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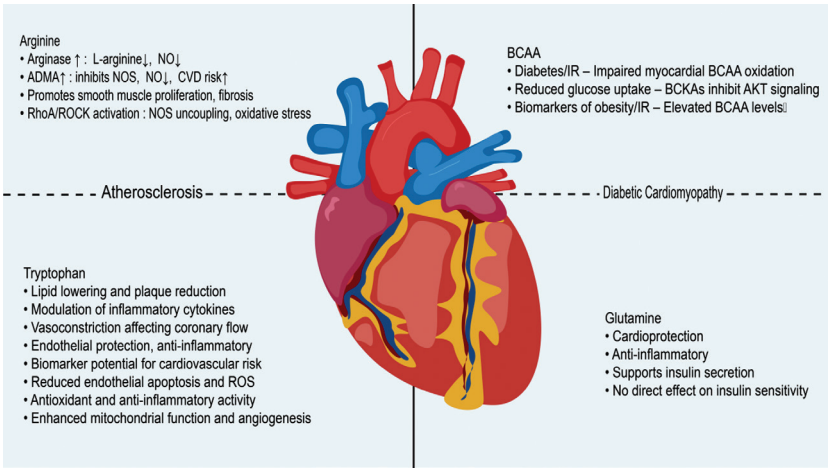
REVIEW

Amino Acid Regulation in Metabolic Heart Disease: Mechanisms and Therapeutic Potential

Graphical Abstract



Highlights

- Links of amino acid metabolism with diabetic cardiomyopathy and atherosclerosis.
- Diabetic cardiomyopathy involves disturbances of BCAA metabolism, while glutamine protects against cardiac injury.
- In atherosclerosis, arginine increases risk, while tryptophan protects the heart through multiple mechanisms.

Authors

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In Brief

This review combines studies on amino acids that are more active in diabetic cardiomyopathy and atherosclerosis.

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REVIEW

Amino Acid Regulation in Metabolic Heart Disease: Mechanisms and Therapeutic Potential

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Abstract

In normal cardiac energy metabolism, 95% of the heart's energy is provided by mitochondria, and preferences for energy-providing substrates vary at different times (Nguyen BY, Ruiz-Velasco A, Bui T, Collins L, Wang X, Liu W. Mitochondrial function in the heart: the insight into mechanisms and therapeutic potentials. Br J Pharmacol 2019;176(22):4302–4318). However, prolonged metabolic alterations impair cardiac function (Hu L, Tang D, Qi B, Guo D, Wang Y, Geng J, et al. Mfn2/Hsc70 complex mediates the formation of mitochondria-lipid droplets membrane contact and regulates myocardial lipid metabolism. Adv Sci (Weinh) 2024;11(14):e2307749). Therefore, this study primarily focuses on the relationship between amino acid metabolism and diabetic cardiomyopathy and atherosclerosis. Changes in metabolic processes also promote the development and worsening of these two diseases. Lipid and glucose metabolism in such diseases have been extensively studied, and emerging evidence suggests that amino acid metabolism also plays major roles in diabetic cardiomyopathy and atherosclerosis. Specific amino acid intake or catabolism might influence oxidative stress, inflammation, and fibrosis, among related processes, thus indirectly highlighting their potential as novel targets for metabolic interventions. However, the mechanisms and clinical relevance of amino acid metabolism in these diseases remain incompletely understood and warrant further investigation.

Keywords: diabetic cardiomyopathy; atherosclerosis; amino acids; metabolism

Introduction

Diabetic cardiomyopathy (DCM) and atherosclerosis (AS) are key metabolic heart diseases. Although related research has traditionally focused on glucose and fatty acids, recent studies have underscored the critical roles of amino acids in these conditions. This narrative review synthesizes literature from 2015 to 2025, which was retrieved via PubMed via search terms associated with amino acids and metabolic heart disease, complemented by earlier seminal references. In DCM, insulin resistance (IR) impairs calcium handling, autophagy, and inflammatory pathways, including PI3K/Akt/mTOR and NLRP3 inflammasomes, whereas O-GlcNAc glycosylation disrupts mitochondrial integrity. Branched-chain amino acids (BCAAs) worsen IR and glucose dysregulation but paradoxically promote cardiac hypertrophy when

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catabolism is defective. In contrast, glutamine (Gln) alleviates oxidative stress, improves insulin sensitivity, and supports mitochondrial function. Evidence suggests that this amino acid might lower cardiovascular risk in diabetes. In AS, arginine-derived nitric oxide (NO) counteracts endothelial dysfunction, whereas asymmetric dimethylarginine (ADMA) promotes vascular inflammation and plaque development. Dietary interventions such as BCAA restriction or Gln supplementation have demonstrated therapeutic promise in preclinical models, although human studies remain limited. Overall, amino acids are emerging as critical modulators in metabolic heart disease that warrant targeted research to harness their therapeutic potential in cardiometabolic disorders.

Methods

This narrative review was conducted by searching PubMed for relevant articles published between 2015 and 2025. Keywords included "amino acids," "metabolic heart disease," "cardiomyopathy," "atherosclerosis," and specific amino acids of interest (e.g., BCAAs, glutamine, arginine, and tryptophan). This review is aimed at providing a comprehensive overview incorporating discussions of amino acid metabolism, the pathophysiological mechanisms underlying diabetic cardiomyopathy and AS, and evidence from relevant clinical trials, to integrate key findings and draw insights from them.

Mechanisms of Diabetic Cardiomyopathy and Atherosclerosis

Diabetic Cardiomyopathy

Patients with diabetes are prone to cardiac dysfunction, according to the current definition of DCM as a disorder of myocardial contractility and/or diastolic function in the presence of diabetes. The main pathophysiological mechanisms are myocardial metabolic alterations, including glucose toxicity, lipid toxicity, oxidative stress, fibrosis, hypertrophy, and diastolic dysfunction.

IR alters metabolism, the cell cycle, and inflammation in the heart. IR promoted calcium ion and CaMKII phosphorylation, and this effect was statistically significant [1]. In addition, it affects the cardiomyocyte cycle by increasing apoptosis. Although the PI3K/Akt/mTOR signaling pathway is inhibited, the Ras/MAPK pathway still plays a role in inducing cardiomyocyte apoptosis and necrosis, and accelerating the progression of DCM [2]. Insulin exacerbates diabetes-related heart damage by influencing the expression of ULK1, an early marker of autophagy, and altering p62 and light chain 3I (LC3I)/LC3II protein expression levels, thereby leading to dysregulation of cardiomyocyte autophagy [3, 4]. Finally, IR increases cardiovascular risk by disrupting the function of endothelial progenitor cells, which play important roles in angiogenesis and the functional recovery of ischemic tissues in DCM [5].

