distinguished by its fundamental approach. The methodological feature of Turaqulov's work is that they seek to identify not only clinical manifestations at the organ level, but also chains of disorders at the cellular and molecular levels, and then combine these chains into a single pathogenetic model. This approach is especially fruitful in understanding such a

polyetiological disease as diabetes, as it allows us to show common biochemical roots between different clinical forms.

This article reviews the main biochemical mechanisms of metabolic disorders in diabetes mellitus based on the conceptual framework of the Turaqulov scientific school - disruption of insulin signaling pathways, impaired carbohydrate and lipid metabolism, oxidative stress and mitochondrial dysfunction, as well as mechanisms of cellular damage associated with glucotoxicity and lipotoxicity. The aim of the study is to analyze these mechanisms within a single pathogenetic continuum and demonstrate their importance in developing treatment strategies in clinical practice .

Main part

Insulin signaling disorders and their biochemical consequences. The central link in the pathogenesis of diabetes mellitus is the disruption of insulin signaling pathways. Under physiological conditions, when insulin binds to the insulin receptor on the cell membrane, its internal tyrosine kinase domain is autophosphorylated and causes phosphorylation of the next substrate - the insulin receptor substrate (IRS-1, IRS-2). This process activates the PI3K/Akt and MAPK signaling cascades, which control the translocation of the glucose transporter GLUT4 to the cell membrane, inhibition of gluconeogenesis, stimulation of lipogenesis, and cell growth. Within the traditions of the Turakulov scientific school, it is considered an important methodological principle to analyze insulin signaling disorders not as separate diseases, but as a chain of closely interconnected metabolic dysfunctions. At the tissue level, insulin resistance occurs through phosphorylation of IRS-1 on the serine residue, which blocks its tyrosine phosphorylation and interrupts the insulin signaling cascade. Inflammatory cytokines such as TNF- α , IL-6, free fatty acids (FFA), and oxidative stress products play an important role in this process .

The effect of fatty acids and lipotoxicity on insulin signaling. Increased triglycerides and excess fatty acid accumulation in tissues are common hallmarks of diabetes and metabolic syndrome. Fatty acids are converted intracellularly to diacylglycerol (DAG) and ceramides, which activate new isoforms of protein kinase C (PKC) and enhance phosphorylation of IRS-1 at the serine residue. This process disrupts insulin signaling in muscle and liver. As Turakulov noted, lipotoxicity is not only a cause of insulin resistance, but also creates a vicious circle that further enhances it: insulin resistance weakens the inhibition of lipolysis , which leads to an increased release of fatty acids into the blood and a further increase in lipotoxic products inside the cells. In this regard, in understanding the pathogenesis of diabetes, it is necessary to consider fat metabolism and carbohydrate metabolism as an integral unit.

Disruption of gluconeogenesis and the metabolic role of the liver. The liver is the central organ that regulates the production and storage of glucose. In a healthy body, insulin suppresses the expression of key enzymes of gluconeogenesis in the liver - PEPCK, FBPase-1 and glucose-6-phosphatase, and activates glucokinase and glycogen synthase. In conditions of insulin deficiency or resistance, this regulation is disrupted: the basal level of gluconeogenesis increases, and as a result, hepatic glucose production increases. This is considered one of the main causes of hyperglycemia, especially in type 2 diabetes. In the scientific approach of Turakulov, the role of the liver is seen not only as a source of glucose, but also as the center of the entire metabolic integration. Disorders occurring in the liver lead to metabolic imbalances at the level of the whole organism, since the metabolites and enzymes produced by the liver affect the activity of the intestinal microbiota, adipose tissue and muscles.

Oxidative stress and mitochondrial dysfunction. Mitochondria are the main energy-producing organelles of the cell and are also the main source of reactive oxygen species (ROS). Under physiological conditions, ROS production is in balance with the antioxidant defense system -

superoxide dismutase (SOD), catalase, glutathione peroxidase and the glutathione system. In diabetes, hyperglycemia causes an increase in electron flow in the mitochondrial electron transport chain, resulting in an increase in superoxide anion. Excessive production of ROS leads to oxidation of lipids, proteins and nucleic acids and disrupts the structural integrity of the cell. Mitochondrial dysfunction, in turn, reduces the production of ATP and disrupts the function of pancreatic beta cells that secrete insulin. Within the traditions of the Turakulov scientific school, oxidative stress should be considered not as an isolated pathogenetic factor, but as a link in a loop chain closely connected with other mechanisms . This approach is not only of theoretical importance, but also important for improving the effectiveness of antioxidant therapy.

The AGE pathway and the sorbitol cascade: cellular mechanisms of glucotoxicity. Prolonged hyperglycemia leads to excessive accumulation of glucose inside cells, which causes a condition called glucotoxicity. There are two important biochemical pathways of glucotoxicity: the first is the conversion of glucose to sorbitol by aldose reductase, and the second is the combination of glucose with proteins to form advanced glycation end-products (AGEs). The sorbitol pathway is dangerous for non-insulin-dependent cells - the pancreas, kidney neurons and peripheral nerves, because sorbitol accumulates without being excreted from the cell and increases the osmotic pressure, resulting in cell swelling and functional impairment. Since the aldose reductase reaction consumes NADPH, it weakens the antioxidant glutathione system and increases oxidative stress. AGE products, in turn, combine with collagen, elastin and other long-lived proteins, changing their structural and functional properties and activating inflammatory and oxidative responses through RAGE receptors. These chains play a central role in the pathogenesis of late complications of diabetes - nephropathy, retinopathy, and neuropathy.

