Relationship between amino acid metabolism and inflammation in coronary heart disease (Review)

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Received March 22, 2025; Accepted May 12, 2025

DOI: 10.3892/ijmm.2025.5561

Abstract. This review delves into the intricate relationship between amino acid metabolism and inflammation in coronary heart disease (CHD). Research shows that disruptions in the metabolism of arginine, glutamate, branched-chain amino acids (BCAAs) and tryptophan exacerbate CHD inflammation via immunometabolic reprogramming and oxidative stress. Nitric oxide (NO), produced from arginine metabolism, regulates CHD progression multifacetedly. Glutamate metabolism dysregulation harms cardiovascular health, while glutamine exerts cardioprotective effects after myocardial infarction. Elevated BCAA levels are associated with atherosclerosis development, and tryptophan and its metabolites have complex effects on CHD. Notably, amino acid metabolism intersects with the immune system, modulating the functions of T cells, B cells and macrophages. These immune cells are crucial for CHD-related inflammation. Inflammatory markers like high-sensitivity C-reactive protein, interleukin family members, interferon-γ and monocyte chemoattractant protein-1 are closely linked to CHD pathogenesis and progression, facilitating risk assessment. Clinical research, including animal and human studies, and technological applications such as metabolomics, offer insights into CHD diagnosis, treatment and prevention. Dietary intervention and drug therapy targeting amino acid metabolism show potential. For example, L-arginine supplementation has cardioprotective effects and novel NO donors like compound-N6 hold promise. However, certain substances like triclocarban have adverse impacts, while colchicine is beneficial. In summary, while current research has advanced the understanding of CHD, significant knowledge gaps remain, particularly regarding rare amino acids and the connection between amino acid metabolism and non-coding RNA. Future research could utilize metabolomics, genomics and artificial intelligence for personalized CHD management, representing a paradigm shift towards individualized precision medicine.

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Key words: amino acid metabolism, coronary heart disease, inflammatory response, immunomodulation

Contents

1. Introduction

Coronary heart disease (CHD) is a globally prevalent cardiovascular disorder with a complex pathogenesis associated with multiple risk factors, including high-level low-density lipoprotein cholesterol, smoking, chronic kidney disease, diabetes and hypertension (1). The primary pathological feature of CHD is coronary atherosclerosis, which can lead to myocardial ischemia, hypoxia and necrosis (2,3). Inflammation assumes a pivotal position in the development of CHD, with atherosclerosis essentially being a chronic inflammatory disease. Inflammatory factors contribute to atherosclerotic plaque formation, rupture and the progression of CHD through processes such as vascular endothelial injury and thrombosis (4,5).

While the role of inflammation in CHD is well-established, emerging evidence has shown that amino acid metabolic disorders can also have a profound impact on the inflammatory response in CHD. Such metabolic disorders can initiate a cascade of events, including the dysregulation of the tricarboxylic acid cycle (TCA), which is integral to the oxidative phosphorylation processes in cardiac myocytes (6). Dysregulation of the TCA cycle can lead to mitochondrial dysfunction, subsequently inducing oxidative stress and promoting an inflammatory state. Furthermore, amino acid metabolic disorders can alter the plaque microenvironment through immunometabolic reprogramming

and oxidative stress, thereby exacerbating inflammation in CHD.

In atherosclerotic plaques, M1-type macrophages secrete pro-inflammatory cytokines such as interleukin-1β (IL-1β), IL-6 and tumor necrosis factor-α (TNF-α). This secretion promotes the progression of the inflammatory response, increasing plaque instability and rupture risk (7). Furthermore, oxidized low-density lipoprotein (ox-LDL) not only promotes the polarization of M1-type macrophages but also inhibits the anti-inflammatory and tissue-repair functions of M2-type macrophages. This disruption of the M1/M2 balance leads to an uncontrolled inflammatory response, which aggravates atherosclerosis (8). These mechanisms illustrate a vicious cycle of CHD inflammation through immunometabolic reprogramming.

During atherosclerosis, various subsets of T lymphocytes play distinct roles. Type 1 T-helper (Th) cells can secrete pro-inflammatory cytokines such as interferon-γ (IFN-γ), which drives macrophage activation and intensifies plaque inflammation (9). Th17 cells produce IL-17, which aggravates endothelial damage and increases plaque instability (10). By contrast, regulatory T cells (Tregs) secrete anti-inflammatory factors such as IL-10 and TGF-β, suppressing excessive immune responses and delaying the progression of atherosclerosis (11). In addition, in acute coronary syndrome, neutrophils release toxic substances such as elastase and myeloperoxidase, and form neutrophil extracellular traps, further intensifying inflammation and thrombosis (12,13). Natural killer (NK) cells and B lymphocytes also participate in the regulation of the plaque microenvironment through their respective unique mechanisms (14-16).

Exposure to harmful stimuli disrupts the balance between oxidants and antioxidants, leading to excessive reactive oxygen species (ROS) production. This imbalance, exacerbated by amino acid metabolic issues, weakens the antioxidant defense, causing ROS accumulation. ROS oxidize molecules like LDL, which macrophages absorb, forming foam cells and releasing inflammatory mediators. Excessive ROS damage endothelial cell membranes, activate the inflammation pathway through molecules like nuclear factor-κB (NF-κB) and increase pro-inflammatory factors like IL-6 and TNF-α. Thus, oxidative stress from amino acid metabolism disruption harms endothelial cells and enhances inflammation (17).

Importantly, the 'metabolism-inflammation' perspective holds great promise for identifying novel therapeutic targets and diagnostic markers for CHD. By re-evaluating CHD through this lens, it is possible to lay a theoretical groundwork for the development of more effective treatment strategies and early-stage diagnostic tools, which are crucial for clinical practice. This perspective not only uncovers additional factors driving CHD development but also offers fresh insights into the intricate interplay between metabolism and inflammation in CHD, an aspect that has been hitherto under-emphasized.

Despite the increasing attention paid to the regulatory role of amino acid metabolism in the inflammatory response associated with CHD, the precise mechanisms and comprehensive functions involved in disease progression remain insufficiently explored. This review seeks to synthesize current research advancements concerning the interplay between amino acid metabolism and the CHD inflammatory response. It aims to systematically elucidate the underlying molecular mechanisms, evaluate the implications for clinical diagnosis and therapeutic applications, and thereby offer novel perspectives and directions for future research in this domain.

2. Overview of amino acid metabolism

Amino acids, the building blocks of proteins, are central to metabolic pathways and also participate in immune regulation and the inflammatory response. Amino acids such as arginine, glutamate, branched-chain amino acids (BCAAs) and tryptophan, can regulate the inflammatory cascade through their metabolites and signaling pathways, influencing the onset and development of CHD.

Arginine. Arginine, a notable non-essential amino acid, plays a vital role in the cardiovascular system, mainly via its involvement in the nitric oxide (NO) synthesis pathway. The synthesis of NO is mediated by the NO synthase (NOS) enzyme family, which includes endothelial NOS (eNOS), neuronal NOS and inducible NOS (iNOS). Notably, NO can also be synthesized through non-enzymatic pathways, particularly under hypoxic conditions (18). NO is essential for modulating immune cell activity, reducing inflammatory responses and enhancing vascular endothelial function (19).

Importantly, eNOS is constitutively expressed in vascular endothelial cells, producing low levels of NO to maintain basal vascular tone. The competition between arginase and eNOS for their common substrate L-arginine impairs NO-mediated vasodilation (20). Specifically, arginase utilizes L-arginine to produce urea and ornithine, limiting the production of NO (21). Disruption of arginine metabolism can result in increased levels of asymmetric dimethylarginine, which serves as a competitive inhibitor of eNOS. This inhibition reduces the production of antioxidant NO and increases the generation of superoxide anions (O^{2-}) (22). Conversely, iNOS is upregulated in response to inflammatory stimuli, generating substantial quantities of NO to facilitate immune defense and inflammatory processes (23,24).

NO's mechanisms in vascular endothelial cells. Under normal physiological conditions, eNOS uses L-arginine to produce NO. NO, a potent vasodilator, reduces intracellular calcium, leading to the relaxation of vascular smooth muscle and vessel dilation. Furthermore, it exhibits anti-atherosclerotic properties by suppressing platelet aggregation, smooth muscle cell proliferation and leukocyte adhesion, and increasing vascular permeability and inflammation (25). In addition, NO decreases arterial stiffness (26), thereby maintaining vascular homeostasis.