In glucose metabolism in DCM, O-GlcNAc glycosylation affects mechanisms including mitochondrial energy metabolism, oxidative stress, cardiomyocyte apoptosis, and autophagy, thereby participating in myocardial injury. O-GlcNAc glycosylation is associated with the hexosamine biosynthesis pathway (HBP), an intracellular branch of accessory glucose metabolism. The first step of the HBP is controlled by the rate-limiting enzyme L-glutamine:fructose-6-phosphate amidotransferase, which uses glutamine to successively convert fructose-6-phosphate to glucosamine-6-phosphate to N-acetylglucosamine-6-phosphate, to N-acetylglucosamine-1-phosphate, and finally to uridine diphosphate-N-acetylglucosamine (UDP-GlcNAc) by acetyl-coenzyme A (acetyl-CoA) and uridine triphosphate [6]. Previous studies have shown that multiple diabetic heart diseases are affected by altering protein O-GlcNAc glycosylation through the following mechanisms:

- Altering intracellular Ca^{2+} distribution
- Modifying β1-adrenergic receptor activity and downstream signaling [7]
- Modulating epigenetic regulators such as histone deacetylase 4, thus conferring cardioprotection [8, 9]

The effects of this pathway and its products on the heart must be clarified and summarized to facilitate positive patient outcomes.

In conclusion, IR and HBP in DCM affect the function and status of cardiomyocytes from multiple

perspectives. The next section summarizes the relationships between DCM and amino acids, such as BCAAs and glutamate, to identify feasible directions for intervention research.

Atherosclerosis

Patients with AS, an important metabolic disease, typically have causes and risk factors including obesity, smoking, high blood glucose, high blood pressure, and other manifestations. The core mechanism of AS involves impaired lipid metabolism and an imbalance in the inflammatory response. The coexistence of causes and risk factors lead to continual damage to the inner wall of arteries and the recruitment of immune cells that transform into lipid-laden foam cells. Persistent accumulation of these foam cells further promotes the proliferation of smooth muscle cells (SMCs) and the formation of atherosclerotic plaques. These changes decrease blood flow and can ultimately result in severe cardiovascular events.

The intima of the blood vessel wall is composed of a single layer of endothelial cells (ECs), followed by a layer of SMCs, and finally a fibrous layer called the adventitia. The normal state of blood flow is laminar flow, whereas under abnormal conditions, the blood flow state changes to turbulence, and EC junctions are easily damaged. Subsequent activation of ECs occurs in the oxidative reaction of lipoprotein lipids and other inflammatory mediators, and results in the expression of P-selectin, E-selectin, VACM1, and ICAM1, thereby promoting the adhesion of chemokines such as monocytes, other leukocytes, and CCR2 [10, 11].

The pathogenesis of AS is complex and has been suggested to include lipid infiltration, thrombosis, oxidative stress, inflammation, and injury response. The currently recognized lipid infiltration hypothesis refers to abnormal metabolism of blood lipids (including cholesterol, low-density lipoprotein, and triglycerides) and lipid deposition in the blood vessel wall, thus leading to vascular stenosis. The inflammatory hypothesis refers to the up-regulation of inflammatory factor expression after vascular endothelial injury in early stages of AS, thereby triggering an inflammatory response, which in turn promotes oxidation of low density lipoprotein and foam cell formation. These two hypotheses compose core mechanisms of AS and are linked to changes in cells, including classical macrophages, EC, and other immune cells, all of which play important roles in early and late stages of AS. Further investigation of these cells and their roles in AS would aid in identifying therapeutic targets.

Atherosclerosis is associated with immune cells. First, oxidized lipids in the vascular wall generate proinflammatory signals by activating macrophage receptors and NLRP3 inflammasomes, thus inducing cytokines such as IL-1β. Second, Th1 cells secrete interferon-γ (IFN-γ), which promotes plaque growth and instability. In contrast, Treg cells release anti-inflammatory cytokines (IL-10 and TGF-β), which regulate macrophage activation and decrease AS [12, 13]. Third, certain B cells produce natural antibodies against oxidized epitopes in lipoproteins and necrotic debris, thereby suppressing inflammation [14]. Notably, macrophage senescence is associated with plaque growth, inflammation, and stability [15, 16], because senescent macrophages secrete various pro-inflammatory cytokines, immunomodulatory molecules, and proteases that act on surrounding cells. For example, M1-like macrophages are major sources of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF [17].

Studies have indicated strong correlations between the metabolism of certain amino acids and AS. This article focuses primarily on relationships among arginine, tryptophan, and AS.

Amino Acids and Metabolic Diseases

Branched-Chain Amino Acids

Metabolism of BCAAs

BCAAs, such as isoleucine, leucine, and valine, are essential amino acids obtained predominantly from dietary sources. The biochemical processing of BCAAs produces a series of metabolic intermediates. First, within the mitochondria, BCAA catabolism is initiated by transamination via BCAA aminotransferases (BCATs), thus yielding branched-chain α-ketoacids (BCKAs), which are crucial intermediates in downstream oxidative pathways. In the second step, BCKAs are decarboxylated in an irreversible process controlled by the BCKA dehydrogenase (BCKDH) enzyme

complex, thus committing them to further catabolic fates. Finally, NADH, CO_2, and various end products are generated. Recent advances in BCAA research have highlighted clinical relevance in metabolic heart disease, particularly in DCM, as discussed below.

BCAAs link diabetes and cardiac dysfunction. One cross-sectional study has suggested that altered BCAA levels might result from diabetes mellitus and altered lipid metabolism [18]. Genome-wide approaches have identified polymorphisms associated with elevated circulating BCAA levels, which are in turn associated with elevated type 2 diabetes (T2D) risk [19].

Relationship between BCAAs and Insulin Resistance

BCAAs have a complex relationship with IR (Figure 1). Under normal conditions, insulin promotes the cellular uptake of BCAAs and suppresses proteolysis, thereby regulating plasma BCAA concentrations. However, this regulatory mechanism can be impaired in pathological states such as IR. In the heart, IR and impaired signaling pathways can decrease myocardial BCAA oxidation. Initially, studies in mice with high-fat diet–induced obesity indicated that BCAA supplementation exacerbates obesity-related hepatic glucose and lipid metabolic disorders and hepatic IR by attenuating Akt2 signaling [20]. In humans, decreased adipose tissue oxygenation in individuals with obesity is associated with elevated plasma BCAA levels and IR [21, 22]. These findings suggest a correlation between BCAA levels and IR.

However, further research has indicated that elevated BCAA concentrations might not directly cause IR [23]. BCKAs, the downstream metabolites of BCAAs, are currently understood to impair insulin-stimulated AKT phosphorylation, and decrease glucose uptake and mitochondrial oxygen consumption [24]. In contrast, in branched chain amino acid transaminase 2 (BCAT2) knockout models, the accumulation of BCAAs does not impair cardiac insulin sensitivity but instead enhances insulin signaling and glucose oxidation in the heart [25]. In addition, studies in mice with high-fat diet–induced obesity have shown that although BCAA supplementation markedly alters metabolomic profiles, it does not exacerbate IR or obesity [26]. Therefore, elevated BCAA levels might serve as biomarkers of obesity rather than direct drivers of IR. Whereas IR can lead to BCAAs accumulation and potentially harm cardiac function, high circulating BCAA levels themselves might not directly induce IR; instead, other metabolic products accompanying BCAAs accumulation might contribute to its development.

