Clinical Nutrition ESPEN 73 (2026) 103134

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Narrative Review

The amino acid arginine: A comprehensive review

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ARTICLE INFO

Article history:
Received 4 January 2026
Accepted 15 March 2026

Keywords:
Arginine
Biomarker
Efficacy
Chronic disorders
Supplements

SUMMARY

Amino acids are the building blocks for producing proteins. They are essential to the efficient operation of body functions and the structure of cells. They supply the energy needed for normal cell division and growth. An amino acid that is classified as semi-essential or conditionally essential is arginine. Arginine is essential for maintaining the immune system and for treating several disorders. Numerous studies have demonstrated the effectiveness of using dietary supplements containing arginine and other amino acids in improving a range of medical conditions. This review will cover the classification, production, and molecular mechanisms of arginine, as well as its role as a biomarker in various diseases and its therapeutic efficacy in treating these conditions. It will also investigate the safety of arginine supplementation, as well as healthy and inadequate arginine levels. This review provides an overview of the critical importance of arginine as both a predictive and prognostic biomarker for the specified diseases and highlights its biological functions and therapeutic potential across a range of pathological conditions. To fully understand the overall function of this amino acid in the diagnosis, aetiology, enhancement, and treatment of many illnesses, more thorough research, including clinical studies, is required.

1. Introduction

Amino acids are the building blocks for the production of proteins. They are fundamental to the structure of cells and the proper function of bodily processes. They provide the energy required for healthy cell growth and division. In humans, amino acids are classified as essential or non-essential. Essential amino acids have more complex structures than non-essential amino acids. An essential amino acid is a type of amino acid that the body needs but cannot produce on its own. These amino acids must be obtained through a proper diet. On the other hand, non-essential amino acids can be produced from simple precursors and do not require food sources. There are twenty proteogenic amino acids, and nine of them are classified as essential for human health [1,2].

For adults with good health, arginine is not a necessary dietary amino acid due to the extent of endogenous production. Nevertheless, arginine is categorized as a semi-essential or conditionally essential amino acid since endogenous arginine synthesis is unable to completely satisfy the requirements of newborns, developing children, individuals under catabolic stress, or those with small intestine or renal failure [3]. Arginine plays a significant role in maintaining the immune system and enhancing various medical conditions, including atherosclerosis, cardiovascular disorders, vascular headaches, peripheral vascular diseases, erectile dysfunction, chest pain, and several other conditions [4].

Several studies have proven the efficacy of taking nutritional supplements containing different amino acids, including arginine, in improving various health conditions, such as the enhancement of liver function and the reduction of the level of triglyceride (TG) and very low-density lipoprotein in polycystic ovary syndrome (PCOS) patients [5,6]. In addition to studying their role in improving gut integrity and enhancing irritable bowel syndrome (IBS) related symptoms [7]. Other studies reported that amino acid supplements such as L-citrulline positively affect endothelial function and aortic blood pressure by increasing L-arginine availability, which indicates the vital role of arginine [8]. This review will focus on the classification, biosynthesis, and molecular mechanisms of arginine, its role as a biomarker in various conditions, and the therapeutic effectiveness of arginine across different health conditions. Additionally, it will examine healthy and

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https://doi.org/10.1016/j.clnesp.2026.103134

deficient levels of arginine as well as the safety of arginine supplements.

2. Classification and biosynthesis

In adult humans, endogenous biosynthesis of arginine occurs primarily through the complex interplay between the intestines and kidneys, known as the intestinal–renal axis [9,10]. The amino acid citrulline is synthesized by the enterocytes of the small intestinal epithelium through the conversion of glutamine and glutamate. Subsequently, citrulline is transported through the circulatory system to the renal proximal tubular cells, where it undergoes the urea cycle to produce arginine through the enzymatic action of arginine-succinate synthetase and arginine-succinate lyase [1,10]. Intestinal citrulline production is regulated by three key enzymes: proline oxidase, N-acetyl-glutamate synthase, and pyrroline-5-carboxylate synthase. These enzymes are exclusively synthesized by mammalian enterocytes, making them pivotal in maintaining citrulline and arginine homeostasis throughout the body. Arginine is transported across cell membranes in various cell-specific manners. Upon entering the cells, it undergoes degradation through various pathways to produce a range of downstream metabolites such as nitric oxide (NO), urea, proline, polyamines, glutamate, agmatine, and/or ornithine. Among these pathways, the arginase pathway is considered the most significant contributor to arginine metabolism in mammals [9]. In humans and other mammals, two types of arginase enzymes are expressed and are responsible for converting arginine into ornithine and urea. Arginase I is found in the cytosol and is abundantly expressed in the liver as a component of the urea cycle. On the other hand, arginase II is located in the mitochondria and is moderately expressed in the kidney [11]. Figure 1 shows the main metabolic pathways of arginine.

The primary function of L-arginine is believed to be as a precursor for the production of nitric oxide, which is a free radical molecule synthesized from arginine by nitric oxide synthase present in all mammalian cells [12]. NO plays a crucial role in regulating numerous cellular processes, including leukocyte adhesion, platelet aggregation, vascular tone, and adhesion molecule expression. Arginine, a dietary nutrient, exerts a wide range of pharmacological and physiological actions through both nitric oxide-dependent and -independent pathways. In the human body, arginine modulates immunological function, vascular tone, wound healing, endothelial function, secretion of hormones, insulin sensitivity and inhibits the formation of tumors and carcinogenesis. Furthermore, arginine has been shown to play a pivotal role in controlling the development of atherosclerotic cardiovascular disease [13].