From the perspective of vascular endothelial cells, NO serves as a crucial mediator in maintaining vascular health through various mechanisms. NO, released by endothelial cells, diffuses into vascular smooth muscle cells, where it inhibits the activation of the TGFβR1 and its downstream Smad signaling pathway. Such inhibition leads to a reduced expression of inflammatory factors and genes related to calcification (27). Additionally, omega-3 polyunsaturated fatty acids, such as eicosapentaenoic acid, enhance the activity of eNOS by activating the PI3K/Akt signaling pathway, thereby increasing NO production and reducing oxidative stress. This

leads to improved endothelial function and mitigates the proinflammatory response induced by IL-6 (28).

Conversely, insufficient NO impairs the endothelium's vasodilatory, antithrombotic and anti-inflammatory functions, resulting in endothelial dysfunction (29,30). Endothelial dysfunction activates NF-κB, which upregulates adhesion molecules like intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (31). These molecules attract leukocytes to adhere to the endothelium. Subsequently, chemokines help leukocytes infiltrate the vessel wall. Activated leukocytes release TNF-α and IL-1β, fueling local inflammation. This cascade promotes atherosclerosis and CHD, worsening plaque development and instability.

Factors influencing NO generation and function. Numerous factors exert a significant influence on the synthesis and functionality of NO, with certain factors having a more pronounced impact on the pathogenesis of CHD. Oxidative stress is highly important in this process. On one hand, oxidative stress can reduce the production of NO and interfere with the NO signaling pathway by oxidatively modifying NO target proteins (32). On the other hand, a large number of ROS generated by oxidative stress, such as superoxide anions and peroxynitrites, can rapidly react with NO, greatly reducing the bioavailability of NO and promoting the occurrence and development of CHD. For instance, angiotensin II activates the angiotensin II receptor type 1/NADPH oxidase pathway, resulting in substantial generation of ROS. These ROS oxidize the co-factor tetrahydrobiopterin (BH4) of endothelial eNOS, rendering eNOS inactive and causing eNOS uncoupling, which ultimately results in an imbalance between NO and ROS (33). Conversely, an adequate supply of BH4 can restore eNOS functionality, enhance NO production and inhibit ROS generation, thus alleviating inflammation and senescence in endothelial cells (34). Furthermore, the orphan nuclear receptor 77 can bind to the promoter region of eNOS, enhancing NO production. Concurrently, it upregulates the expression of antioxidant enzymes, mitigating endothelial damage caused by oxidative stress (35). By contrast, the inhibition of sirtuin (Sirt)3 activates the NF-κB signaling pathway, leading to worsening vascular inflammation, reduced NO production, increased ROS levels and decreased levels of L-arginine, further deteriorating vascular lesions (36).

In the context of macrophage polarization, NOS serves as a marker for M1 polarization of macrophages, while arginase-1 (ARG1) is a marker for M2 polarization (37). Regarding the different isoforms of ARG, ARG2 has a distinct intracellular localization compared with ARG1. ARG2 is mainly restricted to mitochondria and exhibits a lower affinity for L-arginine than NOS (38). ARG2 can regulate NO production and vascular endothelial function by modulating eNOS activity (39). The regulation of inflammatory cytokines and immune cells by arginine and NO is presented in Fig. 1.

Clinically, NO and related factors like BH4 could be potential biomarkers for CHD diagnosis. Monitoring their levels helps assess disease status. For treatment, they offer drug targets, and understanding them aids in optimizing existing drugs and personalized therapy.

Glutamate. Research has provided critical insights into the relationship between glutamate and cardiovascular diseases (CVDs). A comprehensive study conducted by Ottosson *et al* (40), which included 6,865 Swedish participants, demonstrated that glutamate serves as an independent predictor of aortic stiffness. Similarly, the investigation by Vernon *et al* (41) involving 1,002 patients with CHD identified a significant positive correlation between glutamate levels and the presence of non-calcified plaques. Taken together, these findings imply that fluctuations in glutamate levels may play a role in the initiation and progression of CVDs.

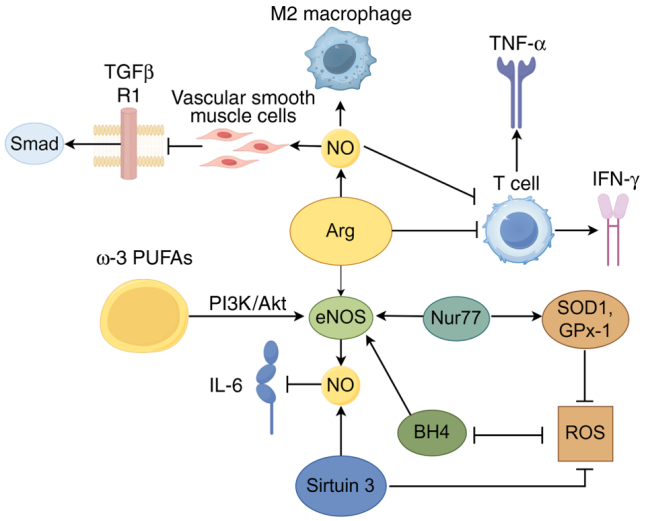

Figure 1. Regulation of inflammatory cytokines and immune cells by Arg and NO (figure generated with Figdraw). NO, nitric oxide; eNOS, endothelial NO synthase; TNF-α, tumor necrosis factor-α; IFN-γ, interferon-γ; ω-3 PUFAs, omega-3 polyunsaturated fatty acids; Nur77, orphan nuclear receptor 77; SOD1, superoxide dismutase 1; GPx-1, glutathione peroxidase 1; BH4, tetrahydrobiopterin; ROS, reactive oxygen species; Arg, Arginine.

Mechanisms of glutamate metabolism dysregulation affecting cardiovascular health. The dysregulation of glutamate metabolism has valuable implications for cardiovascular health through various mechanisms. Notably, it can induce oxidative stress in endothelial cells, initiating inflammatory responses (42). Research conducted by Wang *et al* (43), which utilized liquid chromatography-mass spectrometry (LC-MS) technology, demonstrated a marked increase in serum glutamate levels in patients with atherosclerosis, further validating the involvement of glutamate metabolic disorders in the pathogenesis of atherosclerosis. Glutathione (GSH), a tripeptide composed of glutamate, cysteine and glycine, acts as a crucial intracellular antioxidant. It plays an essential role in scavenging free radicals and maintaining cellular redox homeostasis, mitigating the progression of atherosclerosis (44).

Roles of glutamate and related metabolites in cardiovascular events. Beyond their direct influence on cardiovascular health via metabolic pathways, glutamate and its related metabolites are integral to specific cardiovascular events and immune regulation. Empirical evidence indicates that glutamine enhances left ventricular systolic function post-myocardial infarction, with notable alterations observed in glutamine metabolism-related metabolites within macrophages following such events (45). Furthermore, a significant inverse correlation exists between the glutamine/glutamate ratio and the coronary artery disease (CAD) phenotype, suggesting that this ratio could serve as a potential biomarker

for CAD assessment (46). These findings are particularly noteworthy, as they not only elucidate the protective mechanisms of glutamine in myocardial infarction but also propose a potential biomarker for the early diagnosis and monitoring of CAD, which could transform the management of this widespread cardiovascular condition.