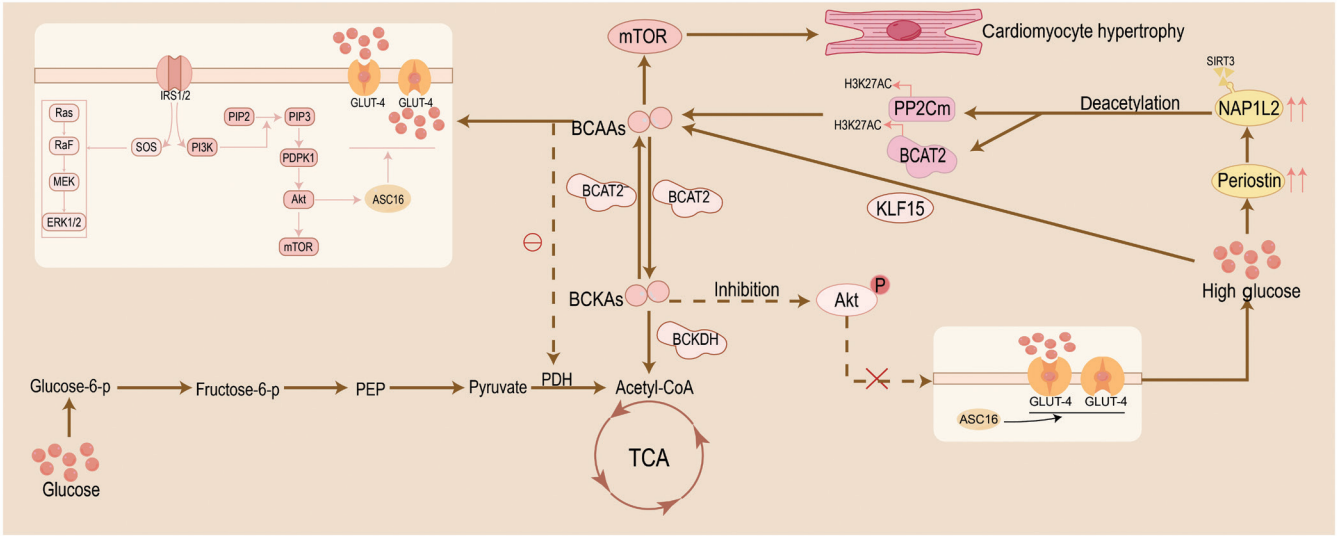

Figure 1 Branched-Chain Amino Acid (BCAA) Metabolism.
BCAT2 deficiency or exposure to a high-glucose environment increases BCAA levels, which triggers stimulation of insulin metabolism and mTOR activation, ultimately resulting in glucose metabolism disorders and cardiomyocyte hypertrophy.

Relationship between BCAAs and Glucose Metabolism

BCAAs are associated with the regulation of glucose metabolism (Figure 1). Accumulation of BCAAs has been reported to exacerbate cardiac ischemia-reperfusion injury by decreasing O-GlcNAc modification of E2 and E3/3 bp subunits, downregulating the HBP, and inactivating PDH [27]. Changes in glucose also affect BCAAs. Glucose negatively regulates the BCAA degradation pathway through a Krüppel-Like Factor 15 (KLF15)-dependent mechanism, thus resulting in BCAA accumulation and promoting cardiac hypertrophy [28]. In addition, the upregulation of NAP1L2 expression due to high glucose can lead to recruitment of SIRT3 and H3K27ac deacetylation on BCAT2 and protein phosphatase 2C family member (PP2Cm) promoters, thus causing BCAAs catabolic disorders [29].

Although BCAAs have become targets for the treatment of DCM, because of their relationships with insulin and glucose, they play important roles in cardiac homeostasis. Complete deprivation of BCAAs can lead to metabolic disorders, such as weight loss, hyperinsulinemia, and hyperleptinemia in BCAA-deficient mice within 4 weeks [30].

Interventions to Decrease Circulating BCAA Levels

Interventions to regulate BCAA levels include drug treatment, dietary adjustments, and physical exercise. Treatment with pyridostigmine can alter gut microbial abundance and improve intestinal barrier function, thereby decreasing BCAA cycle levels. Mechanisms include upregulating BCAT2 and PP2Cm while downregulating p-BCKDHA/BCKDHA and BCKDK, thereby improving cardiac BCAAs metabolism [31]. Furthermore, decreasing dietary intake of BCAAs (leucine, isoleucine, and valine) can also effectively reverse diet-induced obesity and metabolic dysfunction without additional caloric restriction [32]. In addition, the combination of resistance and aerobic exercise can contribute to decreasing circulating BCAA levels and might improve IR [33]. Moreover, baseline plasma BCAA levels might predict the extent of improvement in insulin sensitivity after weight loss interventions [34, 35]. In general, appropriate pharmacological, dietary, and exercise interventions are beneficial in decreasing circulating BCAA levels, which in turn might help mitigate disease progression.

Glutamate

Metabolism of Gln

Glutamate (Gln), a non-essential amino acid obtained from food, is also the most consumed amino acid, and is involved in the synthesis of all non-essential amino acids and proteins. Gln plays important roles in energy metabolism, stress, antioxidant, and anti-inflammatory. Gln enters cells via the amino acid transporter ASCT2/SLC1A5 and is then converted to Gln by glutaminase in the mitochondria. Subsequent catalysis by glutamate dehydrogenase, Gln aminotransferase, or aspartate aminotransferase yields α-ketoglutarate (α-KG), which in turn is incorporated into the TCA cycle and catabolized to lactic acid. Under conditions of hypoxia or mitochondrial dysfunction, Gln is utilized for the HBP (Figure 2).

Protective Effects of Glutamine

Gln is involved in the development and protection of DCM (Figure 2). Patients with diabetes exhibit disordered Gln metabolism, such as diminished plasma levels of Gln and α-KG [36]. In T2D, elevated serum Gln levels are associated with lower disease risk [37], whereas in adolescents with type 1 diabetes, oral Gln supplementation has been found to decrease blood glucose levels [38]. In streptozotocin-induced type 1 diabetes mouse models, dietary Gln supplementation enhances antioxidant capacity, and decreases the expression of leukocyte adhesion molecules in the liver and/or kidneys [39].