Endogenous synthesis, dietary protein, and protein turnover are the body's sources of free arginine. The gut catabolizes around 40% of the arginine that is consumed before it can enter the bloodstream. According to the studies, arginine homeostasis is mostly maintained via controlling arginine catabolism, as evidenced by the finding that the rate of endogenous synthesis is virtually independent of arginine intake [3]. Studies show that L-arginine may be found in watermelon, nuts, seeds, seafood, meat, eggs, grain products, dairy products, and soy protein isolate [14–16]. According to a study, the typical Polish diet is characterized by a significant contribution of meat and meat products, which provide the largest amount of arginine at approximately

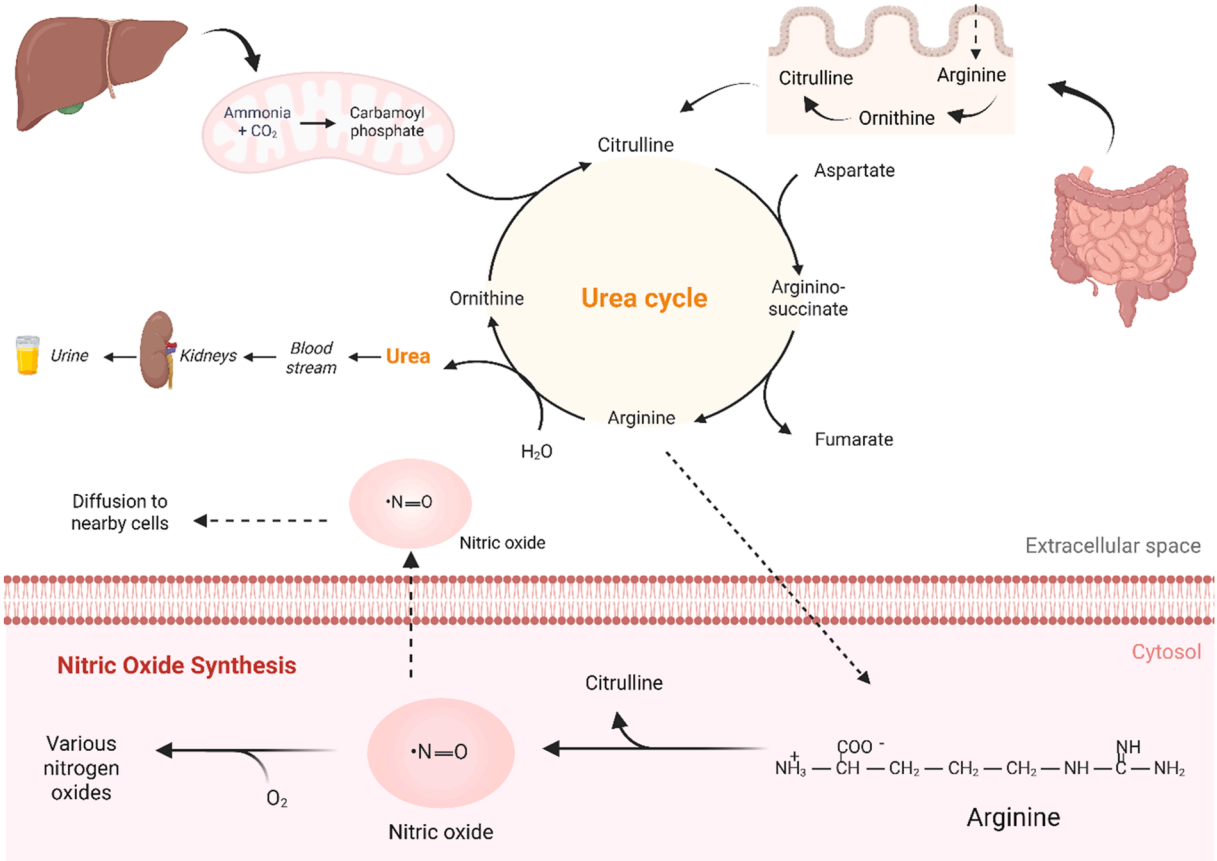

Figure 1. Arginine metabolic pathways. *Created in BioRender (2026)* https://BioRender.com/wmp2p2h.

46.1% [16]. L-citrulline, which is turned into arginine by the urea cycle enzymes, is also abundant in watermelon [15].

3. Normal levels, insufficiency, and deprivation of endogenous arginine

Studies have indicated that even though the levels of intracellular arginine are much higher than those extracellularly in the plasma or extracellular fluid, extracellular L-arginine can still be rapidly absorbed by endothelial cells and help produce NO. Differences in the levels of L-arginine in the plasma across different regions globally might be attributed to dietary differences between populations. The average range of plasma L-arginine levels has been found to be 81.6 ± 7.3 μmol/L in young males and 113.7 ± 19.8 μmol/L in elderly males. In young females, the average range is 72.4 ± 6.7 μmol/L, and in elderly females, it is 88.0 ± 7.8 μmol/L [17]. In general, it is reported that the normal human levels of arginine are 21–137 μM [18].

Most disease states are not significantly associated with decreased plasma arginine levels, except for end-stage kidney failure through hemodialysis therapy [17]. However, arginine deficiency can occur due to three conditions. Firstly, a diet that severely lacks arginine. Secondly, an increase in the breakdown of arginine through arginase enzymes, which can happen during infection and inflammation leading to arginine deficiency. Thirdly, a decrease in the rate of endogenous arginine synthesis. Studies have shown that arginine deficiency is connected to various disorders like phenylketonuria, sepsis without trauma or surgery, chronic hemolytic diseases such as sickle cell disease, and blood hemolysis. In general, there are two primary categories of arginine deficiency syndromes; these can either result in endothelial dysfunction or T-cell dysfunction, depending upon the disease context [11].