Functions of glutamate, glutamine and glutathione in immune regulation. In the realm of immune regulation, glutamine, GSH and glutamate are also important. GSH is essential for maintaining the immune functionality of Th17 cells by facilitating mitochondrial signal transduction and the synthesis of IL-22 protein in these cells (47). Simultaneously, glutamine plays a pivotal role in the activation and proliferation of CD8+ T cells, as well as in the secretion of cytokines such as IFN-γ, underscoring its significance in modulating cellular immune responses (48). Dysregulation of glutamate metabolism leads to multiple pro-inflammatory responses. Firstly, it increases ROS levels. ROS activates the IκB kinase (IKK) complex, which phosphorylates and degrades IκBα. This liberates NF-κB, enabling its translocation into the nucleus to activate inflammation-related genes (49). Furthermore, overactivation of glutamate receptors, such as NMDA receptors, raises intracellular Ca^{2+} levels. Ca^{2+} then activates protein kinase C, which in turn activates the IKK complex. This leads to IκBα phosphorylation and degradation, ultimately activating the NF-κB pathway (50). In macrophages, glutamate activates the NF-κB signaling pathway, which upregulates genes related to NOD-like receptor protein 3 (NLRP3) activation. Subsequently, the NLRP3 complex assembles and proceeds to convert pro-IL-1β into its active form, IL-1β, intensifying the inflammatory response (51). Under high-glucose conditions, NLRP3 expression is upregulated, deteriorating inflammation through the IL/MAPK/NF-κB pathway and accelerating the progression of atherosclerosis (52). The roles of glutamine, GSH and glutamate in immune regulation highlight their potential as therapeutic targets for modulating immune responses in CVDs, indicating promising avenues for future research and treatment. The regulation of inflammatory cytokines and immune cells by glutamate and GSH is shown in Fig. 2.

In clinical diagnosis, the glutamine/glutamate ratio can be a biomarker. A lower ratio indicates a higher risk of CAD, enabling early detection. On the other hand, regarding therapeutic interventions, glutamine supplementation may exert cardioprotective effects after myocardial infarction. Drugs regulating glutamate metabolism to control macrophage-mediated inflammation could also be developed, aiming to improve CVD outcomes.

Role of branched-chain amino acids in CHD

Association with atherosclerosis. BCAAs, a subset of essential amino acids distinguished by their aliphatic side-chain structures, primarily comprise leucine, isoleucine and valine. Considering that carotid intima-media thickness (CIMT) is a critical marker of early atherosclerotic lesions, the positive correlation between elevated levels of BCAAs and increased CIMT suggests a potential role for BCAAs in the early development of atherosclerosis (53). Epidemiological evidence further substantiates the independent association between elevated levels of BCAAs and the incidence of CHD, as well as its

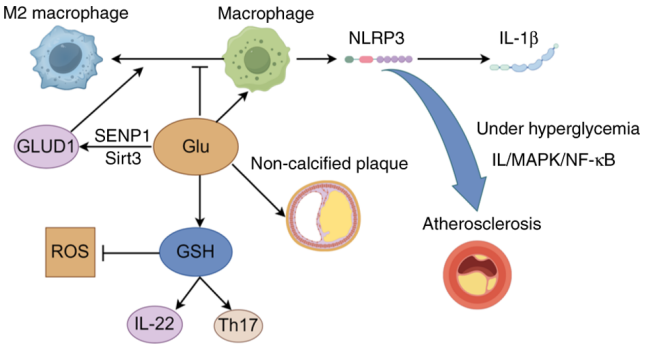

Figure 2. Regulation of inflammatory cytokines and immune cells by Glu and GSH (figure generated with Figdraw). Glu, glutamate; GSH, glutathione; NLRP3, NOD-like receptor protein 3; IL-1β, interleukin-1β; GLUD1, glutamate dehydrogenase 1; ROS, reactive oxygen species; Th17, T-helper 17 cells; Sirt3, sirtuin 3; SENP1, sentrin-specific protease 1.

prevalent traditional risk factors, including insulin resistance, dyslipidemia and endothelial dysfunction. This association significantly heightens an individual's risk of developing CHD and stroke (54,55). Recent research has focused on the potential significance of the ratio of BCAAs to other compounds in the context of CHD. Notably, the ratio of total BCAAs to glycine appears to exert a more substantial influence on CHD than individual indicators. This observation suggests that this ratio may be of considerable importance in the assessment of CHD risk (56).

Recent studies have elucidated the impact of BCAAs on myocardial metabolism, highlighting their potential to disrupt normal triglyceride metabolism via the activation of the mTOR/SREBP-1/betatrophin pathway, a process contingent upon p38-MAPK (57). This hyperactivation of the lipid synthesis pathway results in dysregulated triglyceride metabolism and subsequent myocardial glycolipid metabolic disorders, thereby importantly contributing to the pathological progression of CHD (58). In addition, BCAAs have been shown to enhance macrophage activation and the secretion of pro-inflammatory cytokines, such as IL-6 and TNF-α, through the mTOR/NF-κB signaling pathway, thus promoting inflammatory processes (59-61).

Impact on signaling pathways and inflammatory response. In the pathogenesis of CVDs, the metabolism of BCAAs and their associated signaling pathways play a critical role. The complex mechanisms of interaction among these pathways have become a focal point of contemporary scientific investigation.

Increased levels of BCAAs can trigger a series of adverse physiological reactions. On one hand, they activate the IKK, leading to the phosphorylation and degradation of IκB, and subsequently releasing the NF-κB. After NF-κB translocates into the nucleus, it promotes the transcription of inflammatory genes such as ICAM-1 and E-selectin, which not only disrupts mitochondrial function but also leads to metabolic disorders (62). Furthermore, increased BCAA concentrations can activate macrophages with a pro-inflammatory phenotype, triggering a cascade of inflammatory responses (63). The accumulation of BCAAs also activates the NF-κB signaling pathway in blood cells, resulting in the release of inflammatory mediators that facilitate the adhesion of inflammatory

cells. This sequence of events enhances the production of ROS, ultimately leading to endothelial dysfunction (61). On the other hand, BCAA transaminase acts on all three BCAAs, converting them into branched-chain keto acids (BCKAs) and glutamate. BCKAs can promote the production of ROS due to their ability to cause mitochondrial respiratory dysfunction, indicating that the BCKA-ROS axis may contribute to the development of heart diseases (64). In addition, BCAAs can induce the formation and secretion of disulfide-group-modified high-mobility group box 1 protein (HMGB1) in macrophages through the mitochondrial-nuclear H_2O_2 signaling pathway, which activate pro-inflammatory macrophages and trigger inflammation via the HMGB1/Toll-like receptor 4 (TLR4)/NF-κB pathway, promoting the progression of atherosclerosis (63). In addition, the accumulation of BCAAs can over-activate mTOR, which not only leads to a phenotypic transformation of vascular smooth muscle cells, causing mitochondrial ROS damage and triggering vascular inflammation (65), but also mediates the upregulation of IL-6 and TNF-α. Elevated IL-6 levels can disrupt the normal function of the cardiovascular system by promoting chronic inflammation and inducing endothelial cell activation, leading to the recruitment of immune cells and the release of additional pro-inflammatory factors (66). TNF-α, on the other hand, can damage cardiomyocytes, promote the apoptosis of endothelial cells and contribute to the development of cardiac fibrosis (67,68).

Leucine and valine positively influence the AKT/forkhead box O1 signaling pathway in hepatic and adipose tissues by inhibiting gluconeogenesis and promoting glucose homeostasis. This modulation aids in stabilizing blood glucose levels, enhancing insulin sensitivity and reducing inflammatory processes (69). These physiological effects are particularly significant in the context of CHD, as they mitigate risk factors and offer a potential therapeutic target for both prevention and treatment. In addition, the MAPK signaling pathway plays a crucial role in the inflammatory response associated with amino acid metabolism. In neonatal patients with CHD, elevated leucine levels may suppress the WD repeat containing planar cell polarity effector/MAPK axis, resulting in increased endomucin expression and subsequently impairing the normal function of cardiac microvascular endothelial cells (70). The regulation of inflammatory cytokines and immune cells by BCAAs is exhibited in Fig. 3.

