MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
SUMY STATE UNIVERSITY
ACADEMIC AND RESEARCH MEDICAL INSTITUTE

Eastern Ukrainian Medical Journal

116, Kharkivska st., Sumy 40007, Ukraine
e-mail: eumj@med.sumdu.edu.ua
eumj.med.sumdu.edu.ua
ISSN: 2663-5909 (print)/2664-4231 (online)

How to cite: Garnytska A, Orlyk O, Kochuieva M, Psarova V. The effect of amino acids and vitamin D3 on obese patients and weight loss. Literature review. *East Ukr Med J*. 2025;13(4):931-940. https://doi.org/10.21272/eumj.2025;13(4);931-940

ABSTRACT

Anna Garnytska
https://orcid.org/0000-0002-3554-8864
Shupic National Healthcare University of Ukraine, Kyiv, Ukraine

Olga Orlyk
https://orcid.org/0000-0003-0040-1579
State Scientific Institution "Center for Innovative Medical Technologies of the NAS of Ukraine", Kyiv, Ukraine

Maryna Kochuieva
https://orcid.org/0000-0002-1516-2155
Shupic National Healthcare University of Ukraine, Kyiv, Ukraine

Valentyna Psarova
https://orcid.org/0000-0001-6890-272X
Sumy State University, Sumy, Ukraine

THE EFFECT OF AMINO ACIDS AND VITAMIN D3 ON OBESE PATIENTS AND WEIGHT LOSS. LITERATURE REVIEW

Obesity is a global problem in developed countries, which is becoming increasingly common not only among adults but also among children. The definition of obesity has changed significantly over the past century, from a simplistic view of overeating and laziness to a complex, multifactorial disease with profound consequences for health and society. Potential factors contributing to obesity include environmental, biological, genetic, and economic factors, as well as important influences on eating habits and behavior, the environment associated with food and beverages, and psychological and social factors acting inside and outside the body. The search for effective treatment strategies for this condition continues to this day. Among the auxiliary means of influencing carbohydrate metabolism, various micronutrients and vitamins are widely studied.

Objective: Use literary sources to familiarize yourself with the properties of the amino acids arginine, leucine and vitamin D3, and their effect on carbohydrate metabolism and weight loss in obesity.

Object: arginine, leucine and vitamin D3 as means of correction of carbohydrate metabolism disorders.

Research methods: review of literature sources.

Results: according to research and meta-analyses, certain amino acids, such as arginine and leucine, as well as vitamin D3, can affect metabolism and energy balance in the body. For example, leucine and arginine are amino acids that play an important role in the biochemical processes of the body. Their study in the context of obesity may include an analysis of the effect on metabolism, fat metabolism, insulin resistance and other parameters. In turn, vitamin D is a steroid hormone, the main function of which is the regulation of calcium and phosphorus metabolism. Still, this molecule also exhibits various properties, including the effect on carbohydrate metabolism.

Conclusion: The integration of leucine, arginine and vitamin D3 into the diet may be one of the key strategies in the complex treatment of obesity.

Keywords: obesity, amino acids, leucine, arginine, vitamin D3, treatment, metabolism.

Corresponding author: *Olga Orlyk, PhD, leading researcher of the Department of Diagnostics and Treatment of Metabolic Diseases State Scientific Institution "Center for Innovative Medical Technologies of the NAS of Ukraine", Kyiv, Ukraine*
E-mail: olgaorlyk1982@gmail.com

РЕЗЮМЕ

Анна Гарницька
https://orcid.org/0000-0002-3554-8864
Національний університет охорони здоров'я України імені П. Л. Шупика, Київ, Україна

Ольга Орлик
https://orcid.org/0000-0003-0040-1579
Державна наукова установа «Центр інноваційних медичних технологій НАН України», Київ, Україна

Марина Кочуєва
https://orcid.org/0000-0002-1516-2155
Національний університет охорони здоров'я України імені П. Л. Шупика, Київ, Україна

Валентина Псарьова
https://orcid.org/0000-0001-6890-272X
Сумський державний університет, Суми, Україна

ВПЛИВ АМІНОКИСЛОТ ТА ВІТАМІНУ D3 НА ВТРАТУ ВАГИ У ПАЦІЄНТІВ З ОЖИРІННЯМ. ОГЛЯД ЛІТЕРАТУРИ

Ожиріння – це глобальна проблема в розвинених країнах, яка стає все більш поширеною не лише серед дорослих, а й серед дітей. Визначення ожиріння значно змінилося за останнє століття, від спрощеного погляду на переїдання та лінь до складного, багатофакторного захворювання з глибокими наслідками для здоров'я та суспільства. Потенційні фактори, що сприяють ожирінню, включають екологічні, біологічні, генетичні та економічні фактори, а також важливі впливи на харчові звички та поведінку, навколишнє середовище, пов'язане з їжею та напоями, та психологічні та соціальні фактори, що діють всередині та зовні організму. Пошук ефективних стратегій лікування цього стану триває й донині. Серед допоміжних засобів впливу на вуглеводний обмін широко вивчаються різні мікронутрієнти та вітаміни.