A study found that major depression patients have lower levels of arginine, contributing to cardiovascular disease risks due to a decrease in NO metabolites [19]. Another study showed that arginine from plant-based sources may protect against metabolic syndrome, while arginine from animal sources may act as a risk factor for metabolic syndrome [20]. Numerous studies have revealed that the levels of arginine tend to be low following trauma, severe injury, and in both children and adults with sickle cell disease. Additionally, it has been observed that arginine levels decrease significantly in acute disease-specific complications across all age groups, which is usually linked with low levels of NO metabolites [21]. According to a recent study, cancer patients who suffer from hypertension have been found to exhibit higher levels of arginine, and arginine levels are associated with an increased risk of developing colorectal cancer and overall digestive cancers [22]. However, a study found that malignant tumors linked to varying degrees of metabolic disruptions are all linked to lower plasma arginine levels [23].

4. Arginine at molecular levels

The researchers found that arginine, along with glutamine and leucine, is one of the amino acids that activates the mammalian target of the rapamycin (mTOR) signaling pathway, which is the major mechanism that regulates protein synthesis [1]. In a manner particular to each cell, these amino acids promote mTOR's phosphorylation, which in turn phosphorylates ribosomal protein S6 kinase-1 and eukaryotic translation initiation factor 4E-binding protein-1, resulting in the development of the translation initiation complex [24].

Thus far, three distinct mechanisms of regulating gene expression have been identified: (1) a translational control (2) a post-transcriptional component involving stabilization of mRNA under starved conditions has been demonstrated for the C/EBP Homologous Protein (CHOP) and asparagine synthetase (AS); and (3) a transcriptional control [25]. Reduced availability of arginine due to catabolic stress can change the expression of certain proteins involved in arginine metabolism. The effect of arginine on gene expression is related to a field called “Argenomics” which is the subset of the nutrient's impacts on gene expression. Robert Schimke demonstrated that the activities of argininosuccinate synthetase and argininosuccinate lyase in a number of mammalian cell lines are inhibited by arginine and increase when arginine is substituted with citrulline, which is regarded as the start of argenomics in the early 1960s. The reduction of arginine availability, which may result from a decreased arginase activity, affects several genes, such as decreasing the expression of the inducible nitric oxide synthase (iNOS) gene and the T-cell receptor zeta-chain and increasing the expression of cationic amino acid transporter-1 (CAT-1) gene [3].

Numerous studies conducted in vitro and in vivo have indicated that arginine plays a significant role in the proliferation of cancer cells, especially when its synthesis is hindered by the deficiency of argininosuccinate synthetase. A study carried out on patients with colorectal cancer revealed that the levels of arginine and citrulline in their serum are lower when compared to those of normal individuals. This could be attributed to the accumulation of arginine and citrulline in the cancerous tissue, which is associated with the overexpression of the CAT-1 gene in colorectal cancer tissues [26]. In cases of hepatocellular carcinoma, there is an increase in arginine intake and a decrease in the conversion of arginine to polyamines by enzymes arginase-1 and agmatinase, which leads to higher arginine levels. These elevated arginine levels promote tumorigenicity despite the suppressed synthesis of arginine. Arginine plays a crucial role in controlling metabolic gene expression by binding to RNA-binding motif protein-39 (RBM39), which in turn promotes the expression of asparagine synthetase, leading to the synthesis of asparagine. This process further enhances the uptake of arginine, resulting in sustained oncogene metabolism and high arginine levels [27].

5. Arginine as a biomarker

5.1. Cancer

Studies have recently been conducted to understand the effects of arginine on several diseases, especially cancer. Lower availability of arginine and decreased arginine serum levels are the common characteristic of various cancer types, including pancreatic cancer, melanoma, glioma, renal cell carcinoma, breast cancer, lymphoma, mesothelioma, and hepatocellular carcinoma. These conditions could potentially lead to impaired immunity and contribute to the development of tumors [28]. For example, a study was conducted to measure the levels of arginine in the blood of patients suffering from different types of cancers, such as breast, pancreatic, and colonic cancers, compared to age and sex-matched control subjects. The study revealed that arginine levels in cancer patients were significantly lower compared to the control group. From the study, it can be inferred that the availability of arginine is a specific characteristic in the presence and development of cancer [23]. Additionally, studies conducted on patients with breast cancer found that arginine could be used to predict breast cancer with an area under the curve (AUC) of 0.721 and 0.659, which suggests that arginine could be used as a biomarker for breast cancer. In addition, breast cancer patients had significantly lower levels of plasma arginine compared to the control group, suggesting that arginine could be associated with the molecular

subtypes of breast cancer [28,29]. Furthermore, researchers have revealed that individuals diagnosed with prostate cancer exhibit lower levels of arginine in their plasma and urine, suggesting that arginine plays a role in the development of this cancer and can be used as a biomarker for its detection. The decrease in arginine levels in these biofluids can be attributed to a rise in arginine degradation and a decline in its synthesis [30,31]. As stated earlier, an increased level of plasma arginine is linked to a higher risk of developing colorectal cancer [22]. These findings suggest that arginine bioavailability and serum levels may contribute to the pathogenesis of cancer types.

