

Advances in Research on the Mechanism of Association Between Amino Acid Metabolism and Diabetes & Its Complications

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Abstract. Diabetes is a multifaceted metabolic and endocrine disease marked by abnormalities not only in glucose processing but also in lipid and amino acid metabolism. Amino acids are key contributors to the development and progression of diabetes. Beyond their role as essential components of proteins, they are actively involved in modulating insulin sensitivity and maintaining glucose balance. Growing research indicates that increased concentrations of specific amino acids are linked to greater insulin resistance and a higher likelihood of developing diabetes, while decreased levels of other amino acids may be associated with better metabolic health.

Keywords: Diabetes, Amino acid metabolism, Diabetes complications, Amino acids, Insulin.

1. Introduction

Diabetes mellitus is a metabolic disorder primarily characterized by chronic hyperglycemia [1]. Epidemiological evidence indicates a rapid increase in the prevalence of diabetes, rendering it a significant public health concern [2], particularly in developing nations such as China. The condition is linked to a range of both acute and chronic complications, including cardiovascular disease, diabetic nephropathy, peripheral neuropathy, and retinopathy, all of which substantially impair patients' quality of life. Recent research has highlighted the central role of amino acid metabolic processes in the pathogenesis of diabetes and its associated complications. Consequently, modulation of amino acid metabolic pathways is emerging as a promising therapeutic strategy to enhance glycemic control and mitigate the development of diabetic complications.

2. The Interrelationship Between Diabetes and Amino Acid Metabolism

2.1. Effects of Diabetes on Amino Acid Metabolic Processes

Diabetes mellitus represents a multifaceted endocrine and metabolic disorder that profoundly influences amino acid metabolism. Comparative studies have demonstrated significant alterations in amino acid metabolic profiles in individuals with diabetes relative to non-diabetic controls. These metabolic perturbations are intricately linked not only to insulin resistance and dysregulated glucose metabolism but also to the pathogenesis of diabetic complications, thereby contributing to their increased incidence.

In investigations focusing on type 2 diabetes mellitus, branched-chain amino acids (BCAAs) and aromatic amino acids have been identified as biomarkers indicative of diabetic pathology [3]. The aberrant accumulation of amino acid metabolites is posited to be a critical factor underlying disturbances in glucose and lipid metabolism. L-serine, a nonessential amino acid, serves as a vital precursor for the biosynthesis of proteins and phospholipids, notably phosphatidylserine, as well as sphingolipids—including ceramides, phosphosphingolipids, and glycosphingolipids—which are abundant constituents of white matter and myelin sheaths in nerves. Empirical data reveal a consistent

reduction in L-serine concentrations within the plasma and tissues of diabetic patients [6]. Two principal mechanisms may account for this decline: first, diminished glycolytic flux in diabetic individuals leads to reduced L-serine synthesis across various tissues, resulting in decreased availability of glycerol 3-phosphate; second, L-serine undergoes enhanced catabolism via deamination to pyruvate by serine dehydratase or conversion to hydroxy pyruvate and subsequently glucose through serine-oxoacetate transaminase. This augmented gluconeogenic activity, a hallmark metabolic feature of diabetes mellitus, thereby accelerates L-serine catabolism in hepatic and renal tissues.

2.2. Impact of Amino Acid Metabolism on Diabetes

Alterations in amino groups acid metabolism exert a profound influence on glucose metabolism and insulin resistance in diabetes mellitus. Amino acid metabolism is intricately linked not only to energy homeostasis but also to the regulation of insulin secretion and action. Consequently, the status of amino acid metabolic processes holds considerable importance for glycemic control and the overall metabolic condition of individuals with diabetes. Empirical evidence indicates that elevated concentrations of certain amino acids, particularly branched-chain amino acids, may enhance lipogenesis while inhibiting lipolysis, thereby exacerbating insulin resistance and facilitating the onset and progression of type 2 diabetes [4]. Moreover, disturbances in amino acid metabolism frequently coexist with other metabolic abnormalities, such as hypertension and dyslipidemia, which collectively heighten the risk of developing metabolic syndrome.

Tyrosine, a key aromatic amino acid, has been implicated in insulin resistance through its metabolic dysregulation. In patients with type 2 diabetes, the expression of enzymes involved in tyrosine metabolism, including tyrosine transaminases, is diminished, leading to elevated tyrosine levels [5]. This accumulation may disrupt insulin signaling pathways, intensifying insulin resistance and contributing to sustained hyperglycemia [6].

3. Role of Amino Acid Metabolism in Diabetic Complications

3.1. Diabetic Cardiovascular Disease

Cardiovascular disease represents the principal cause of mortality among diabetic patients, accounting for over 70% of diabetes-related deaths. Chronic hyperglycemia induces vascular endothelial dysfunction, accelerates atherosclerotic processes, and ultimately precipitates cardiovascular and cerebrovascular events. Among these complications, microangiopathy is closely associated with aberrations in amino acid metabolism. Observational studies have demonstrated a significant correlation between elevated plasma homocysteine levels and vascular pathology [7]. Homocysteine contributes to vascular injury through multiple mechanisms, including endothelial dysfunction, lipid metabolism disturbances, upregulation of inflammatory mediators, increased platelet activation, enhanced procoagulant states, and proliferation of vascular smooth muscle cells, thereby promoting atherogenesis and thrombosis. Even moderate elevations in homocysteine adversely affect the diastolic function of coronary and peripheral vessels, thereby increasing cardiovascular event risk [8].