Mechanistically, the cardioprotective effects of Gln in DCM are mediated primarily through antioxidant effects, maintenance of cardiac structural integrity, and regulation of protein O-GlcNAcylation. Under hyperglycemic conditions, cardiac tissue is prone to oxidative stress, excessive production of reactive oxygen species (ROS), and cardiomyocyte apoptosis. Gln supplementation increases the activity of endogenous

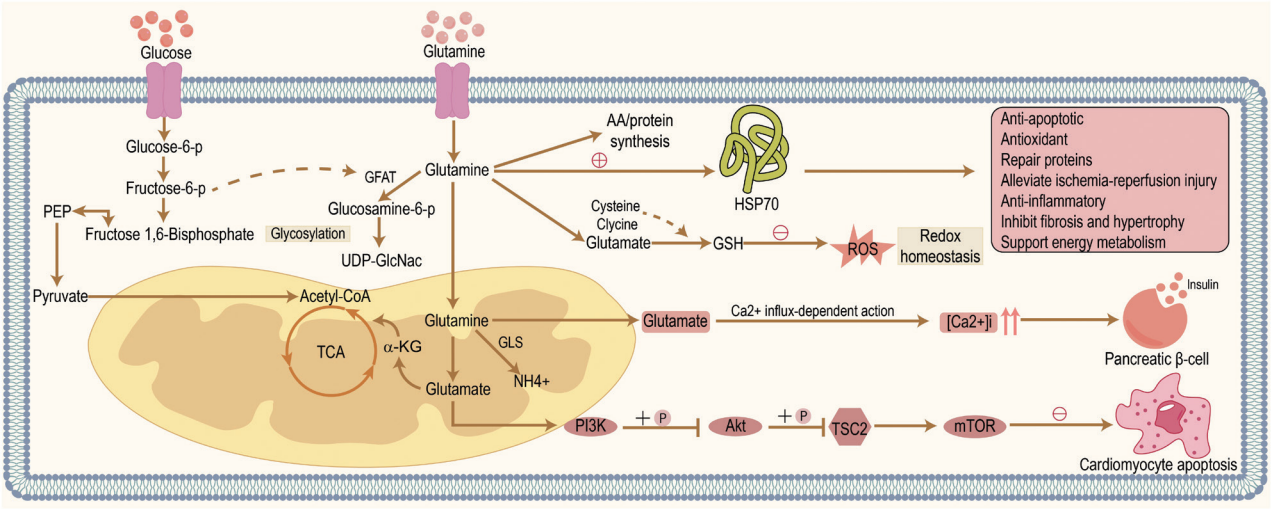

Figure 2 Glutamine (Gln) Metabolism.
Gln enters the cell and participates in glucose metabolism; produces glutamic acid, glutathione (GSH), and other substances that participate in HSP70 production, insulin secretion, and PI3K-Akt pathway activation; acts as an antioxidant; protects the heart; regulates glucose; and performs other functions.

antioxidant enzymes (such as superoxide dismutase and glutathione) while decreasing malondialdehyde levels in diabetic rats [40]. In addition, Gln protects cardiomyocytes against hypoxia/reoxygenation-induced apoptosis [41] and increases the expression of heat shock protein 70 in the myocardium in diabetic rats, thus contributing to cardioprotection [42]. Moreover, Gln plays important roles in myocardial energy metabolism, and its homeostasis is critical for mitochondrial oxidative phosphorylation [43]. Supplementation with Gln has been shown to improve mitochondrial oxidative phosphorylation [44] and to decrease myocardial injury and associated clinical complications [45]. For example, in vitro studies have demonstrated that Gln supplementation in H9C2 cells alleviates mitochondrial dysfunction, enhances antioxidant capacity, and decreases apoptosis induced by high glucose and hypoxia/reoxygenation, potentially through inhibition of the TGF-β1/Smad3 signaling pathway [41]. Given that TGF-β1/Smad3 signaling is a key driver of myocardial fibrosis, ventricular remodeling, and diastolic dysfunction in DCM, its inhibition might provide a therapeutic strategy to limit structural progression and preserve cardiac function.

Gln might also exert protective effects by modulating inflammation. Studies have shown that Gln, either alone or in combination with insulin, regulates inflammatory cytokine levels under hyperglycemic conditions, thereby decreasing oxidative stress and apoptosis in ECs [46] (Figure 2). For example, the antioxidant and anti-inflammatory activities of Gln have been demonstrated to alleviate the progression of diabetic nephropathy in type 2 diabetic rats, thus suggesting potential benefits for other diabetic complications [47]. Specifically, conversion of Gln to Glu amplifies glucose-stimulated insulin secretion in pancreatic β-cells through enhanced Ca^{2+} signaling. In addition, Gln is metabolized to α-KG, which in turn provides fuel for the TCA cycle and further supports insulin secretion [48]. Gln also regulates the biosynthesis and secretion of the autocrine factor IGF2, thereby influencing β-cell mass and function, and activates Akt phosphorylation pathways, thereby protecting cells against cytokine-induced apoptosis [49]. Furthermore, Gln does not significantly alter insulin sensitivity, regardless of baseline IR or insulin stimulation [50].

Effects of Glutamine Supplementation

Both animal and clinical studies have indicated beneficial effects of Gln supplementation on metabolic regulation.

In animal research, Gln supplementation has demonstrated a variety of advantageous effects.

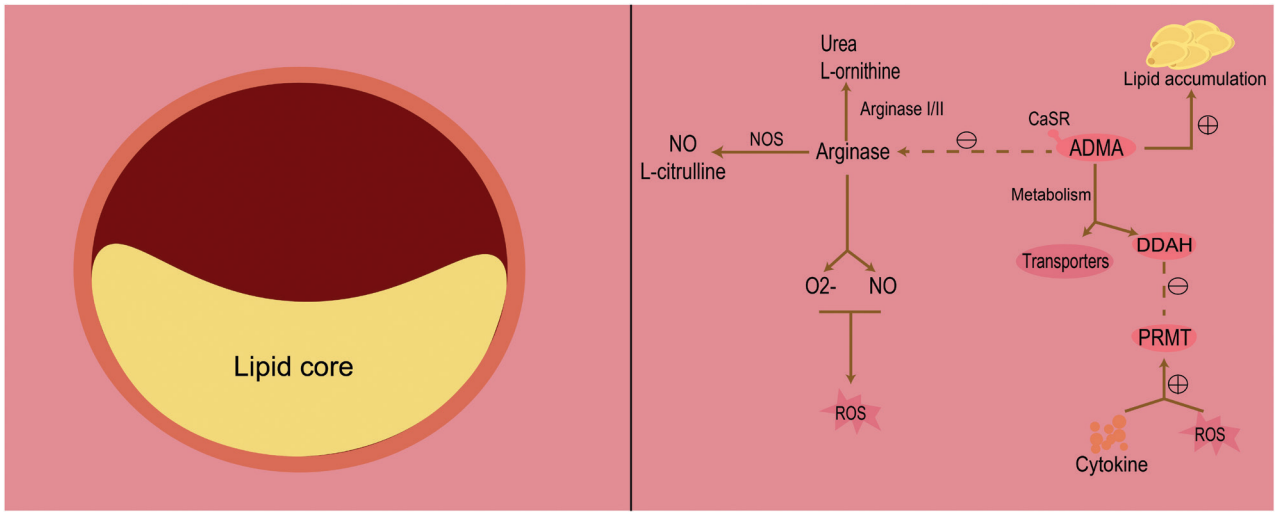

Figure 3 Arginine Metabolism.
In atherosclerosis, increases in reactive oxygen species (ROS) and cytokines lead to abnormal metabolism of the arginine metabolite asymmetric dimethylarginine (ADMA), thus promoting lipid accumulation. The increase in arginase leads to the uncoupling of nitric oxide synthases (NOS) through the RhoA/Rock pathway, production of superoxide compounds, and promotion of atherosclerosis development.