Metabolic regulation of adipokines and inflammatory mediators. Adipose tissue is not only an energy reserve, but also an active endocrine organ. Adipokines produced by adipose tissue — leptin, adiponectin, resistin, visfatin, etc. — participate in metabolic regulation at the whole organism level. In diabetes and metabolic syndrome, the adipokine profile is disturbed: the level of adiponectin decreases (it is an adipokine that increases insulin sensitivity and reduces inflammation), while the level of resistin and visfatin increases. TNF- α and IL-6 produced by macrophages in adipose tissue directly disrupt insulin signaling. In Turakulov's scientific approach, the function of adipose tissue and the inflammatory process are inextricably linked to an integrated analysis: a chronic inflammatory state — meta-inflammation — is considered one of the central links in the pathogenesis of diabetes. This conceptual approach allows us to understand diabetes not only as an endocrine disease, but also as an inflammatory-metabolic disease.

A look at treatment strategies based on a pathogenetic approach. The biochemical mechanisms described above serve as an important basis for the development of pathogenetic treatment strategies for diabetes. Modern antidiabetic drugs — metformin (AMPK activator), GLP-1 analogues (incretin effect), SGLT2 inhibitors (glucose excretion in the urine), PPAR- γ agonists (increasing insulin sensitivity) — affect specific biochemical targets. The practical significance of Turaqulov's scientific legacy is that he recommends a comprehensive approach that simultaneously affects many links in pathogenetic chains, not limiting treatment strategies to symptomatic hypoglycemic control. In such an approach, goals such as reducing inflammation, suppressing oxidative stress, restoring mitochondrial function, and reducing intracellular lipotoxicity play an important role, along with glycemic control. This strategy is aimed not only at improving glycemic control, but also at preventing late complications of diabetes.

Conclusion

Analysis of the biochemical mechanisms of metabolic disorders in diabetes mellitus shows that this disease is not a set of separate pathological processes, but a complex pathogenetic continuum consisting of interconnected cellular chains. Impaired insulin signaling, increased gluconeogenesis, lipotoxicity, oxidative stress, mitochondrial dysfunction, AGE formation, activation of the sorbitol pathway, and chronic inflammation - each of these chains is connected by mutually reinforcing loop mechanisms. The conceptual approach within the traditions of the Turakulov scientific school - considering metabolic disorders within a single pathogenetic framework - serves as an effective methodological basis for understanding such a polyetiological disease as diabetes.

This analysis also leads to important practical conclusions. First, for the early diagnosis of diabetes, it is necessary to use accurate biochemical biomarkers - measuring complex indicators such as inflammatory cytokines, oxidative stress markers, and adipokine profile in addition to glycated hemoglobin (HbA1c). Second, treatment strategies require a comprehensive approach that simultaneously affects multiple links in the pathogenetic chains, not limited to symptomatic hypoglycemic control. Third, therapeutic interventions aimed at suppressing oxidative stress, preserving mitochondrial function, and reducing inflammation are important to prevent late complications of diabetes. Further research in the direction of Turaqulov requires continuing research to further study the pathogenetic chains of diabetes, identify new molecular targets, and develop innovative therapeutic strategies based on them.

References

1. Turaqulov YX Physiology and biochemical foundations of the endocrine system. — Tashkent: O'qitut Publishing House, 2018. — 384 p.
2. Turaqulov YX, Nazarov OT Biochemical mechanisms of metabolic disorders. — Tashkent: Medical Publishing House, 2020. — 256 p.
3. Turaqulov YX Hormonal regulation and cell signaling. Journal of Biology of Uzbekistan. 2019. — No. 3. — P. 12–18.
4. Turaqulov YX, Karimov SA The role of insulin resistance in the pathogenesis of diabetes. Medical Journal of Uzbekistan. 2021. — No. 2. — P. 45–51.
5. American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes — 2023. Diabetes Care. 2023. Vol. 46, Suppl. 1. P. S19–S40.
6. International Diabetes Federation. IDF Diabetes Atlas. 10th edition. Brussels: IDF, 2021. — 152 p.
7. Petersen MC, Shulman GI Mechanisms of Insulin Action and Insulin Resistance. Physiological Reviews. 2018. Vol. 98, No. 4. P. 2133–2223.
8. Samuel VT, Shulman GI The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. Journal of Clinical Investigation. 2016. Vol. 126, No. 1. P. 12–22.
9. DeFronzo RA, Ferrannini E., Groop L. et al. Type 2 diabetes mellitus. Nature Reviews Disease Primers. 2015. Vol. 1, article 15019.
10. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes. 2005. Vol. 54, No. 6. P. 1615–1625.
11. Giacco F., Brownlee M. Oxidative stress and diabetic complications. Circulation Research. 2010. Vol. 107, No. 9. P. 1058–1070.
12. Wellen KE, Hotamisligil GS Inflammation, stress, and diabetes. Journal of Clinical Investigation. 2005. Vol. 115, No. 5. P. 1111–1119.

13. Hotamisligil GS Inflammation and metabolic disorders. Nature. 2006. Vol. 444, No. 7121. P. 860–867.
14. Boden G. Obesity, insulin resistance and free fatty acids. Current Opinion in Endocrinology, Diabetes and Obesity. 2011. Vol. 18, No. 2. P. 139–143.