5.2. Cardiovascular disease (CVD)

Numerous studies have elucidated the pivotal role of arginine and its metabolic pathways in CVD and atherosclerosis. For example, homoarginine, which is synthesized by the mitochondrial enzymes from arginine and lysine, has emerged as a potential biomarker for CVD, where lower blood levels of homoarginine are associated with a higher risk of adverse cardiovascular events and mortality [32]. However, a study found that higher levels of homoarginine are not associated with any changes in the risk of cardiometabolic diseases, and more investigations are needed to support its use as a biomarker for cardiometabolic disorders [33]. In addition, numerous studies have shown that both asymmetric and symmetric dimethylarginine are independent risk factors for CVD and mortality [34]. A meta-analysis study suggests a potential use of asymmetric dimethylarginine to predict CVD risk in rheumatoid arthritis patients by assessing endothelial dysfunction [35]. Regarding atherosclerosis, arginine plays different roles in the body depending on whether it is processed by pro-resolving macrophages or pro-inflammatory macrophages. In pro-resolving macrophages, arginine is converted into ornithine, while in pro-inflammatory macrophages, it is used to produce NO. It is interesting to note that the enzymes arginase-1 and ornithine decarboxylase-1 are responsible for converting arginine into polyamines. This conversion is necessary for eliminating dead cells and for the production of the pro-resolving mediator interleukin-10 by macrophages after a stroke and atherosclerosis regression, respectively [32]. A cross-sectional investigation concluded that a low plasma arginine/asymmetric dimethylarginine ratio was an independent risk factor for the development of atherosclerosis [36]. In patients with coronary artery disease and high immune-inflammatory states, arginine metabolism was identified as a key metabolic characteristic [37]. A study has shown that asymmetric dimethylarginine can serve as a reliable biomarker for patients suffering from pulmonary arterial hypertension and who have congenital heart disease and indicates that the presence of plasma asymmetric dimethylarginine could be an indicator for the identification of severe pulmonary arterial hypertension with a sensitivity of 90% and a specificity of 82.8% [38].

5.3. Miscellaneous diseases

Several studies have highlighted the significance of arginine as a biomarker in various diseases. For instance, a study revealed that in cases of acute ischemic stroke, the levels of arginine, asymmetric, and symmetric dimethylarginine in the serum showed a significant increase within 6 h of the onset of a stroke as compared to healthy individuals. Moreover, in patients with significant carotid stenosis, the levels of symmetric dimethylarginine were significantly lower than those of healthy controls. The study observed that arginine levels slightly increased while asymmetric dimethylarginine levels slightly decreased within 24 h of the stroke, whereas symmetric dimethylarginine levels continued to rise. This indicates that the increase in arginine levels plays a critical role in the hyperacute phase of acute ischemic stroke. It further suggests that the availability of extracellular arginine may boost brain perfusion by raising NO, which induces vasodilation. The elevated levels of asymmetric dimethylarginine may lead to endothelial cell dysfunction and atherosclerosis. Overall, the study hypothesized that an increase in arginine may be explained as an adaptive mechanism [39].

Furthermore, a study has shown that patients with acute exacerbation of chronic obstructive pulmonary disease have higher serum levels of arginine, asymmetric, and symmetric dimethylarginine. The production of asymmetric and symmetric dimethylarginine is more pronounced, likely due to a more severe hypoxia insult. These findings suggest that asymmetric dimethylarginine and, in particular, symmetric dimethylarginine are biomarkers in these patients and factors of endothelial dysfunction [40]. Studies have shown that patients with obesity and diabetes are linked to arginine serum levels. For instance, a study found that morbid obesity is connected to changes in arginine metabolism, including reduced production of de novo arginine, particularly in females, and increased production of NO [41]. Another study discovered that arginine plasma levels were notably lower in women with obesity in comparison to non-obese women. Furthermore, it revealed a negative correlation between arginine levels and both inflammation and oxidative stress [42]. Additionally, a study noted changes in arginine metabolism in individuals with obesity-related insulin resistance and type 2 diabetes mellitus [43]. Patients with diabetes and macrovascular complications were found to have higher plasma levels of the ornithine/arginine ratio. This suggests a change in arginine metabolism due to increased arginase activity, possibly contributing to endothelial dysfunction [44]. Additionally, a comprehensive analysis of biomarkers revealed a strong link between arginine biosynthesis and diabetic retinopathy [45]. In women with gestational diabetes mellitus, it has been revealed that arginine concentrations were significantly lower compared to normoglycemic women, indicating that arginine could serve as a potential biomarker for this disease and its risk, as well as for type 2 diabetes mellitus [46].

Arginine amino acid has also been linked to metabolic syndrome, a disorder characterized by a set of factors such as hyperglycemia, abdominal obesity, hypertension, and dyslipidemia. For instance, a study proposed that there is a metabolic change in arginine biosynthesis in the prediabetic metabolic syndrome subjects compared to the control [47]. Another study suggested that alterations in the metabolic pathway of arginine may play a significant role in the diagnosis, prevention, and pathophysiology of metabolic syndrome [48].

6. Therapeutic efficacy of arginine

6.1. Hypertension

Hypertension is a chronic condition that affects a significant proportion of the global population. It is characterized by an elevated systolic pressure above 140 mmHg and a diastolic pressure above 90 mmHg [49]. One of the underlying causes of hypertension is endothelial dysfunction, which results from insufficient production of the vasodilator NO, leading to hypertension [49]. Sufficient production of NO derived from L-arginine by the action of endothelial nitric oxide synthase (eNOS) is crucial for maintaining normal blood pressure and preventing the development of hypertension [50].

Numerous randomized, double-blind, and placebo-controlled trials have confirmed the effectiveness of L-arginine as a dietary supplement in controlling blood pressure in hypertensive patients.

For example, one of the studies indicated that adding 3 g/day of arginine for two weeks to the standard hypertension therapy of hypertensive adults resulted in a significant reduction in mean arterial pressure compared to those who only took the standard therapy [51]. Likewise, another clinical trial observed that taking one dose as a sachet containing 8 g of arginine significantly reduces the post-exercise systolic hypotension in hypertensive patients [52]. A study conducted on adults with elevated BP during outside walks under traffic-related air pollution showed a clear reduction in systolic BP and diastolic BP and mean arterial pressure by (5.3,4.3 and 4.6 mmHg), respectively, compared with the control group after administering 9 g/day L-arginine for 2 weeks [53]. Other studies reported that 5 g/day L-arginine supplementation for 12 weeks in metabolic syndrome patients resulted in a significant decrease in the systolic BP, diastolic BP, and mean arterial pressure, but had no significant effect on the pulse pressure [54]. Further research is required to determine the effective dose and the duration of administration accurately.