- Co-administration of L-alanine and L-glutamine improves overall metabolic status in alloxan-induced diabetic rats by enhancing tissue antioxidant enzyme activity and decreasing pancreatic β-cell damage [51].
- The combination of Gln with quercetin and α-tocopherol attenuates myocardial fibrosis in diabetic rats [52].
- Oral Gln supplementation improves insulin sensitivity and signaling in the liver and skeletal muscle in diabetic rats [53].
- In mice with high-fat diet–induced obesity, a Gln-enriched diet improves blood glucose levels and decreases IR under limb ischemia stress conditions [54].
- The increased Gln uptake and oxidation after transplantation of cardiac progenitor cells might enhance mitochondrial function and activate the mTORC1 signaling pathway, thereby promoting their metabolic activity, proliferative potential, and cardiac repair capacity [55].

In clinical trials, Gln supplementation has similarly demonstrated potential therapeutic value.

- A 6-week intervention providing 30 g of Gln daily led to a statistically significant improvement in certain cardiovascular risk factors in patients with type 2 diabetes [56].
- Oral L-glutamine combined with intact protein has been shown to improve first-phase insulin secretion in patients with T2D [57].
- In patients with well-controlled T2D, 4 weeks of Gln supplementation, either alone or in combination with sitagliptin, has been found to be safe and to be associated with decreased HbA1c levels [57].
- In critically ill patients with polytrauma, parenteral Gln supplementation has been associated with decreased incidence of hyperglycemia and lower daily insulin requirements [58].

Although these findings are promising, further high-quality animal and clinical studies are needed to better define the functions and safety of Gln supplementation in the management of diabetes and its complications.

Arginine

Metabolism of Arginine

Arginine, a raw material for protein synthesis and an intermediate product of the urea and NO cycles, plays important roles in cell division, wound healing, and immune function. In catabolism, arginine is methylated during enzymatic hydrolysis by arginine methyltransferases, thus forming ADMA and symmetric dimethylarginine (Figure 3).

Role of Arginine in Atherosclerosis

Disorders of arginine metabolism have been implicated in the development of AS. Some studies have reported an association between lower L-arginine/L-ornithine ratios in patients with coronary angiography and poorer cardiovascular outcomes [59]. L-arginine supplementation has shown potential for improving endothelial function in certain populations, although its effects on lipid profiles appear limited [60]. Animal studies have suggested that dietary L-arginine might enhance endothelium-dependent vasodilation, promote NO production, and possibly decrease oxidative stress and vascular lesion progression [61]. In interventional settings, short-term local delivery of high-concentration L-arginine has been reported to influence in-stent neointimal responses, while maintaining overall lumen integrity [62]. Collectively, these findings suggest the promise of L-arginine in AS prevention or management, although its precise mechanisms of action and appropriate patient populations warrant further clarification.

L-arginine is the precursor of NO, which in turn plays important roles in vasodilation and AS prevention (Figure 3). The production of NO is regulated by multiple factors, including L-arginine availability, NO synthase expression and activity, and levels of the cofactor tetrahydrobiopterin (BH4) and endogenous NOS inhibitors, such as ADMA and NG-monomethyl-L-arginine (L-NMMA), in a complex metabolic regulatory system.

Within this system, arginase acts as a key negative regulator of NO synthesis by competitively consuming L-arginine. Arginase exists in two isoforms: type I and type II. Type I is expressed primarily in the liver and is involved in systemic nitrogen metabolism, whereas type II is mitochondrial and is expressed in the kidneys, vasculature, gastrointestinal tract, and prostate. The tissue-specific distributions of these enzymes suggest distinct roles in systemic metabolism and local vascular regulation. Importantly, arginase expression is markedly upregulated under inflammatory conditions. Various proinflammatory stimuli, including lipopolysaccharide (LPS), tumor necrosis factor-α (TNF-α), and IFN-γ, induce arginase expression and activity [63–67]. In animal models of AS, numerous studies have reported significantly elevated arginase activity. For example, ECs are the main source of arginase in the aorta. In apoE-deficient mice fed a high-fat diet, aortic arginase activity is elevated, and endothelial denudation further influences its activity [68, 69]. Active arginase activity has also been detected in the atherosclerotic plaques of hyperlipidemic rabbits [70, 71]. Macrophages are key immune cells within atherosclerotic plaques, and their polarization states are closely associated with arginase isoform expression. Classically activated M1 macrophages express primarily arginase II, whereas anti-inflammatory M2 macrophages express arginase I [72–75]. This divergence suggests a dual role of arginase in both inflammation resolution and tissue repair. Mechanistically, increased arginase activity decreases the availability of L-arginine for NOS-mediated NO synthesis through competitive consumption. In addition, the arginase pathway promotes the biosynthesis of proline and polyamines, thereby facilitating smooth muscle cell proliferation and fibrosis. Arginase upregulation might be accompanied by activation of the RhoA/ROCK signaling pathway, thus promoting NOS uncoupling and superoxide production, and further diminishing NO bioavailability [76]. In summary, arginase not only regulates L-arginine metabolic partitioning but also is a potential therapeutic target in endothelial dysfunction and the progression of AS. Future research should further explore the efficacy and safety of selective arginase inhibitors in prevention and treatment of AS.

Among the products of arginine metabolism, ADMA is notable for its inhibitory effect on NO synthesis, acting mainly through competitive inhibition of NOS activity and thereby decreasing NO production. ADMA is metabolized primarily by dimethylarginine dimethylaminohydrolase (DDAH) or transported out of cells via specific transporters [77, 78] (Figure 3). In a meta-analysis of 30 prospective studies, Schlesinger et al. have reported that higher plasma ADMA concentrations are significantly associated with elevated risk of fatal and nonfatal cardiovascular events and coronary heart disease (relative risk [RR] = 1.33, 95% confidence interval [CI]: 1.22–1.45) [79]. Similarly, Zhou et al., in an analysis of data from 34 studies involving 137 participants, have found that higher circulating ADMA levels predict major cardiovascular events

(RR = 1.18, 95% CI: 1.10–1.27) and cardiovascular mortality (RR = 1.19, 95% CI: 1.12–1.25) [80]. Mechanistic studies have suggested that excessive ADMA activates calcium-sensing receptor signaling, thereby promoting lipid accumulation [81], and ROS and pro-inflammatory cytokines upregulate the activity of protein arginine methyltransferases, thereby inhibiting DDAH-mediated ADMA degradation. Moreover, increased ADMA levels might be associated with upregulated arginase expression, thus further decreasing L-arginine availability, collectively suppressing NO synthesis, and exacerbating endothelial dysfunction.