Recent investigations have identified genetic variants proximal to the glutamic acid ammonia ligase (GLUL) gene as modulators of cardiovascular health. The GLUL-encoded enzyme catalyzes the synthesis of glutamine from glutamate and ammonia. In human umbilical vein endothelial cells homozygous for the risk allele, a decreased glutathione-to-glutamate ratio has been observed, accompanied by increased levels of methylglyoxal [9]. Under physiological conditions, methylglyoxal is detoxified via glutathione-dependent pathways linked to gluconeogenesis. Pyrrolidine glutamic acid, a critical intermediate in the γ -glutamine cycle, is essential for glutathione biosynthesis. Therefore, impairment of this metabolic pathway may represent a molecular mechanism by which GLUL gene variants contribute to elevated coronary heart disease risk [9].

3.2. Diabetic nephropathy

Diabetic nephropathy (DN) represents a prevalent microvascular complication of diabetes mellitus and constitutes the primary cause of end-stage renal disease (ESRD). Although microalbuminuria is frequently employed as a significant clinical marker for assessing diabetic nephropathy, its limited specificity and sensitivity preclude its use as a definitive diagnostic criterion. Consequently, renal biopsy remains the definitive "gold standard" for diagnosis [10].

The hallmark pathological characteristics of DN are glomerular lesions, typified by diffuse and nodular mesangial expansion alongside thickening of the glomerular basement membrane. Beyond glomerular involvement, lesions affecting the renal tubulointerstitial and small blood vessels also contribute substantially to DN pathogenesis. Recent investigations have identified ferroptosis, a newly discovered variant of programmed cell death, as a key mechanism implicated in DN progression. Ferroptosis is primarily initiated by Fenton-like reactions involving lipid peroxides and ferrous ions (Fe^{2+}), resulting in the generation of excessive reactive oxygen species (ROS) and subsequent cellular apoptosis. Under diabetic conditions, depletion of glutathione (GSH) and diminished activity of glutathione peroxidase 4 (GPX4) impair the effective clearance of lipid peroxides, thereby promoting ferroptosis [11]. Critical regulatory proteins within the glutathione system include GPX4 and the cysteine transporter SLC7A11. Knockdown of SLC7A11 reduces cysteine uptake, inhibiting glutathione synthesis, indirectly decreasing GPX4 activity, facilitating lipid peroxide accumulation, inducing ferroptosis, and accelerating disease progression [12, 13].

3.3. Diabetic Neuropathy

Diabetic neuropathy is classified into peripheral neuropathy and autonomic neuropathy, with peripheral neuropathy (DPN) being the most prevalent form. Clinically, DPN manifests as numbness, pain, and paresthesia in the extremities, with advanced stages potentially leading to muscle atrophy or deformities of the foot [14]. Pain associated with diabetic peripheral neuropathy significantly impairs patients' quality of life.

Homocysteine (Hcy) is a sulfur-containing amino acid that does not form proteins; it is produced during the metabolic processing of dietary proteins, can accumulate in the body due to excessive protein intake or deficiencies in vitamins B6, B12, and folic acid, resulting in hyperhomocysteinemia (hHcy). Hyperhomocysteinemia has been implicated in cellular and tissue damage and is increasingly recognized as closely associated with neurodegenerative disorders, diabetes, and megaloblastic anemia [15]. Emerging research indicates a significant association between increased homocysteine concentrations and the development of these disease states.

4. Regulation of Diabetes via Amino Acid Metabolism: Therapeutic Approaches

4.1. Direct Amino Acid Supplementation

Targeted supplementation with specific amino acids has demonstrated potential in enhancing metabolic outcomes in diabetic conditions. For instance, branched-chain amino acids (BCAAs) have been shown to augment insulin sensitivity through activation of the mammalian target of rapamycin (mTOR) signaling pathway. Dysregulation of the mTOR pathway is widely recognized as being intricately associated with diabetes mellitus and various metabolic disorders [16]. Fluctuations in amino acid concentrations correspondingly influence glucose and lipid metabolism, thereby offering novel therapeutic avenues for diabetes management.

4.2. Indirect Modulation of Amino Acid Metabolism

Modulation of amino acid metabolic processes via indirect mechanisms also holds significant clinical relevance in diabetes treatment. BCAAs, for example, can enhance insulin responsiveness by modulating multiple metabolic pathways. Early interventions targeting amino acid metabolism—

particularly through dietary modifications and the administration of specific amino acids—may contribute to delaying or preventing the onset of diabetic complications.[17]

5. Conclusion and Future Perspectives

Amino acid metabolic processes are centrally involved in the underlying mechanisms of diabetes and its related complications. Empirical evidence indicates that amino acids not only regulate glucose and lipid homeostasis but are also closely linked to the development of diabetic complications. Future investigations should aim to elucidate the regulatory mechanisms of amino acid metabolism further and explore their therapeutic potential in preventing and managing diabetic complications. Implementing diverse treatment modalities and nutritional interventions tailored to diabetic patients could facilitate earlier diagnosis and intervention, thereby enhancing clinical outcomes. It is anticipated that forthcoming advances will enable more rational and personalized strategies for the management and mitigation of diabetes along with its associated complications.

Acknowledgement

The work is financially supported by National Natural Science Foundation of China (No. 82370837).

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