Мета: Використати літературні джерела для ознайомлення з властивостями амінокислот аргініну, лейцину та вітаміну D3, а також їх впливом на вуглеводний обмін та втрату ваги при ожирінні.

Об'єкт: аргінін, лейцин та вітамін D3, як засоби корекції порушень вуглеводного обміну.

Методи дослідження: огляд літературних джерел.

Результати: згідно з дослідженнями та метааналізами, певні амінокислоти, такі як аргінін та лейцин, а також вітамін D3, можуть впливати на метаболізм та енергетичний баланс в організмі. Наприклад, лейцин та аргінін – це амінокислоти, що відіграють важливу роль у біохімічних процесах організму. Їх вивчення в контексті ожиріння може включати аналіз впливу на метаболізм, жировий обмін, інсулінорезистентність та інші параметри. У свою чергу, вітамін D – це стероїдний гормон, основною функцією якого є регуляція обміну кальцію та фосфору. Однак ця молекула також проявляє різні властивості, включаючи вплив на вуглеводний обмін.

Висновок: Інтеграція лейцину, аргініну та вітаміну D3 у раціон може бути однією з ключових стратегій у комплексному лікуванні ожиріння.

Ключові слова: ожиріння, амінокислоти, лейцин, аргінін, вітамін D3, лікування, метаболізм.

Автор, відповідальний за листування: *Ольга Орлик, Державна наукова установа «Центр інноваційних медичних технологій НАН України», Київ, Україна*
e-mail: olgaorlyk1982@gmail.com

INTRODUCTION

Obesity is a global pandemic worldwide, which has not bypassed Ukraine. According to research results from the last five years, 25% of Ukrainian adults suffer from obesity, and the number of children of early school age with obesity is already approaching 10% (according to the COSI study). The acquired knowledge about the role of biology and genetics in the occurrence of obesity has led to the recognition of obesity as a disease, and not a character flaw or weak willpower. It is obvious that obesity is not the same condition for everyone. Like cancer, which is a set of diseases with different causes, symptoms, treatment and prognosis, obesity can also be a set of diseases with individual, albeit similar, signs.

Potential factors contributing to obesity include environmental, biological, genetic/developmental, economic, behavioral/environmental factors related to food and drink, psychological, and social factors that act both internally and externally. These factors increase energy intake and/or decrease energy utilization. In some cases, the cause of obesity is very specific, such as a deficiency in the receptors in the brain responsible for regulating food intake and energy expenditure (melanocortin 4 receptors, MC4R), or a lack of leptin (a hormone that determines body fat levels), leading to overeating with excessive calorie intake. In other cases, there is not one specific cause, but many factors that interact to increase the susceptibility to obesity. For example, suboptimal sleep, certain viral infections, gut microbial imbalance, or insufficient levels of metabolically active brown adipose tissue. With the rapid progress in understanding the biology of obesity, we are entering a new era of enhanced opportunities for its prevention, treatment and control. These advances benefit people at risk of developing obesity and the approximately one billion people worldwide who live with this disease [1].

In this regard, the study of new approaches to the treatment of obesity is an important task to ensure the effectiveness and safety of therapeutic strategies.

According to research, certain amino acids, as well as vitamin D, can affect metabolism and energy balance in the body. Leucine and arginine are amino acids that play an important role in biochemical processes in the body. Their study in the context of obesity may include the analysis of their effects on metabolism, fat metabolism, insulin resistance and other parameters. In turn, vitamin D is a steroid hormone, the main function of which is the regulation of calcium and phosphorus metabolism, but this molecule also exhibits various properties, including effects on carbohydrate metabolism.

This scientific article examines the effects of amino acids and vitamin D on the treatment of obesity and explores new perspectives and mechanisms of this interaction.

Analysis of literature data.

Mechanisms of influence of amino acids leucine and arginine on carbohydrate metabolism

Appetite reduction. Leucine and arginine interact with appetite control systems in the central nervous system. Some studies show that these amino acids can affect the production of leptin and reduce hunger. Leptin is a peptide hormone of adipose tissue that acts on receptors in the hypothalamus, reducing appetite and increasing thermogenesis.

Improving fat metabolism. Leucine is an essential aliphatic amino acid that is not synthesized by the body's cells but enters the body exclusively with proteins that are part of natural food. Leucine can stimulate protein synthesis and activate pathways associated with fat burning. Arginine is an essential alpha-amino acid, the L-form of which is one of the 20 amino acids encoded by the genetic code and forms the basis of proteins. For humans, arginine is a semi-essential amino acid, but during certain periods of life, particularly during intensive growth and development, during some diseases, the human body requires additional arginine intake. Arginine also interacts with fat metabolism and can contribute to the increase in nitric oxide, which can affect the efficiency of fat burning.

Role in insulin regulation. Arginine can affect the sensitivity of cells to insulin, which is an important factor in glycemic control and prevention of insulin resistance, which often accompanies obesity.

Integration of these amino acids into the diet may be one of the key strategies in the complex treatment of obesity. For more reliable evidence, additional clinical studies are needed to determine the optimal doses, duration and effective methods of administration of these amino acids for maximum benefit and safety [2-4].