Clinical significance and dietary considerations of BCAAs in CHD. In the context of clinical relevance, BCAAs have emerged as key players in multiple aspects related to cardiovascular health. Plasma levels of BCAAs are valuable biomarkers for cardiac-metabolic complications following orthotopic liver transplantation (71). High intakes of BCAAs, including isoleucine, leucine and valine, are independently associated with an increased risk of the progression of coronary artery calcification (72). This indicates that the amount of BCAAs in the diet can directly impact CVD progression. In terms of dietary impacts, BCAAs from different sources show distinct effects on cardiometabolic health. BCAAs from poultry, whole grains and nuts, soy, as well as vegetables and fruits may be beneficial for cardiometabolic health, while those from red meat, processed meat, fish and refined grains are detrimental (73). Such dietary differences in BCAA sources highlight the importance of dietary choices in modulating

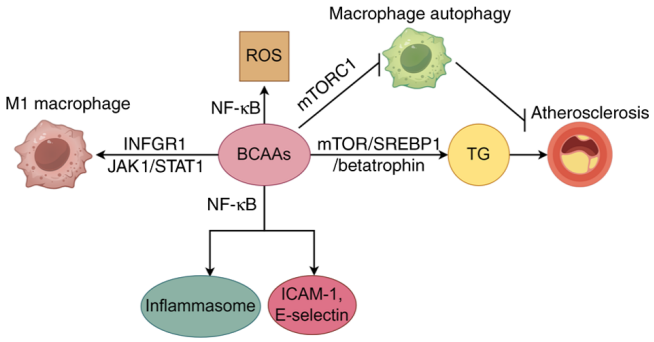

Figure 3. Regulation of inflammatory cytokines and immune cells by BCAAs (figure generated with Figdraw). BCAAs, branched-chain amino acids; TG, triglyceride; ICAM-1, intercellular adhesion molecule 1; ROS, reactive oxygen species; SREBP1, sterol regulatory element-binding protein 1.

CVD risk. Furthermore, 3-mercaptopyruvate sulfurtransferase-derived mitochondrial H_2S may play a regulatory role in BCAA catabolism and mediate critical cardiovascular protection in heart failure (74). This reveals an additional layer of complexity in the regulation of BCAA metabolism and its connection to cardiovascular protection. Dietary supplementation with BCAAs can alleviate atherosclerosis induced by high lipoproteins in apolipoprotein (Apo)$E^{-/-}$ mice. The mechanisms involve improving dyslipidemia and inflammation, modulating the gut microbiota and promoting bile acid excretion (75).

In clinical diagnosis, integrating BCAA-related markers with traditional biomarkers could potentially enhance the early detection of CHD. Regarding treatment, small-scale human trials have investigated BCAA-targeted therapies. However, large-scale, long-term clinical trials are urgently needed to validate the efficacy and safety of such interventions. These findings add to the existing knowledge about BCAAs, which in turn help us better understand the implications of the current study.

The complex roles of tryptophan metabolism in CHD. In contrast to the mechanisms of BCAAs in CVDs, tryptophan and its metabolites exhibit complex roles within this context. Recent evidence suggests an inverse relationship between tryptophan levels and CVD risk, indicating that higher tryptophan levels are associated with a decreased risk of CVD. However, tryptophan metabolites, such as kynurenine and serotonin, are positively correlated with an increased risk of CVD (76). Elevated kynurenine levels are remarkably associated with insulin resistance and β-cell dysfunction, potentially contributing to the pathogenesis of diabetes through mechanisms involving inflammatory responses and oxidative stress, influencing the pathological progression of CHD (77).

Pro-inflammatory effects mediated by tryptophan metabolites. Regarding the regulation of the inflammatory response, tryptophan metabolites influence the process by activating the aryl hydrocarbon receptor (AhR), which significantly impacts the stability of atherosclerotic plaques, endothelial function and the myocardial inflammatory microenvironment (78). Upon activation, the AhR signaling pathway promotes the activation of inflammatory cells and the substantial release of inflammatory mediators, intensifying the inflammatory response within the cardiovascular system (79). Specifically,

activated AhR translocates to the nucleus and binds to specific DNA sequences, leading to the upregulation of genes encoding pro-inflammatory cytokines such as TNF-α and IL-6, as well as chemokines like C-X-C motif chemokine ligand (CXCL)8. These cytokines and chemokines subsequently recruit and activate immune cells, perpetuating the inflammatory cascade in cardiovascular tissues. Efferocytosis enhances tryptophan metabolism and indoleamine 2,3-dioxygenase 1 (IDO1) activity, facilitating the kynurenine-mediated catabolic process through the production of IL-10. This mechanism may elucidate why macrophage IDO1 deficiency hinders the regression of atherosclerosis (80). However, the role of tryptophan metabolites in inflammation regulation is not one-sided. Intriguingly, certain tryptophan metabolites operate in an opposing manner, acting as guardians against inflammation rather than its instigators (81).

Anti-inflammatory tryptophan metabolites and their clinical potential. It is important to note that not all tryptophan metabolites exhibit pro-inflammatory effects. For instance, 5-methoxytryptophan (5-MTP), an endogenous tryptophan metabolite, has been shown to possess anti-inflammatory properties and to inhibit cell proliferation and migration. 5-MTP may serve as a valuable marker for assessing the long-term prognosis of patients with acute myocardial infarction following percutaneous coronary intervention (82). Another tryptophan-derived metabolite, indole-3-acetic acid (IAA), inhibits the TLR4/MyD88/NF-κB signaling pathway in M1 macrophages, promotes M2 macrophage polarization and restores the balance of M1/M2 polarization, thereby reducing aortic inflammation (83). The anti-inflammatory and anti-proliferative properties of 5-MTP and IAA, along with their potential utility in evaluating the long-term prognosis of patients with acute myocardial infarction post-percutaneous coronary intervention, make them highly promising as biomarkers and prospective therapeutic targets. Further research into their underlying mechanisms and clinical applications may reveal novel strategies for the management of CHD.

Tryptophan metabolism and cardiovascular-related conditions. Coronary thrombosis has been associated with elevated levels of circulating l-tryptophan, which is associated with gut microbiota dysbiosis (84). Reduced circulating tryptophan levels are associated with an increased risk of CVD events (85). The metabolism of L-tryptophan is related to lower limb ischemia and thrombosis (86). Taurine stimulates tryptophan metabolism, reducing the inflammatory response and oxidative stress in the paraventricular nucleus through gut-brain communication, thereby decreasing sympathetic nerve activity and blood pressure in hypertensive rats (87).

The tryptophan metabolite indole-3-propionic acid can alleviate the occurrence and severity of aortic dissection (AD) in mice (88). Although this finding is mainly related to AD, inflammation is involved in the pathogenesis of various diseases, and there may be potential connections between the role of tryptophan metabolites in AD and CVDs. Further research in this area may provide new insights into the relationship between tryptophan metabolism and CVD.

The anti-inflammatory and other properties of tryptophan-related substances and their metabolites further enhance the understanding of the intricate relationship between tryptophan metabolism and CVDs. In clinical diagnosis, the levels of tryptophan and key metabolites, such as kynurenine, may serve as novel biomarkers for CHD. Monitoring the kynurenine-to-tryptophan ratio may be particularly useful in assessing disease progression, particularly in patients with diabetes, where tryptophan metabolism is often disrupted. Regarding treatment, drugs that target tryptophan metabolism pathways hold promise. For instance, inhibitors of IDO1 could potentially reduce inflammation. Additionally, supplementing with anti-inflammatory metabolites like 5-MTP and IAA is an area worth exploring. However, more research is needed to determine optimal dosages, effective delivery methods and long-term safety for these potential therapeutic approaches.

3. Relationship between amino acid metabolism and the immune system

In the analysis of the roles of various amino acids in the inflammation associated with CHD, it is imperative to understand the interplay between amino acid metabolism and the immune system, which is integral to the pathogenesis of CHD. Furthermore, amino acid metabolism has the potential to modulate immune cell functions, thereby influencing the inflammatory response in the context of CHD.

Amino acid metabolism serves a dual function: Supplying energy and substrates essential for intracellular protein synthesis, while also directly modulating immune cell functions and activities via its metabolites. This progression is critical in the inflammatory response associated with CHD. The functional states of T cells, B cells and macrophages-key constituents of the immune system-are intricately connected to amino acid metabolism, collectively impacting the onset and progression of atherosclerosis.