6.2. Type 2 diabetes mellitus and glycemic levels

Type 2 diabetes mellitus (T2DM) is regarded as a multifactorial disease, progressing through both genetic and environmental factors, which is categorized by chronic hyperglycemia and insulin resistance. Several studies suggest that L-Arg may help treat diabetes. L-Arg can induce insulin secretion and glucagon [55]. In addition, research on rats has shown that L-Arg can reduce plasma glucose levels and improve glucose tolerance [56].

A recent systematic review analyzed 10 randomized clinical trials that investigated the impact of arginine supplements on serum glucose, insulin, HOMA-IR, and HbA1c levels [57]. The findings suggest that a dose of L-arginine greater than 6.5 g/day for a minimum of 12.8 weeks for non-diabetic individuals and when the baseline insulin level is higher than 20 μIU/mL could decrease serum insulin levels [57]. However, no significant effect was observed on HOMA-IR and HbA1c [57]. Another meta-analysis of 12 randomized clinical trials conducted in T2DM patients showed the same results regarding HOMA-IR and HbA1c but found no significant effect on serum fasting blood glucose (FBG) or serum insulin [58]. The studies on using arginine supplements in treating T2DM are limited, and further clinical trials on large samples are needed to confirm the results.

Studies on patients with metabolic syndrome have shown conflicting results regarding the effects of arginine supplementation on glycemic status. One randomized, double-blind, placebo-controlled trial found that taking 5 g/day of L-arginine for 12 weeks significantly reduced FBG compared to the control group but did not have a significant impact on HOMA-IR, insulin sensitivity, and β-cell function [59]. In contrast, A mono-center, randomized, double-blind, parallel-group, placebo-controlled, phase III trial on metabolic syndrome patients who took 6.4 g/day of arginine for 18 months showed a significant improvement in insulin sensitivity and β-cell function [60]. The differing outcomes may be due to variations in dosage and duration of the intervention. Further studies are necessary to establish the effective dosing regimen.

6.3. Dyslipidemia

Hyperlipidemia is elevated serum lipid levels, including cholesterol, triglycerides (TG), and LDL. The danger of a high lipid profile lies in the fact that it is considered a direct cause of cardiovascular diseases, which are considered a top cause of morbidity and mortality in the United States [61].

The impact of Arginine supplements on human lipid profile has been well-studied by conducting numerous RCTs in different communities. Two meta-analysis studies included healthy and diseased adults analyzed 17 and 12 RCTs with an intervention period not less than 2 and 4 weeks, respectively and found that arginine supplements could reduce blood TG serum levels without a significant decline in cholesterol, low density lipoprotein (LDL), and high-density lipoprotein (HDL) levels [62,63]. While in healthy people who are at risk of CVD, recent RCTs showed a significant reduction in TG, cholesterol, LDL, and HDL levels after 2 g/day of arginine administration for 45 days [64]. However, there is a lack of clinical trials that specifically target patients with dyslipidemia. Furthermore, larger sample sizes are needed in different geographical areas to generalize the findings.

There is limited research on the impact of arginine supplements on the lipid profile of people with metabolic syndrome. However, a clinical study found that taking 5 g/day of L-arginine for 12 weeks notably decreased TG levels and the cholesterol/HDL ratio [59].

6.4. Injuries

Bed sores or pressure injuries (PIs) can occur when you stay in bed for a long time, sit in a wheelchair for a long time, or wear a cast for an extended period. These wounds can be severe and expensive to treat, affecting the quality of patients' lives. Nutritional supplements such as vitamins A and C, and zinc have been studied in wound healing in individuals with PIs [65]. Arginine has also been studied clinically to prove its effect on PIs and to find the appropriate dose regimen.

A systematic review of eight clinical studies on adults with PIs showed that administering arginine supplements either orally or enterally tube-fed for at least two weeks resulted in significant reductions in Pressure Ulcer Scale for Healing (PUSH) and Pressure Sore Status Tool (PSST) scores [66]. The review also revealed that higher doses of arginine supplements (>15 g/day) had a greater impact on reducing PIs development and promoting healing [66]. Arginine was studied in combination with other amino acids and micronutrients in RCTs. For example, 4.5 g of arginine and 10 g of glutamine per day were given to patients with enterocutaneous fistula for seven days before surgery [67]. The study found that the experimental group had a lower recurrence rate of fistula (10%) compared to the control group (45%) [67]. Additionally, infectious complications were noted in the control group but not in the experimental group with lower preoperative serum concentrations of interleukin 6 and C-reactive protein [67]. Another A controlled clinical trial investigated the impact of a supplement enriched with arginine, zinc, and vitamins A, C, and E on healing venous ulcers [68]. The supplement was administered orally thrice a day in a dosage of 200 mL for eight weeks [68]. The results showed that the intervention group experienced a significant decrease in the injury area and PUSH score [68]. However, further research is necessary to better understand the impact of arginine as a standalone intervention for wound healing.

6.5. Cancer

Cancer is the second leading death globally; 19.3 million new cases of cancer and 10 million deaths worldwide were documented in 2020 [69]. Female breast cancer, lung and prostate cancers were the most commonly diagnosed cancers. Lung, liver, and stomach cancers were the leading causes of cancer death [69]. Studies have suggested that lifestyle factors play an essential role in the etiology of cancers such as colorectal cancer (CRC) [70]. Unhealthy diets are considered a crucial risk factor for cancer. Hence, scientists have recently focused on developing strategies to treat cancer by introducing specific dietary components. Depletion

of these amino acids, including asparagine, glutamine, arginine, serine, and methionine, could be targeted therapies for auxotrophic cancers [71].