Clinical Trials of Arginine

In clinical research, L-arginine supplementation has demonstrated generally positive and complex effects. Supplementation with L-arginine has been shown to decrease monocyte-EC adhesion, decrease platelet aggregation, and improve endothelial function [82]. In a double-blind, placebo-controlled study, 22 patients with stable angina who received 3 days of oral L-arginine showed an enhancement in exercise capacity [83]. In another study, patients with coronary AS who received daily supplementation with 3 g L-arginine for as many as 6 months showed significantly enhanced vasodilatory responses to acetylcholine [84]. The combined use of arginine and B vitamins improves endothelial function and lowers blood pressure in patients with mild to moderate hypertension [85]. Importantly, long-term oral administration of arginine has been found to prevent renal loss of nitrite, a compound essential for NO production [86]. Decreases in ADMA levels can also be achieved through other interventions. Studies have demonstrated that aerobic exercise, resistance training, and flexibility exercises can all lower plasma ADMA concentrations in patients with coronary artery disease [87]. In addition, statin therapy has been found to significantly decrease plasma ADMA levels in a meta-analysis of nine randomized controlled trials by Serban et al., which involved 1134 patients (33–71 years of age, treatment duration 2–24 months) [88]. Carlström et al., in a study in rats subjected to unilateral nephrectomy and chronic high-salt diets, observed significantly lower plasma ADMA concentrations after nitrate supplementation than observed in the control group [89]. In summary, methods to increase L-arginine intake, inhibit arginase activity, and decrease ADMA levels have provided a series of promising approaches to improve NO bioavailability and offer potential therapeutic strategies for the treatment of coronary artery disease.

Currently, no consensus exists regarding the optimal dosage, administration route, or appropriate target population for L-arginine supplementation.

In patients with CAD, supplementation with L-arginine at 9 g/day for 1 month has been found to significantly increase plasma L-arginine levels, but not to improve NO bioavailability or endothelial function [90]. Similarly, in a cohort study involving more than 10 years of follow-up in older men, higher dietary intake of L-arginine did not decrease the risk of coronary heart disease mortality [91].

Administration routes also critically influence the effectiveness of high-dose L-arginine supplementation. Hirooka et al. have demonstrated that intra-arterial infusion of L-arginine effectively reverses impaired endothelium-dependent vasodilation in patients with heart failure [92]. In contrast, parenteral L-arginine administration (3 g three times daily for 6 months) in patients after acute myocardial infarction has not been found to improve arterial stiffness or left ventricular ejection fraction [93]. In addition, renal medullary interstitial infusion of L-arginine has been observed to effectively prevent salt-induced hypertension in rats, whereas the same plasma levels of L-arginine achieved by intravenous administration did not have the same effects [94]. In spontaneously hypertensive rats, oral L-arginine did not correct severe hypertension but significantly decreased renal injury. In patients with essential hypertension, oral L-arginine has been found to acutely improve brachial artery endothelium-dependent, flow-mediated dilation [95]. Overall, these findings indicate that the optimal dosage and administration strategy for L-arginine require further clarification and optimization.

Another important limitation of L-arginine supplementation is the selection of target populations. In a study in Japanese patients, acute intravenous infusion of L-arginine (500 mg/kg over 30 minutes) effectively decreased arterial blood pressure in both salt-sensitive and salt-resistant individuals [96]. In similar studies in African American populations, the

same dosage of L-arginine decreased blood pressure in salt-sensitive individuals [97]. Currently, researchers have suggested that an elevated ADMA/arginine ratio might be a useful indicator for identifying patients who stand to benefit most from L-arginine supplementation. However, large-scale, prospective, randomized clinical trials remain necessary to better define the target populations and precise dosing plans.

Overall, these findings suggest that the effectiveness of L-arginine supplementation depends on multiple factors, including patients' underlying disease states, dosing regimens, administration routes, and formulation release characteristics. Whereas short-term or acute high-dose supplementation has not demonstrated clear benefits in healthy individuals or patients with CAD receiving standard therapy, long-term, rational supplementation strategies might still improve NO synthesis and vascular function in selected patients with endothelial dysfunction or cardiometabolic risk. Future research should focus on more precisely defining the target populations, optimizing dosing, and systematically evaluating the long-term effects and safety of L-arginine supplementation on AS.

Tryptophan

Metabolism of Tryptophan

Tryptophan, an essential amino acid in mammals, plays important roles in immunity, and the endocrine and nervous systems. The three main metabolic pathways of tryptophan are as follows. The kynurenine (Kyn) metabolic pathway is the main pathway of tryptophan metabolism. The Kyn produced via this pathway plays important roles in nerve and immunity. The second pathway is the serotonin (HT) pathway, which is associated with neurotransmitters, melatonin, and platelets in the brain. The third pathway is the indole pathway, which generates corresponding metabolites under the action of intestinal bacteria and related enzymes, thereby regulating gastrointestinal and immune diseases (Figure 4).

Role of Tryptophan in AS

Tryptophan and its metabolites are closely associated with the development and progression of cardiovascular disease. For example, the EPIC-Norfolk prospective cohort study has indicated that plasma Kyn levels and the Kyn/tryptophan ratio are