T-cell activation and function dependence on amino acid metabolism. The activation and normal functioning of T-cells are critically dependent on amino acid metabolism. Extensive research has demonstrated that diminished arginine bioavailability significantly affects T-cell metabolism and function. This metabolic alteration results in enhanced activation and differentiation of T-cells, culminating in the excessive production of pro-inflammatory cytokines, such as IFN-γ and TNF-α. These inflammatory mediators contribute to endothelial dysfunction, foam cell formation and plaque progression, thereby exacerbating the pathogenesis of atherosclerosis (89,90). Arginine is a critical substrate for NOS in T-cells, where NO typically functions as a negative regulator of T-cell activation. In the absence of adequate NO, T-cells are more susceptible to overactivation, disrupting the immune response balance. This imbalance results in the overproduction of pro-inflammatory cytokines, which facilitate the recruitment and activation of additional immune cells, further amplifying the inflammatory process in atherosclerosis. In studies related to non-small cell lung cancer, it has been observed that a reduction in amino acid metabolism, along with the inactivation of the mTOR signaling pathway, can lead to the exhaustion of $CD8^+$ T cells, thereby diminishing the body's immune defense capabilities (91). Given the close association between immune regulation and CHD, it is imperative to conduct in-depth investigations to ascertain whether a

similar phenomenon occurs in the pathogenesis and progression of CHD.

Beyond the well-established link between T-cell activation and amino acid metabolism, it is crucial to explore the distinct roles of various T-cell subsets in conditions related to CHD. Notably, individuals with premature coronary artery disease (PCAD) exhibit significantly enhanced cytotoxic and proliferative capabilities mediated by T-cells, underscoring their pivotal role in the early stages of disease progression (92). By contrast, Tregs demonstrate a protective effect in patients with CAD and type 2 diabetes mellitus, with Treg levels showing an inverse correlation with the severity of coronary artery lesions (93). A risk-prediction model incorporating peripheral blood IL-6 levels and Treg percentages presents a novel method for the early detection of CHD risk in patients with primary Sjögren's syndrome (94). These findings underscore the potential of targeting Tregs as a therapeutic strategy for CHD.

Amino acid metabolism and B-cell function in CHD. In recent years, the role of B-cells in the pathogenesis and progression of CHD has attracted increasing scholarly attention. Amino acid metabolism is pivotal in regulating the metabolic reprogramming and functional activities of B-cells, a process that is of significant importance for the immune response and the modulation of inflammation within the body.

Glutamine, an essential energy substrate for B-cell activation, is vital for maintaining B-cell survival and proper function by supporting mitochondrial integrity and protein synthesis (95,96). The metabolism of glutamine inhibits glycogen synthase kinase 3 activity by activating mammalian target of rapamycin complex 1 (mTORC1), thereby enhancing the expression of IL-10 in B-cells (97). Additionally, tryptophan metabolism primarily produces AhR ligands via the kynurenine, serotonin and indole-3-pyruvate pathways. Activation of AhR can modulate B-cell polarization and promote the secretion of IL-10 by B-cells (98,99). Collectively, these findings underscore the influence of amino acid metabolism on B-cell functionality, with potential implications for the inflammatory response and the pathogenesis of CHD.

In individuals diagnosed with CHD, the functional states of B-cell subsets are intricately associated with the severity of the disease. Circulating $CD11c^+$ B-cells include various subsets, notably age-related B-cells and IgD^-CD27^- double-negative B-cells, which demonstrate a positive correlation with CHD severity (100). Among patients with low-severity CAD, there is an observed increase in the negative regulators of B-cell receptor signaling mediated by CD72, which may potentially slow disease progression by maintaining B-cell homeostasis. Furthermore, elevated levels of B-cell-activating factor (BAFF) are linked to the severity of CAD and acute myocardial infarction (101), suggesting that BAFF could serve as a viable biomarker for disease diagnosis and assessment. The p62 protein promotes the proliferation of B1B cells through the regulation of the NF-κB signaling pathway and exhibits a degree of resistance to CHD (102).

Macrophages play a dual role in atherosclerosis. Macrophages play a dual role in vascular homeostasis and the pathogenesis of atherosclerosis. They contribute to vascular homeostasis through the clearance of ox-LDL. However, they also secrete pro-inflammatory cytokines, such as TNF-α and IL-6, which exacerbate inflammatory responses and facilitate atherosclerosis progression (103).

Leucine is known to activate the mTORC1 signaling pathway, thereby inhibiting macrophage autophagy and leading to macrophage accumulation on the endothelial surface of blood vessels, which accelerates atherosclerosis development (104). Furthermore, BCAAs promote macrophage polarization towards the pro-inflammatory M1 phenotype through the INFGR1/JAK1/STAT1 signaling pathway, thereby enhancing inflammatory responses and insulin resistance (105). By contrast, glutamate metabolism enhances the activity of glutamate dehydrogenase 1 via the sentrin-specific protease 1-Sirt3 axis, inducing macrophage polarization towards the anti-inflammatory M2 phenotype (106). In addition, small extracellular vesicles found in the pericardial fluid of patients with CHD influence macrophage phenotypes, resulting in the upregulation of pro-inflammatory markers such as CD86 and inflammatory cytokines including IL-1β and TNF-α, thereby augmenting the inflammatory response (107).

Given the pivotal role of macrophages in the pathogenesis of CVDs, a variety of targeted therapeutic strategies have been developed. These strategies frequently achieve their therapeutic effects by modulating amino acid metabolism or related signaling pathways. For instance, cannabidiol has been demonstrated to regulate the TLR4/MyD88/NF-κB signaling pathway, effectively inhibiting the polarization of macrophages towards the pro-inflammatory M1 phenotype and exhibiting important anti-atherosclerotic properties (108). Furthermore, the alkaloid SZ-A, derived from mulberry twigs, enhances endothelial cell function and mitigates inflammatory responses by reducing CXCL-10 secretion from M1 macrophages, offering a novel therapeutic approach for atherosclerosis treatment (109). In addition, the mitochondria-targeted ROS scavenger MitoTEMPO and the lon peptidase 1, mitochondrial inhibitor bortezomib have been shown to restore mitochondrial homeostasis in foam cells and reduce oxidative stress-induced damage (110). Furthermore, the long non-coding (lnc)RNA lnc-MRGPRF-6:1 has been identified as a promoter of ox-LDL-induced macrophage ferroptosis through the inhibition of GSH peroxidase 4, thereby influencing the progression of atherosclerosis (111).

In recent years, chimeric antigen receptor macrophage (CAR-M) therapy has shown considerable promise in the treatment of CVDs. Fibroblast activation protein CAR-Ms have been demonstrated to alleviate myocardial fibrosis and maintain cardiac function, presenting a novel therapeutic strategy for myocardial ischemia-reperfusion injury and other CVDs characterized by a fibrotic phenotype (112). Furthermore, the expression of circulating RNA ARCN1 in macrophages plays a pivotal role in the pathogenesis of atherosclerosis by regulating HuR-mediated ubiquitin-specific protease 31 mRNA stability and NF-κB activation (113). Glutamine, as a crucial metabolic substrate, not only inhibits the excessive production of ROS and the activity of matrix metalloproteinases in vascular smooth muscle cells but also suppresses the activation of M1 macrophages and the apoptosis of vascular smooth

muscle cells (114). This effectively safeguards the cardiovascular system against inflammation and damage.

These intervention strategies underscore the pivotal role of macrophages in atherosclerosis and provide novel insights for therapies targeting amino acid metabolism and its associated signaling pathways.

In summary, amino acid metabolism exerts a substantial influence on the inflammatory response and progression of atherosclerosis by intricately modulating the functions of T cells, B cells and macrophages. Extensive research into these mechanisms is anticipated to establish a more robust theoretical foundation for the prevention, diagnosis and treatment of CVDs, facilitate the development of innovative intervention strategies and potentially lead to remarkable advancements in the prevention and management of cardiovascular conditions. The specific effects of arginine, glutamic acid, BCAAs and tryptophan on inflammation, immune cells and CHD outcomes are detailed in Table I.

4. Inflammatory markers and risk assessment of CHD

The interplay between amino acid metabolism and the immune system exerts a profound influence on the inflammatory state in CHD. This section will concentrate on the inflammatory markers intricately linked to the pathogenesis and progression of CHD. These markers not only facilitate the assessment of CHD risk but also elucidate the underlying inflammatory mechanisms.

Inflammation emerges as a central theme in the pathogenesis and progression of CHD, serving as a critical determinant of disease advancement and prognosis. Within this complex pathophysiological framework, a wide array of inflammatory cytokines and markers are involved, each playing an indispensable role and notably impacting the developmental trajectory of CHD. Notably, C-reactive protein (CRP), IL-6 and TNF-α have been widely recognized as significant risk factors for CHD (115).