Arginine is a semi-essential amino acid present in all cells. It helps increase the concentration of NO, which is involved in various biological pathways like neurotransmission and macrophage-mediated immunity [72]. Recent studies show that arginine has a dual role in tumor growth, acting both as a stimulant and an inhibitor, depending on the stage of cancer [9]. Many clinical studies investigated the effect of arginine and other immune nutrients on cancer patients.

According to a recent systematic review of 9 RCTs, 450 mL of an oral product with arginine, omega-3 fatty acid taken for 7 days during the preoperative period reduces cell proliferation in colorectal tumor and enhances immunization after tumor removal, which may reduce the probability of recurrence [70]. However, the included RCTs were restricted to Asian countries, and some of these studies do not use arginine as a mono intervention but with omega-3 fatty acids and other micronutrients. A pilot study showed that arginine-containing amino acid supplements suppressed inflammation and improved immune status by enhancing $CD4^{+}$T cell function in unresectable non-small-cell lung cancer (NSCLC) patients receiving chemotherapy [73]. A prospective randomized controlled Trial on patients undergoing total gastrectomy for gastric cancer suggested that early enteral nutrition rich in arginine improves nitrogen balance to the preoperative range [74]. None of these clinical studies have studied arginine as a single intervention, which makes other combined nutrients cofounder factors; other clinical studies need to use arginine as a single amino acid intervention.

In terms of enhanced survivability, Oral arginine-enriched supplements improved the long-term survival of compliant head and neck squamous cell cancer patients undergoing chemoradiotherapy [75]. In contrast, the impact of early postoperative feeding with arginine-enriched supplements on short- and long-term mortality was studied in patients undergoing surgery for esophagogastric and pancreaticobiliary cancer and showed no significant difference compared to isocaloric, isonitrogenous control feed [76].

6.6. Immune system

Arginine plays a crucial role in regulating the immune system. It enhances immune responses and impacts immune cell biology, specifically macrophages, dendritic cells, and T-cells. The synthesis, availability, and breakdown of arginine are interconnected processes that can lead to either pro-inflammatory or anti-inflammatory immune outcomes [77]. An Animal studies showed that Arginine supplementation increased cytokine expression in the mouse ileum, promoting secretory IgA secretion through T cell-dependent and T cell-independent pathways [78]. Another suggested mechanism for arginine's effect on the immune system is that it can remodel gut microbiota by increasing B. pseudopodium, which enhances the immune defense against Nontuberculous mycobacterial (NTM) infection [79].

L-arginine deficiency reduces T-cell proliferation and response in T-cell-mediated memory. In cancer models, myeloid-derived suppressor cells (MDSCs) cause immune suppression through L-arginine depletion and lymphocyte mitochondrial dysfunction [80]. These MDSCs were also observed to suppress the proliferation of T-cells and the production of interferon (IFN) in COVID-19 patients via an arginase-dependent mechanism [81]. Moreover, L-arginine deficiency weakens T-cell response, making humans more vulnerable to infections. L-arginine supplementation decreases the IL-21 level and increases NO, which leads to suppressing the function of Th17 cells, which are responsible for cytokine storms and hyperinflammatory phenomena seen in COVID-19 patients [80]. Another clinical trial was conducted on COVID-19 patients hospitalized with severe symptoms [82]. The study revealed that the addition of oral L-arginine (1.66 g L-arginine twice a day) to standard therapy significantly reduced the length of hospitalization and respiratory support after 10 days of starting the treatment, but no significant reduction in respiratory support was noted after 20 days of starting treatment [82].

Arginine, found in a dentifrice, has been shown to help defend against dental caries [83]. A clinical cohort study on caries-free and caries-active individuals normalized oral microbiota in caries-active individuals, bringing them to levels similar to caries-free individuals [83]. Arginine combined with fluoride is even more effective than arginine alone enriching alkali-generating Streptococcus sanguinis while suppressing acidogenic/aciduric Streptococcus mutans, thus reducing the demineralizing capability of oral biofilm [83].

6.7. Preeclampsia

Preeclampsia presents a significant risk to both the pregnant women and the developing fetus during pregnancy. It is one of the leading causes of maternal mortality and is defined by elevated blood pressure due to endothelial dysfunction. This condition may cause premature delivery, intrauterine growth restriction (IUGR), and in severe instances, may result in the loss of both mother and child [84]. It has been observed that only one agent, which is acetylsalicylic acid, has been effective in preventing the onset of Preeclampsia [85]. L-arginine supplementation has been studied as an intervention to prevent preeclampsia due to its potential to increase vascular NO synthesis, as NO deficiency in pregnant women can cause changes in uteroplacental structure [86].

Several clinical trials have approved the effectiveness of L-arginine in preventing preeclampsia, preterm births, intrauterine growth restriction, increased birth weight, and prolonged gestational age at labor of IUGR fetuses [86–88]. For instance, a recent randomised controlled trial was conducted on primigravida women found that using about 4 g/day of L-arginine as a preventive therapy instead of acetylsalicylic acid (ASA) significantly reduced the incidence of preeclampsia and other perinatal complications. Pregnant women with early-onset gestational endotheliopathy who received L-arginine did not develop placental dysfunction in the second and third trimesters of pregnancy, and no cases of fetal growth retardation were observed [85]. Another randomized, double-blind, placebo-controlled trial studied the effect of arginine and antioxidant vitamins in pregnant women with a history of pre-eclampsia to prevent the condition by adding arginine and antioxidant vitamins in a nutrient bar for pregnant women, which significantly reduced the incidence of pre-eclampsia in a population at high risk of the condition compared with antioxidants alone or the placebo group [89].

In general, most clinical trials have demonstrated that providing L-arginine supplements in a dose of about (3 g/day) to women at risk of preeclampsia for three to four weeks, consistently initiated at 20 weeks of gestation, can significantly reduce the risk of preeclampsia [86]. However, further research is required on a larger scale to determine the optimal treatment protocol for prophylactic or therapeutic effects.