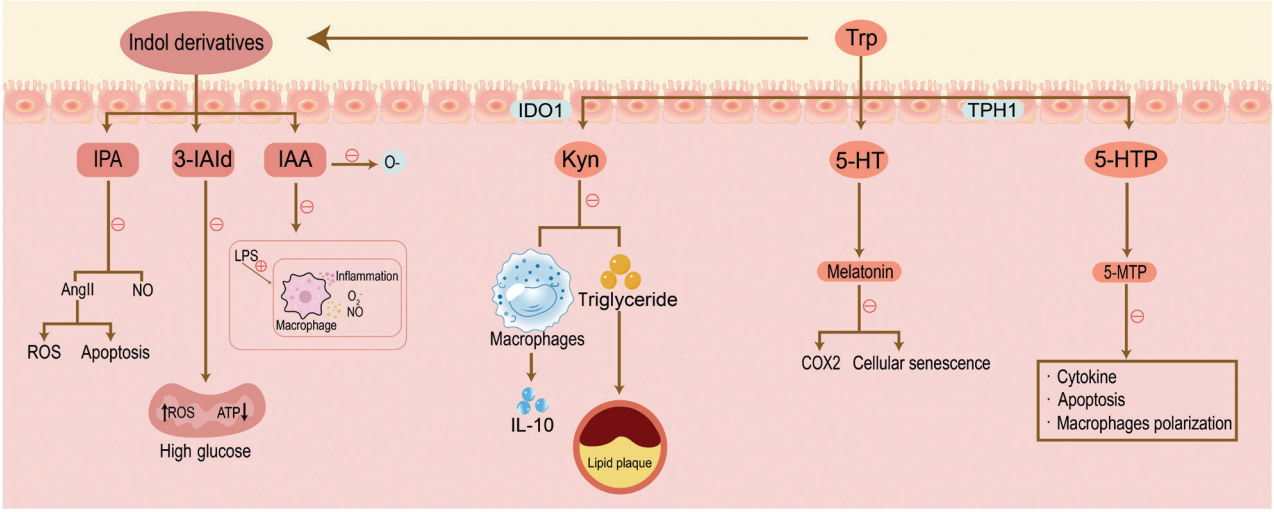

Figure 4 Tyrosine Metabolism.
In atherosclerosis, the kynurenine pathway (KP) of tryptophan is not conducive to the secretion of IL-10 and cholesterol accumulation by macrophages. Among the indole derivatives produced by tryptophan, indole-3-propionic acid (IPA) inhibits reactive oxygen species (ROS) and apoptosis caused by NO and AngII; 3-IAId inhibits mitochondrial dysfunction under high glucose; and IAA inhibits superoxide and inhibits LPS-induced macrophage activation in response to heme oxygenase-1 (HO-1). In the 5-HT pathway of tryptophan, 5-HT produces melatonin, which is anti-inflammatory, anti-stress, and anti-aging; 5-methoxytryptophan (5-MTP), produced by 5-hydroxytryptophan (5-HTP), promotes macrophage polarization and inhibits cytokines and apoptosis.

inversely associated with cardiovascular disease risk, and the Kyn/tryptophan ratio is directly associated with AS occurrence [98]. In addition, serotonin produced via the serotonin metabolic pathway can enhance the procoagulant properties of platelets, thus suggesting a potential role in thrombosis [99].

The first step of the tryptophan-Kyn pathway is catalyzed by indoleamine 2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO) (Figure 4). Studies have confirmed the colocalization of IDO and TDO with lymphocytes and macrophages in human atherosclerotic plaques [100]. IDO expression and activity are strongly regulated by the inflammatory microenvironment, in a central pathological feature of AS. The primary immunomodulatory mechanisms of IDO include depleting tryptophan, activating stress sensors (e.g., GCN2), thus limiting cell proliferation [101], and generating a range of bioactive metabolites along the Kyn pathway that mediate immune regulation [102]. Regulatory T cells (Tregs) interact with IDO-mediated tryptophan metabolism within the vascular wall, and jointly promote immune tolerance and limit vascular inflammation, thereby potentially slowing AS progression [103]. In addition, IDO can form feedback loops through its metabolites, thus further regulating inflammation and AS development [104]. Specifically, the downstream Kyn pathway metabolite 3-hydroxyanthranilic acid (3-HAA) decreases plasma lipid levels (including cholesterol and triglycerides) and attenuates atherosclerotic burden in hypercholesterolemic mice. However, signaling pathways induced by kynurenine quinolinic acid have been found to suppress production of the anti-inflammatory cytokine IL-10 [105].

In summary, existing studies suggest that IDO might represent a promising therapeutic target for the prevention and treatment of AS by modulating immune and inflammatory responses.

The second pathway is known as the serotonin pathway. Tryptophan is converted to serotonin by tryptophan hydroxylase 1 (TPH1). Enteric 5-HT participates in melatonin synthesis and is stored in platelets, where it performs physiological functions (Figure 4). 5-HT acts on multiple receptor subtypes, and itself has varying degrees of vasoconstrictive effects [106], which might exacerbate coronary artery spasm and impair coronary perfusion recovery in patients with UC undergoing CP/CPB [107]. Moreover, 5-HT2A receptors are expressed in coronary arteries. Activation of 5-HT2A with the selective agonist R-DOI decreases pro-inflammatory markers in the aortic arch [108]. In spontaneously hypertensive rats, calcium signaling dysfunction mediated via the 5-HT2AR/PLC/IP3R and 5-HT2AR/Rho/PKCδ/Cav1.2 pathways is associated with impaired coronary artery contraction [109]. Melatonin has beneficial effects in preventing replication- and stress-induced cellular senescence. Melatonin has been suggested to exert anti-inflammatory actions by suppressing the expression of pro-inflammatory genes such as cyclooxygenase-2 [110]. TPH1 also catalyzes the conversion of tryptophan to 5-HTP, which is subsequently converted by hydroxyindole O-methyltransferase to 5-MTP [111]. TPH1 expression is suppressed by pro-inflammatory cytokines and has also been detected in ischemic cardiac tissue, where it leads to decreased 5-MTP production and endothelial dysfunction [112, 113]. Adding 5-MTP to human umbilical vein ECs has been found to maintain intercellular tight junctions by preventing degradation of vascular endothelial cadherin and protecting the endothelium against LPS and cytokine-induced barrier disruption [113]. This treatment might decrease EC loss through two primary mechanisms. First, 5-MTP prevents oxidant-induced endothelial apoptosis and has been shown to protect cardiomyocytes against H_2O_2-induced cell death [114]. Second, 5-MTP might rescue endothelial growth driven by vascular endothelial growth factor, by blocking the actions of pro-inflammatory cytokines [115]. Moreover, 5-MTP regulates macrophage activation. For example, pre-treatment of macrophages with 5-MTP suppresses the LPS-enhanced interaction between p-p38 and Prdx-1 [116]. These results suggest that 5-MTP mitigates tissue injury and decreases mortality through multiple inflammatory pathways. Consequently, 5-MTP might be developed as a novel therapeutic agent for systemic inflammation and might also serve as an early biomarker for inflammation-mediated disease detection and severity assessment. A recent report has indicated that plasma 5-MTP levels might predict post-myocardial infarction heart failure [117]. Therefore, circulating 5-MTP might serve as a valuable diagnostic and therapeutic biomarker.

In the third pathway, the gut microbiota converts small amounts of tryptophan into indole and its derivatives, such as indoleacetic acid, indole-3-acetic acid (IAA), indole-3-propionic acid (IPA), and indole-3-acetaldehyde (Figure 4). Among these, IPA has attracted particular attention. Recent studies using ultra-high-performance liquid chromatography–tandem mass spectrometry have measured plasma tryptophan and IPA levels in 1,829 patients with CAD and revealed a significant association between higher IPA levels and lower cardiovascular and all-cause mortality risk [118]. Furthermore, a comprehensive microbiome-metabolomics analysis in 30 Chinese patients with CAD has identified the IPA/miR-142-5p/ABCA1 axis as a potential surrogate marker for atherosclerotic cardiovascular disease [119]. Collectively, studies have demonstrated multiple effects of IPA:

1. It influences endothelial NO production, thereby negatively affecting the physiological regulation of vascular tone [119].
2. It inhibits AngII-induced endothelial apoptosis, ROS production, inflammation, and the loss of endothelial tight junctions, and offers protective effects against CAD [120].

In addition, IAA exhibits anti-inflammatory and antioxidant properties. Specifically, IAA induces HO-1 expression and directly scavenges free radicals, thereby attenuating LPS-induced macrophage inflammatory responses and oxidative stress through an AhR-independent mechanism [121].

Finally, indole-3-acetaldehyde has been shown to ameliorate mitochondrial dysfunction induced by hyperglycemic conditions, decrease oxidative stress and apoptosis, and thereby enhance angiogenesis [122].