High-sensitivity (hs)-CRP. hs-CRP is a vital biomarker for assessing systemic inflammation and predicting the risk of CHD (116). Together with the plasma atherogenic index (AIP), hs-CRP and AIP act as independent risk factors for PCAD. The simultaneous evaluation of these biomarkers improves the precision of predicting PCAD occurrence and the severity of arterial lesions. Furthermore, their levels demonstrate a significant positive correlation with the severity of coronary artery lesions (117). In patients with chronic coronary syndrome, persistent low-grade inflammation remarkably influences disease prognosis, with hs-CRP serving as an effective marker for assessing this impact (118). Furthermore, elevated hs-CRP levels are strongly associated with an increased risk of abdominal aortic aneurysm, particularly among smokers and the elderly (119), underscoring the importance of hs-CRP in CVD risk assessment.

Arginine intake exhibits a negative correlation with elevated CRP levels (>3.0 mg/l). However, L-arginine supplementation does not exert a notable impact on CRP levels (120). Conversely, glutamine supplementation has been shown to reduce hs-CRP levels (121). In addition, increased intake of BCAAs is associated with a decrease in inflammation, as indicated by reduced hs-CRP levels (122). Within the context of metabolic syndrome, a correlation exists between the kynurenine/tryptophan ratio and hs-CRP levels (123). Further comprehensive research is warranted to elucidate the specific regulatory mechanisms involved.

CRP primarily exerts its effects through binding to Fcγ receptors on immune cells, initiating downstream signaling pathways, particularly the NF-κB pathway (124). This activation results in the production of pro-inflammatory cytokines and enhanced immune cell activation. In the context of CHD, these processes contribute to the recruitment of inflammatory cells to the arterial wall, accelerate the progression of atherosclerotic plaques, and increase the risk of plaque rupture and subsequent cardiovascular events (125).

The interleukin family. IL-6, a pivotal pro-inflammatory cytokine, exhibits a positive correlation with an elevated risk of cardiovascular mortality and the incidence of major adverse cardiovascular events (66). In a study conducted on patients with CAD, researchers found that IL-6 concentrations in blood samples obtained from the left anterior descending artery distal to the stenosis were higher compared to those from the healthy left internal thoracic artery ($P<0.01$) (126). Mechanistic studies have demonstrated that IL-6 activates the JAK1/STAT3 signaling pathway, leading to the upregulation of divalent metal transporter 1 expression. This upregulation results in a substantial accumulation of intracellular Fe^{2+}, causing tissue damage (127). Furthermore, IL-6-induced phosphorylation of STAT3 at Tyr705 promotes the degradation of mitofusin 2 through an unconventional mitochondrial localization mechanism. This signaling cascade accelerates the senescence of vascular smooth muscle cells and the onset of mitochondrial dysfunction, thereby remarkably advancing the progression of CHD (128). IL-1β promotes the transcytosis of LDL via a specific pathway reliant on the LDL receptor and Rab27a, contributing to the early stages of atherosclerosis formation (129).

In patients with ST-segment elevation myocardial infarction, IL-22 levels are markedly lower compared to those in healthy control subjects (130). Importantly, resveratrol has been shown to modulate bone marrow-derived dendritic cells, subsequently affecting the secretion levels of IL-22 and IL-10, thereby influencing the progression of atherosclerosis (131).

IL-33 enhances cardio-endothelial angiogenesis post-myocardial infarction by activating the AKT/eNOS/NO signaling pathway. This mechanism is significant for cardiac repair and functional recovery, playing a pivotal role during the myocardial injury repair phase in CHD (132).

In conclusion, the interleukin family members demonstrate diverse and interrelated roles in the pathogenesis of CHD. Specifically, IL-6-induced inflammation may facilitate an environment conducive to IL-1β-mediated initiation of atherosclerotic plaque formation. Simultaneously, the regulatory functions of IL-22 and IL-33, characterized by anti-inflammatory and cardio-reparative effects, respectively, may counteract the pro-inflammatory actions of IL-6 and IL-1β at various stages of the disease. A detailed investigation of these complex interactions is crucial for achieving a more comprehensive understanding of the inflammatory mechanisms underlying CHD.

Table I. Comparison of the effects of different amino acids on inflammation, immune cells and outcomes of CHD.

Amino acids	Impact on inflammation	Effect on immune cells	Impact on the outcomes of CHD
Arginine	Reduces NO production during metabolic disorders and promotes inflammation; iNOS is upregulated under inflammatory stimulation.	Influences the activation of T cells; when there is a deficiency of arginine, T cells are over-activated and the amount of pro-inflammatory factors increases.	Supplementation with L-arginine can reduce plaques and vascular inflammation; arginine methylation regulates vascular calcification; high arginine levels are associated with CHD.
Glutamate	Metabolic disorders trigger oxidative stress and inflammatory responses, activating the NF-κB pathway.	Glutathione maintains the function of Th17 cells; glutamine promotes the function of CD8+ T cells; metabolic disorders interfere with the function of immune cells.	The level of glutamate is associated with cardiovascular diseases; gluta mine has a cardioprotective effect and the ratio of glutamine to glutamic acid can be used to evaluate CHD.
BCAAs	An increase in the level activates the inflammation-related pathways, promotes the polarization of macrophages towards the M1 phenotype and releases pro-inflammatory factors.	Leucine inhibits macrophage. autophagy; BCAAs promote the polarization of macrophages towards the M1 phenotype; glutamine inhibits the activation of M1 macrophages	It is positively correlated with CIMT and affects the incidence risk of CHD; high intake is related to the progression of coronary artery calcification and different food sources have different effects; BCAA metabolic defects affect cardiac function.
Tryptophan	The level of tryptophan is negatively correlated with the risk of CHD, while some of its metabolites, such as kynurenine, are positively correlated. Some metabolites activate the AhR and exacerbate inflammation.	Tryptophan metabolites regulate the polarization of B cells and the secretion of IL-10; tryptophan metabolism in macrophages affects inflammation.	Circulating tryptophan levels are associated with CHD events; 5-MTP and IAA have anti-inflammatory properties and can be used to evaluate the prognosis.

CHD, coronary heart disease; iNOS, inducible NO synthase; NO, nitric oxide; NF-κB, nuclear factor-κB; Th17, T-helper 17 cells; CD8+ T cells, cytotoxic T lymphocytes; CIMT, carotid intima-media thickness; AhR, aryl hydrocarbon receptor; 5-MTP, 5-methoxytryptophan; IAA, indole-3-acetic acid; BCAAs, branched-chain amino acids.

IFN-γ. IFN-γ is crucial for exacerbating inflammation and advancing the progression of atherosclerotic plaques following anti-programmed death-1 therapy (133). Concurrently, M1 macrophages possess the ability to activate NK T cells to secrete IFN-γ, thus accelerating the development of early-stage atherosclerosis (134). Spatial transcriptomics analyses have revealed that within the intimal and medial regions of atherosclerotic plaques, there is a marked increase in the expression of IFN-γ and major histocompatibility complex (MHC) class II molecules, accompanied by the presence of pro-inflammatory and pro-thrombotic signaling pathways (135).

The increased expression of IFN-γ and MHC class II molecules, along with the activation of pro-inflammatory and pro-thrombotic signaling pathways, is intricately associated with the vulnerability of atherosclerotic plaques. This escalation in inflammation and alteration of immune-related molecular expressions can undermine the structural integrity of the plaque's fibrous cap, making it more prone to rupture. When rupture occurs, the plaque exposes underlying pro-thrombotic substances, leading to platelet aggregation and thrombus formation, which are key processes in the pathogenesis of acute coronary syndromes, such as myocardial infarction and unstable angina.

Monocyte chemoattractant protein-1 (MCP-1). An elevation in MCP-1 levels has been shown to be positively correlated with an increased risk of PCAD (136). MCP-1 facilitates the chemotactic migration of monocytes beneath the vascular intima, thereby promoting the aggregation and activation of inflammatory cells, which in turn accelerates the formation and progression of atherosclerotic plaques.

Furthermore, MCP-1 engages in complex interactions with other inflammatory mediators within the context of CHD. For instance, increased levels of IL-6 can upregulate MCP-1 expression in endothelial cells and macrophages, establishing a positive feedback loop that amplifies the inflammatory

response (137). Similarly, CRP may affect the production and function of MCP-1, highlighting the intricate network of inflammatory mediators involved in the pathogenesis of CHD (138).