6.8. Skeletal muscle and physical performance

As mentioned earlier, arginine is essential in producing NO, which is synthesized from Arginine by NOS. NOS is present in high levels in skeletal muscle, and there are three types of NOS found in

Table 1
Summary of clinical trials investigating the therapeutic efficacy of a arginine.

Condition/Outcome	Study Design	Population	Intervention & Regimen	Key Findings & Clinical Outcomes	Ref.
Hypertension	Randomized, double-blind, placebo-controlled trial	Patients diagnosed with hypertension	3 g/day for 2 weeks	Mean arterial pressure (MAP) is significantly reduced.	[51]
Hypertension	Randomized, double-blind, placebo-controlled trial	Treated hypertensive individuals	Single dose (8 g sachet)	Post-exercise systolic hypotension is significantly attenuated.	[52]
Hypertension	Randomized, double-blind, placebo-controlled trial	Susceptible individuals with elevated BP between	9 g/day for 2 weeks	Reductions in systolic blood pressure (SBP), diastolic blood pressure (DBP), and MAP by 5.3, 4.3, and 4.6 mmHg, respectively.	[53]
Hypertension	Randomised, double-blind, placebo-controlled trial	Metabolic syndrome patients	5 g/day for 12 weeks	1. Significant decrease in SBP, DBP, and MAP. 2. No significant effect on pulse pressure.	[54]
Type 2 diabetes & glycemic control	Two meta-analysis studies of 10 and 12 RCTs	Patients with T2DM	>6.5 g/day for ≥12.8 weeks	1. A reduction in serum insulin in non-diabetic subjects with high baseline insulin (>20 μIU/mL). 2. No significant effect on HOMA-IR, HbA1c, or FBG.	[57,58]
Glycemic levels	Randomized, double-blind, placebo-controlled trial	Metabolic syndrome patients	5 g/day for 12 weeks	1. Significant reduction in fasting blood glucose (FBG). 2. No significant impact on HOMA-IR, insulin sensitivity, or β-cell function.	[59]
Glycaemic levels	Mono-center, randomized, double-blind, parallel-group, placebo-controlled, phase III trial.	Metabolic syndrome patients	6.4 g/day for 18 months	Significant improvement in insulin sensitivity and β-cell function.	[60]
Dyslipidaemia	Two meta-analyses studies included (17 and 12 RCTs)	Healthy and diseased adults	≥2–4 weeks duration	1. Reduction in serum triglycerides (TG). 2. No significant effect on total cholesterol, LDL, or HDL levels.	[62,63]
Dyslipidaemia	Randomized, double-blind, placebo-controlled trial	Adults at risk of CVD	2 g/day for 45 days	TG, total cholesterol, LDL, and HDL levels were significantly decreased.	[64]
Pressure injuries (PIs)	Systematic review on 8 clinical studies	Adults with PIs	Oral or enteral (≥2 weeks)	1. Significant reduction in PUSH and PSST scores. 2. Doses>15 g/day enhanced healing and prevention.	[66]
Enterocutaneous fistula	Randomized controlled trial	Patients with enterocutaneous fistula	Combined with 10 g glutamine (4.5 g/day for 7 days pre the surgery)	1. Reduced recurrence rate (10% vs. 45%). 2. Lower preoperative inflammatory markers (IL-6, CRP). 3. No infectious complications.	[67]
Venous ulcers	A controlled clinical trial before–after treatment	Venous ulcers under outpatient treatment	Combined with zinc, Vit A, C, and E (3x daily for 8 weeks)	1. Significant reduction in ulcer area and PUSH scores.	[68]
Colorectal cancer	Systematic review of 9 RCTs	Colorectal cancer patients	Combined with Omega-3 (450 mL for 7 days pre-op)	1. Reduced tumour cell proliferation. 2. Enhanced postoperative immunization. 3. Reduced recurrence risk.	[70]
Lung cancer (NSCLC)	Pilot study	Lung cancer patients receiving chemotherapy	Arginine-containing amino acid supplements	Uppression of systemic inflammation and the enhancement of immune status through improved CD4+ T cell function are evident and impactful.	[73]
Gastric cancer	Prospective randomized controlled trial	Total gastrectomy patients	Arginine-rich early enteral nutrition	Ameliorated nitrogen balance and returned levels to the preoperative range.	[74]
COVID-19	Randomized, double-blind, placebo-controlled trial	COVID-19 hospitalized patients (severe symptoms)	1.66 g twice daily (oral)	1. Significant reduction in hospitalization duration and respiratory support at 10 days; 2.No significant difference at 20 days compared to standard care.	[82]
Dental caries	Clinical cohort study	Caries-free individuals with no clinical evidence of caries experience	Arginine combined with fluoride	1.Normalized oral microbiota. 2.Enriched alkali-generating S. sanguinis 3.Suppressed acidogenic S. mutans 4. Reducing biofilm demineralization.	[83]
Preeclampsia	Single-blind randomized clinical trial	Primigravida women	4 g/day	1. Significant reduction in the incidence of preeclampsia and perinatal complications.	[85]

(*continued on next page*)

Table 1 (*continued*)

Condition/Outcome	Study Design	Population	Intervention & Regimen	Key Findings & Clinical Outcomes	Ref.
				2. Prevented placental dysfunction and fetal growth retardation.	
Preeclampsia	Randomized, double-blind, placebo-controlled trial	High-risk pregnant women	Arginine	1. Significant reduction in preeclampsia incidence compared to antioxidants alone or placebo.	[89]
Athletic performance	Double-blinded, randomized and placebo-controlled trial	Male athletes	2 g/day for 45 days	1. Significant improvement in sports performance. 2. No significant effect on BMI, body fat mass, or lean body mass.	[91]
Athletic performance	Prospective cohort study	Resistance-trained individuals	5 g powder (pre-exercise) for 6 months	1. Significant increase in muscle mass, 2. Reduction in body fat, 3. A significant decrease in blood pressure.	[92]

muscle: eNOS, neuronal NOS (nNOS), and iNOS, with nNOS being the most common. NO in muscle regulates force, differentiation, protein turnover, biogenesis, oxidation, and glucose homeostasis. It modulates respiration and induces muscle hypertrophy. Many studies claimed that administering arginine supplements might be beneficial for increasing muscle mass and strength, especially for athletes [90].