Clinical Trials of Tryptophan

Current evidence suggests that, although clinical trials of tryptophan supplementation in humans remain in exploratory stages, modulation of tryptophan metabolism has therapeutic potential for controlling the progression of AS. Dietary tryptophan enrichment has been shown to decrease caloric intake and weight gain in rodent models [123, 124], and similar metabolic effects have been observed after oral gavage administration in mice [125]. Exogenous tryptophan infusion induces antihypertensive responses in spontaneously hypertensive rats [126], a finding supported by observations of decreased blood pressure in patients with essential hypertension after oral supplementation [127]. Behr et al. have demonstrated that broad-spectrum antibiotic regimens (including fluoroquinolones, tetracyclines, and aminoglycosides) markedly suppress the microbial synthesis of IPA, and have indicated that aminoglycosides show the strongest inhibitory effect [128]. Pharmacological targeting of key enzymes in the Kyn pathway, including indoleamine 2,3-dioxygenase 1 (IDO1), kynurenine 3-monooxygenase, kynureninase, and kynurenine aminotransferase II, has been shown in preclinical models to mitigate cardiovascular pathology via resolution of inflammation. [129] These findings highlight these pathway nodes as promising therapeutic targets for structure-based drug design. IDO1 inhibitors such as 1-methyl-D-tryptophan (Indoximod) are classic competitive inhibitors, whereas subsequent generations, including INCB024360 and NLG919, are potent imidazoisoindole-derived small molecules under clinical evaluation [130]. However, both genetic deletion and pharmacological inhibition of IDO1 have demonstrated pro-atherogenic effects through dysregulation of upstream and downstream inflammatory responses. Notably, the clinical-stage IDO1 inhibitor epacadostat has shown macrophage-specific suppression of tissue factor expression, thus underscoring the cell-type-specific regulatory mechanisms within the metabolism–immunity axis [131].

Conclusion and Future Perspectives

BCAAs include leucine, isoleucine, and valine, which participate in the citric acid cycle through the production of acyl-CoA derivatives via BCATs, BCKDH, and acetyl-CoA in a subsequent series of reactions.

BCAAs are involved in the occurrence and development of DCM. The relationships between insulin and BCAAs are complex. Researchers initially believed that excessive intake of BCAAs would lead to IR, but subsequent studies suggested that IR in DCM leads to BCAA accumulation and affects heart function, and that IR increases blood glucose. The decomposition of BCAAs, which is associated with KLF15, is further limited. Some researchers

have concluded that the accumulation of BCAAs increases insulin sensitivity, whereas the metabolites of BCAAs induce IR; however, an acute increase in BCAAs does not lead to IR. Further comprehensive investigation is required to elucidate the relationship between BCAAs and insulin. The presence of BCAAs has benefits for the growth of the heart – such as by participating in the tricarboxylic acid cycle, promoting fatty acid oxidation for energy, and preventing cardiac hypertrophy – but only if BCAAs are at normal levels, and the catabolic pathway is normal. Otherwise, excessive BCAAs cause problems in the metabolism of the heart, such as by downregulating the HBP; decreasing cardiac glucose utilization; and activating mTORC1, thereby promoting abnormal cardiac hypertrophy. To balance excess BCAAs, researchers have used pyridostigmine to decrease the abundance of BCAA-producing microorganisms in mice. Modulating the expression of enzymes involved in BCAA metabolism promotes their catabolism. Adopting dietary modifications and engaging in regular physical activity can help reduce systemic inflammation.

Gln enters cells via the amino acid transporter ASCT2/SLC1A5, and is subsequently converted to Glu in mitochondria by glutaminase, which is subsequently converted to α-KG by glutamate dehydrogenase, glutamate aminotransferase, or aspartate aminotransferase, and is finally incorporated into the TCA cycle. In addition to its role via glutamate, glutamine (Gln) itself can promote insulin secretion by stimulating the release of glucagon-like peptide-1 (GLP-1). The above findings have indicated the importance of Gln in blood glucose stability. Furthermore, Gln has cardioprotective properties, such as ATP elevation, antioxidant activity, apoptosis inhibition, and anti-inflammatory actions, and therefore is a highly beneficial amino acid for DCM.

Arginine has a crucial role in regulating AS risk factors and progression. For example, supplementation with high amounts of arginine decreases blood viscosity and inhibits angiotensin-converting enzyme, thereby regulating blood pressure, particularly in individuals with salt-sensitive blood pressure. Arginine supplementation in young adults with hypercholesterolemia has also showed a clinically meaningful improvement in endothelial function. Arginine supplementation in AS development alleviates plaque expansion and preserves endothelial function in patients with CAD. Mechanistically, arginine is associated with NO production, which is mediated by NO synthase and arginase. In people with AS, the activity of arginase is elevated, and activated macrophages express arginase. Consequently, excessive consumption of arginine by NO synthase might lead to endothelial dysfunction. In addition, ADMA and symmetric dimethylarginine, formed through the methylation of arginine by protein arginine methyltransferases, also play roles in AS. For example, ADMA inhibits NO synthase and regulates calcium-sensitive receptors, thus leading to lipid accumulation. The production of reactive oxygen species and pro-inflammatory cytokines in AS also increases ADMA, because the catabolic dimethylarginine DDAH of ADMA is inhibited. Arginine has been clinically identified as a targeted therapeutic amino acid for the treatment and prevention of AS, but many prospective clinical studies remain needed to confirm the mode of administration of arginine and the drug dosage.

Tryptophan is involved in the occurrence and development of diseases through the production of Kyn, serotonin, and indole metabolites via three main metabolic pathways. Among them, IDO in the Kyn pathway participates in the immune response in AS, which promotes cardiac hypertrophy. Moreover, IDO1 deletion aggravates VSMC reprogramming and calcification. In the serotonin pathway, 5-HT and melatonin have anti-inflammatory and antioxidant activity, and inhibit cell aging. IPA in the indole pathway affects the production of NO and inhibits AngII-induced apoptosis, ROS, and inflammation. IAA also has anti-inflammatory and antioxidant activity. The specialized tryptophan derivative 5-MTP inhibits endothelial dysfunction; exhibits antioxidant and anti-inflammatory properties; protects cardiac mitochondrial integrity; and contributes to the prevention of AS. Particular attention should be paid to the role of IPA. Current research has indicated that IPA enhances the autophagy levels of senescent macrophages by activating the PI3K-Akt-mTOR signaling pathway [132], and might play crucial roles in the prevention and treatment of AS.

Currently, using amino acids as therapeutics faces several key challenges. First, most metabolic studies have relied on animal models that significantly differ from humans in transporter expression, enzyme activity, and substrate preference,

thus limiting the translation of findings to human disease. More human-derived models (e.g., iPSC cardiomyocytes) are needed. Second, cardiac amino acid metabolism might vary widely across disease stages and treatment contexts, thus requiring stratified study designs and multi-omics approaches to capture these dynamic changes. Third, the lack of standardized clinical assays and reference ranges limits their use as biomarkers. Future work should develop high-throughput, sensitive, standardized platforms validated in multicenter cohorts.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

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