Inflammatory markers and cytokines, through a complex network of signaling pathways and mechanisms, are profoundly involved throughout the continuum of CHD.

5. Clinical research and technological applications

In the preceding sections, the intricate interconnections between amino acid metabolism, inflammation and the immune system within the context of CHD were examined. It is now imperative to investigate how these insights can be applied to clinical research and technological innovations. This field of study seeks to devise effective strategies for the diagnosis, treatment and prevention of CHD, grounded in our comprehension of amino acid-related mechanisms.

Insights from animal experimentation. Animal studies are fundamental in elucidating the pathological connections between amino acid metabolism and CHD. For instance, supplementation with L-arginine has been demonstrated to reduce plaque formation and vascular inflammation in Sirt3 endothelial cell knockout mice (36). In cholesterol-fed rabbits, supplementation with L-aspartate and L-glutamate has been shown to inhibit the thickening of the aortic intima and the development of liver injury (139). Mice with defects in BCAA metabolism exhibit cardiac dysfunction and remodeling post-myocardial infarction, which is closely associated with inflammation (140). Restricting isoleucine intake in young mice has been found to improve metabolic health, resulting in weight loss, improved blood glucose control and an extension of lifespan (141). The specific knockout of IDO in intestinal epithelial cells leads to the formation of larger atherosclerotic plaques in mice fed a high-fat and high-cholesterol diet (142). Additionally, indole-3-acrylic acid, through activation of the AhR, inhibits the TGF-β/Smad pathway, thereby improving endothelial-mesenchymal transition in atherosclerotic mice (143).

Findings of human studies. In the domain of human studies, research has revealed complex relationships between various amino acids and cardiovascular-related conditions. Arginine methylation has been shown to regulate vascular calcification through multiple signaling pathways, including NF-κB, WNT, AKT/PI3K, TGF-β/bone morphogenetic protein/SMAD and IL-6/STAT3 (144). Lower levels of homoarginine have been identified as an independent predictor of a high atherosclerotic burden in patients with ST-elevation myocardial infarction (145). A reduction in glutamate levels is correlated with an increase in macrophages and a pro-inflammatory phenotype in unstable plaques (146). The deletion of glutaminase 2 raises the glutamine/glutamate ratio, accelerating atherosclerotic lesion progression (147). The research conducted by Ruiz-Canela *et al* (148) has proved a significant correlation between plasma levels of BCAAs and the risk of CVDs, but the limitations of observational studies, such as confounding factors related to diet and physical activity, affect the robustness of this relationship. Laferrère *et al* (149) reported decreased BCAA, CRP and IL-6 levels after gastric bypass surgery, yet the small sample size and the physiological changes induced by surgery limit the generalizability of these findings. In adolescent patients with type 2 diabetes, the lipoprotein insulin resistance index and elevated levels of BCAAs are associated with suboptimal blood glucose regulation and early onset of atherosclerosis (150). In addition, a high intake of BCAAs is independently correlated with the progression of coronary artery calcification (72), while reduced circulating levels of tryptophan are linked to an increased risk of CVD (85). Collectively, these varied findings concerning different amino acids underscore the complex relationship between amino acid metabolism and atherosclerosis. This suggests that targeting amino acid metabolism could serve as a potential therapeutic approach to reduce inflammation in patients with CHD.

Metabolomics applications. Metabolomics, an advanced and rapidly developing technical field, provides highly effective methodologies for in-depth analysis of the complex interaction mechanisms between amino acid metabolism and CHD. Numerous studies have employed metabolomics techniques, yielding a range of valuable findings in this area.

Regarding the relationship between amino acid metabolism and CHD, several studies have evidenced the crucial roles of specific amino acids. Research shows that Huang-lian-Jie-du decoction can reduce oxidative stress by upregulating arginine biosynthesis, suggesting a novel CHD prevention and treatment target (151). Additionally, metabolomics-based analyses reveal a positive correlation between aortic stiffness and the levels of glutamate and cystine (40). At the plaque level, the concentration of glutamate within the plaque significantly influences its vulnerability. Metabolic pathway analysis demonstrates that D-glutamine and D-glutamate metabolism, as well as tryptophan metabolism, are involved in the regulation of plaque vulnerability (152).

In the realm of technical methodologies, the non-targeted metabolomics approach utilizing LC-MS offers robust analytical capabilities, enabling a comprehensive and systematic examination of metabolite profiles within biological samples. Employing this technique, researchers have discovered a negative correlation between arteriosclerosis markers and metabolites associated with BCAAs, as well as indicators of energy metabolism and oxidative stress (153). This finding provides novel insights into the pathogenesis of atherosclerosis. Furthermore, the distinctive features of the amino acid metabolome hold promise as potential biomarkers for accurately differentiating between myocardial infarction-induced mortality and asphyxia-induced mortality in murine models (154). This advancement paves the way for the early and precise diagnosis of CHD-related conditions and facilitates the scientific evaluation of the disease.

The integration of nuclear magnetic resonance spectroscopy with metabolomics has enhanced the precision of CAD diagnosis. This synergistic approach facilitates dynamic and real-time disease monitoring while furnishing clinicians with more comprehensive and reliable data, thereby enabling the optimization of treatment strategies (155). Consequently, it offers promising prospects for the personalized treatment of patients with CHD.

Machine learning contributions. Machine learning techniques, renowned for their robust data analysis capabilities, have brought new breakthroughs to the diagnosis of CHD. For instance, a machine learning model developed by combining immunoglobulin light chains with clinical data has demonstrated high accuracy and sensitivity in CHD diagnosis (156), potentially enhancing the early diagnosis rate of the condition. Due to its non-invasive nature and rapid analytical capabilities, this model holds substantial promise for application in large-scale screening endeavors. Furthermore, machine learning has been applied to analyze key metabolites associated with atherosclerotic CVD (157) and to investigate diagnostic and immune markers (158,159). Although a direct connection with amino acid metabolism has not yet been established, these metabolites and markers may contain amino acid-related information, offering potential insights for further in-depth research on the role of amino acids in CHD.

Microfluidic technology advancements. Microfluidic technology offers a unique experimental platform for the research of CHD, particularly in exploring the macrophage-mediated cardiac immune mechanisms. The advancement of microfluidic co-culture models allows for an in-depth exploration of macrophage functions within the cardiac immune process, thereby providing novel insights for the development of therapeutic strategies for CHD (160).

In addition, microfluidic technology facilitates the study of arterial thrombosis formation by constructing artificial blood vessels and accurately simulating hemodynamics (161). The 3-dimensional microfluidic atherosclerotic model demonstrates stability under perfusion conditions and enables real-time observation of immune cell behavior, thus serving as a valuable tool for atherosclerosis research (162). Additionally, the microfluidic model allows for systematic and reproducible investigation of the effects of arrhythmic blood flow on the mechanobiology of vascular endothelium (163). In spite of these microfluidic models being available for research, challenges such as scalability must be thoroughly addressed to achieve wider applications.

In summary, research on amino acid metabolism and its role in CHD has enhanced the diagnosis, treatment and prevention of this condition. It is imperative to further explore the intricate mechanisms of amino acid metabolism and its specific pathways in the pathogenesis of CHD. The development of innovative diagnostic and therapeutic strategies, utilizing metabolomics and artificial intelligence, should be actively pursued to broaden the scope for the prevention and management of CVDs.

6. Clinical applications and future directions

Building on the knowledge from clinical research and technological advancements, this chapter focuses on the practical clinical applications of modulating amino acid metabolism in CHD and the future directions of this research field. These aspects are crucial for translating scientific findings into effective patient care and for advancing the understanding of CHD.

In the context of CVD risk reduction, the regulation of amino acid metabolism has gained prominence as an important research focus, primarily involving two main strategies: Dietary intervention and pharmacotherapy. The primary aim of these interventions is to enhance cardiovascular health by precisely modulating amino acid metabolism.