A double-blinded, randomized, and placebo-controlled trial was conducted on male athletes by taking 2g of arginine supplements daily for 45 days [91]. The results showed that taking 2g of arginine supplements daily significantly improved sports performance in male athletes. However, the supplements had no effect on anthropometric measurements such as body mass index (BMI), body fat mass (BFM), and lean body mass (LBM) [91]. A 6-month clinical study on healthy individuals who did resistance training showed that a 5g oral arginine powder supplementation before their exercise routine significantly decreased blood pressure [92]. The group that consumed arginine showed a significant increase in muscle mass compared to the control group. Additionally, body fat decreased by 1%. The arginine group gained twice the amount of muscle mass and lost twice as much body fat as the control group [92].

Regarding the optimal dose of arginine supplements, a recent systematic review analyzed 15 clinical studies to determine the appropriate dose of arginine supplements that can enhance athletic performance [93]. The review concluded that for acute arginine supplementation protocols, a dosage of 0.15 g/kg of body weight should be ingested between 60 and 90 min before exercising to improve both aerobic and anaerobic performance [93]. For chronic arginine supplementation, a dosage of 1.5–2 g/day over 4–7 weeks is recommended to enhance aerobic performance, while a dosage of 10–12 g/day over 8 weeks can improve anaerobic performance [93]. Table 1 summarizes clinical trials that assess the therapeutic effectiveness of arginine.

7. Arginine supplements' safety profile

To evaluate the safety of arginine supplements, essential points must be taken into account, including the dosage regimen, route of administration, population origin, age, and nutrient combination in which they are delivered [94]. No available studies investigated all these factors to determine the optimal dose regimen for various health conditions. However, based on the available research, we can conclude that L-arginine delivered through the enteral route is safe and does not cause any toxicity when supplied at the doses available in commercial formulations [95]. However, if L-arginine is supplied through the oral route as a bolus without any other macronutrients, doses greater than 30 g/day may result in low blood pressure, stomach pain, bloating, and diarrhea, and for adult humans, the long-term safe level of dietary arginine supplementation is at least 30 g/day [96,97].

Arginine supplementation may increase the risk of certain types of cancer. Arg deprivation chemotherapy has been used to treat various cancers, including metastatic melanoma, Mesothelioma, hepatocellular carcinoma, prostate cancer, and Acute Myeloid Leukemia [98,99]. Over 20 clinical trials of ADI-PEG20 on over 12 types of cancer have been completed or are ongoing, with hepatocellular carcinoma and mesotheliomas being the most advanced ones [99]. However, only a few studies suggest that L-arginine supplementation may stimulate tumor growth. The safety of supplemental L-arginine in individuals in individuals who may be predisposed to or who have undiagnosed malignancies has yet to be established. Regarding pregnancies, a randomised controlled trial conducted on pregnant women who took 4 g/day of L-arginine in the first trimester showed no associated side effects or adverse reactions. In contrast, the supplement benefited both the mother and fetus [85].

8. Conclusion

The previously discussed findings underscore the critical importance of arginine as both a predictive and prognostic biomarker for the specified diseases. Additionally, they highlight its biological functions and therapeutic potential across a range of pathological conditions. Further extensive investigations are needed to elucidate the comprehensive role of this amino acid in the diagnosis, pathogenesis, augmentation, and treatment of various diseases.

Author contributions

M.N. and **S.B.** contributed equally to conceptualizing the article, outlining its structure, and editing and revising the manuscript. **M.N., S.A., and Q.A.** contributed to the literature review, wrote the first draft, and compiled references. All others reviewed and approved the final manuscript.

Artificial intelligence

No AI tools were used to write the manuscript. However, the Grammarly app was used for minor grammar edits.

Funding

Not applicable.

Conflict of interest statement

The authors declare no conflicts of interest. **S.A.** and **Q.A.** are family members who contributed to this work. This relationship has been disclosed in the interest of transparency and does not affect the integrity or objectivity of the review.

Acknowledgements

Not applicable.

List of Abbreviations

AS	Asparagine synthetase
ASA	Acetylsalicylic acid
AUC	Area under the curve
BFM	Body fat mass
BP	Blood pressure
CAT-1	Cationic amino acid transporter-1
CD4+ T	Helper T cells
CHOP	C/EBP Homologous protein
COVID-19	Coronavirus disease 2019
CRC	Colorectal cancer
CVD	Cardiovascular disease
eNOS	Endothelial nitric oxide synthase
FBG	Fasting blood glucose
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
IBS	Irritable bowel syndrome
IFN	Interferon
IgA	Immunoglobulin A
IL-21	Interleukin-21
iNOS	Inducible nitric oxide synthase
IURG	Intrauterine Growth Restriction
LBM	Lean body fat
LDL	Low-density lipoprotein
MDSCs	Myeloid-derived suppressor cells
mTOR	Mammalian target of the rapamycin
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NSCLC	Non-small cell lung cancer
NTM	Nontuberculous mycobacterial
PCOS	Polycystic ovary syndrome
PI	Pressure injuries
PSST	Pressure sore status tool
PUSH	Pressure ulcer scale for healing
RBM39	RNA-binding motif protein-39
RCT	Randomized control trial
T2DM	Type 2 diabetes mellitus
TG	Triglyceride

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