Dietary intervention. Dietary intervention constitutes a fundamental strategy for regulating amino acid metabolism, with adjustments in protein intake and composition exerting substantial effects. For instance, the accumulation of glycated human serum albumin around cardiac cells can lead to the dysregulation of Nrf-2, exacerbating oxidative stress. L-arginine, at a low concentration of 20 mM, has been shown to upregulate Nrf-2 expression, promote its nuclear translocation and enhance the antioxidant capacity of cardiomyocytes (164). In an experimental rat model of isoproterenol-induced myocardial infarction, supplementation with L-arginine at a dosage of 50 mg/kg/day significantly mitigated the pathophysiological risks associated with myocardial infarction (165). In a C57BL/6J mouse model, glutamine supplementation at 1 g/kg has been found to alleviate atherosclerosis by downregulating O-GlcNAcylation, glycolysis, oxidative stress and pro-inflammatory pathways (166). Furthermore, leucine, glutamate and glutamine remarkably influence the atherogenicity of macrophages through modulating cellular triglyceride metabolism (167). In the context of BCAA-enriched diets, each 100 g of diet supplemented with BCAAs contains additional quantities of 0.56 g of L-leucine, 0.40 g of L-isoleucine and 0.40 g of valine. This dietary intervention has been demonstrated to be advantageous in $ApoE^{-/-}$ mice, as it leads to reductions in serum cholesterol and low-density lipoprotein cholesterol levels, decreases macrophage infiltration and suppresses the systemic inflammatory response. Specifically, it lowers serum levels of inflammatory markers such as MCP-1, TNF-α, IL-1β and IL-6, thus alleviating atherosclerosis (75). Furthermore, in young individuals with subclinical atherosclerosis, a high intake of BCAAs (≥18.5 mg/day) is of considerable importance for primary prevention dietary adjustments (72).

In addition, dietary composition impacts tryptophan metabolism. Research has shown that a high-fat diet substantially enhances the activity of IDO1 in the intestine. This increase leads to an elevated conversion of tryptophan into kynurenine, a notable reduction in the production of indole-type metabolites, and an exacerbation of atherosclerosis (142). Another study discovered that intraperitoneal administration of kynurenine (100 mg/kg) regulated the interaction between cullin 4B and the AhR. This interaction forms an E3 ubiquitin ligase complex that binds to RUNX family transcription factor 2, promoting its ubiquitination and subsequent proteasomal degradation, thereby reducing arterial calcification (168). Separately, the tryptophan metabolite indole-3-propionic acid, derived from the intestinal microbiota, influences the miR-142-5p/ATP-binding cassette transporter A1/reverse cholesterol transport axis in macrophages, affecting the progression of atherosclerotic plaques in $ApoE^{-/-}$ mice (169). Collectively, these findings highlight the complex role of tryptophan metabolism in atherosclerosis and propose that targeting this metabolic pathway offers a novel strategy for atherosclerosis intervention.

The close association between hepatic fat accumulation and the increased susceptibility to CHD is a particular

concern (170). Metabolic-dysfunction-associated fatty liver disease (MAFLD) has been identified as an independent risk factor for adverse cardiovascular outcomes in patients with CHD, even when LDL-C <1.8 mmol/l (171). Research indicates that moderate to high protein intake is correlated with a 1.45-fold increase in the risk of developing MAFLD (172), which subsequently heightens the risk of CHD and myocardial infarction (173).

Therefore, dietary interventions aimed at prevention and treatment of CVD should emphasize a balanced intake of specific amino acids. For instance, adequate consumption of L-arginine-rich foods may provide cardioprotective effects. Regulating fat intake to affect tryptophan metabolism and monitoring protein consumption to reduce MAFLD-related cardiovascular risks are essential strategies. These dietary modifications should be based on a comprehensive understanding of nutritional biochemistry and its implications for cardiovascular health.

Drug therapy. Pharmacological interventions represent a potent strategy for modulating amino acid metabolism, providing sophisticated approaches for the treatment of CVDs. Nanoliposomes encapsulating L-arginine and cerium-zirconium oxide nanoparticles have demonstrated the ability to scavenge ROS, inhibit cholesterol absorption and promote the phenotypic transformation of macrophages. These actions confer antioxidant and anti-inflammatory effects that mitigate the progression of atherosclerosis (174). Significant progress has been achieved in the research domain of NO donors. In hypoxic microenvironments, the enzyme nitroreductase is highly expressed and facilitates the reduction of the nitro group in N6. This reduction initiates intramolecular electron transfer, thereby enhancing the electronegativity of the relatively stable NO donor moiety within the molecule. Consequently, N6 exhibits an increased affinity for binding to the positively charged active site of the catalyst cytochrome P450, which ultimately results in the release of NO. Its effectiveness in preventing and treating myocardial hypoxic injury exceeds that of the conventional drug isosorbide mononitrate (175). Furthermore, the curcumin-encapsulated NO peptide-conjugated hydrogel offers an innovative approach to cardiovascular protection. This hydrogel is designed to release NO in response to β-galactosidase stimulation while simultaneously facilitating the gradual release of curcumin through hydrogel hydrolysis. Such a distinctive characteristic equips it with the capacity to effectively protect vascular endothelial cells from oxidative stress-induced damage (176). Recent advancements in research have established a reliable theoretical framework for the development of novel NO donor drugs, offering renewed hope for the treatment of CVDs. Although the investigation of BCAAs and tryptophan in the context of CVDs has gradually attracted attention, there remains a paucity of pharmaceutical studies focused on the treatment of CHD using these two amino acids. Future research should aim to further elucidate their mechanisms of action and develop relevant therapeutic drugs.

It is important to acknowledge that not all pharmacological agents confer benefits to the cardiovascular system. For instance, the antibacterial compound triclocarban (TCC) has been shown to exert adverse effects. TCC disrupts amino acid metabolism in cardiac organoids and induces oxidative stress responses in human umbilical vein endothelial cells. Specifically, it upregulates the expression of iNOS, resulting in increased protein nitrosylation, which impairs endothelial cell function and heightens the risk of CVDs (177). These findings support the importance of vigilance in clinical medication safety and the management of environmental chemical exposures. They emphasize the necessity for increased awareness and monitoring of potential cardiovascular risks associated with substances like TCC in both clinical and environmental settings.

In contrast, colchicine demonstrates a beneficial effect on cardiovascular protection by mitigating the release of inflammatory mediators, including IL-1 receptor antagonist, IL-18, IL-6 and hs-CRP, through the inhibition of NLRP3 inflammasome activation. Additionally, colchicine reduces the release of myeloperoxidase and elastase during neutrophil activation (178). These combined effects substantially diminish vascular inflammation, enhance the stability of coronary plaques in patients with acute coronary syndrome (ACS), effectively lower the risk of cardiovascular events and offer a valuable therapeutic option for the management of patients with ACS.

7. Conclusion and prospects

Current consensus. Amino acid metabolism is closely associated with inflammation in CHD. Metabolic disorders of amino acids such as arginine, glutamate, BCAAs and tryptophan can affect immune cell function, inflammatory mediators and vascular endothelial function through mechanisms of immunometabolic reprogramming and oxidative stress, thus contributing to the pathogenesis of CHD. Inflammatory biomarkers, such as hs-CRP and interleukins, serve as indicators for assessing disease risk. Advances in clinical research and technological applications have introduced novel perspectives to related studies, while dietary interventions and pharmacological treatments exhibit promising potential.

Remaining challenges. Current research predominantly addresses common amino acids and traditional pathways, resulting in a limited understanding of the roles of rare amino acids and the interplay between amino acid metabolism and non-coding RNAs. Furthermore, dietary and pharmacological interventions lack validation through large-scale clinical trials and the translation of research findings into precision medicine continues to encounter significant challenges. For instance, factors such as interference with dietary patterns (104) and metabolic variability among individuals (179) contribute to these ongoing difficulties.

Future directions. Advanced technologies offer the capability to accurately evaluate amino acid metabolic status, while machine learning can be employed to extract valuable information. It is imperative to enhance clinical trials to validate the efficacy of interventions and to formulate personalized treatment plans. In addition, a comprehensive examination of the interactions between amino acid metabolism and other variables may unveil novel strategies for the prevention and management of CHD, thereby facilitating the transition towards precision medicine.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

YZ designed the study and analyzed the literature. RS drafted the manuscript. All authors contributed toward data analysis, drafting and revision of the manuscript, and have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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