Effect of leucine on the activation of key enzymes in protein synthesis after physical activity.

Physical activity plays a key role in maintaining health and building muscle mass. Branched-chain amino acids, in particular leucine, are considered key participants in the molecular processes associated with protein synthesis.

The results of a study examining the effect of leucine on the activation of key enzymes involved in protein synthesis after physical activity are presented below.

The study participants were healthy, physically active individuals who did not have serious diseases or limitations, and they performed aerobic and anaerobic exercises. Half of the participants received a supplemental leucine intake after physical activity, while the other half received a placebo.

The measurement of enzyme activation was carried out using biochemical and molecular methods, and the activation of key enzymes, such as mitochondrial ribosomal protein kinase and others involved in protein synthesis, was also studied.

*Results.*The leucine group showed a statistically significant increase in key enzyme activity compared to the placebo group. The analysis showed that participants who took leucine showed increased protein synthesis after physical activity, which may indicate a positive effect of branched-chain amino acids.

Leucine dosage can vary depending on various factors such as age, gender, physical activity, health status and specific needs of the body.

General recommendations for leucine doses in different groups.

For athletes, and active people and for maintaining muscle mass during weight loss, it is recommended to consume approximately 2-3 g of leucine per day to support muscle growth and recovery from physical activity. For general use, the recommended dose of leucine is 0.7-1 g per 1 kg of body weight per day.

Conclusion. The results obtained suggest that leucine may influence the activation of key enzymes in protein synthesis after physical activity. This study makes an important contribution to the understanding of the molecular mechanisms that support the role of branched-chain amino acids in muscle physiology during exercise.

The role of leucine as a modifier of insulin resistance and its effects on various metabolic levels.

Environmental factors, such as dietary micronutrient composition, can have a profound impact on the risk of developing type 2 diabetes and metabolic syndrome. The following is a study that demonstrates how a single dietary factor–leucine–can modify insulin resistance by affecting multiple tissues at multiple metabolic levels. The aim of this study was to evaluate the role of leucine as a modifier of insulin resistance and its effects on various metabolic levels.

To assess the role of leucine on metabolism, mice were fed a normal- or high-fat diet. Dietary leucine was supplemented in their drinking water. RNA, protein, and a complete metabolomic profile were assessed in key insulin-sensitive tissues and serum and correlated with changes in glucose homeostasis and insulin signalling. After 8 weeks on a high-fat diet, mice developed obesity, fatty liver, inflammatory changes in adipose tissue, and insulin resistance, as well as changes in the metabolomic profile of amino acid metabolites, glucose, cholesterol, and fatty acids in liver, muscle, adipose tissue, and serum. Dietary leucine supplementation induced significant improvements in glucose tolerance and insulin sensitivity, without changes in food intake or weight gain. Dietary leucine supplementation was also associated with reduced hepatic steatosis and reduced inflammation in adipose tissue. These changes occurred despite an increase in insulin-stimulated phosphorylation of p70S6 kinase, indicating increased mTOR activation, a phenomenon associated with insulin resistance.

Conclusion. These data suggest that dietary modification can alter multiple metabolic pathways and modify the metabolic syndrome by acting at a systemic level. This study supports the role of leucine as a modifier of insulin resistance while indicating its potential effects at different levels of metabolism. These data also suggest that increasing dietary leucine intake may be an adjunct in the treatment of obesity-related insulin resistance [5].

Effects of leucine in older adults with sarcopenia: a systematic review and meta-analysis of randomized controlled trials.

According to the literature, there is a decline in muscle mass and protein synthesis in older adults with age, which may lead to the development of certain diseases and a decrease in quality of life. Sarcopenia is a type of muscle loss that occurs with ageing and/or lack of physical activity, characterized by a degenerative loss of skeletal muscle mass, quality, and strength. The rate of muscle loss depends on age, level of physical activity, comorbidities, diet, and other factors.

Currently, one of the main treatments for sarcopenia is resistance exercise and nutritional supplementation, as pharmacological agents are not currently available [6]. Despite the effectiveness of resistance exercise in addition to diet [7], nutritional interventions remain the most promising treatment and prevention strategy for many older adults who are unable to exercise [8]. Supplementation of the branched-chain amino acid, leucine, or a leucine-rich protein (whey/casein protein) is one of the most common interventions for the treatment of sarcopenia in the elderly [7–9].

Leucine is an essential branched-chain amino acid that regulates muscle function in part through the mTOR pathway [10]. Leucine has been shown to regulate protein metabolism in skeletal muscle by reducing proteolysis and increasing protein synthesis [11–14]. Furthermore, leucine can increase glucose uptake by skeletal muscle and induce insulin release from pancreatic cells, which is an important anabolic signal in skeletal muscle [14]. Therefore, dietary leucine supplementation is currently being widely studied as a strategy to increase muscle protein synthesis, which is a promising approach for the treatment of sarcopenia [8].

However, recent studies supporting the effects of dietary interventions with leucine have not been conducted specifically in patients with sarcopenia [15] or have used a combination of different nutrients including leucine [16]. Therefore, the authors conducted a meta-analysis to assess the effects of protein-rich supplements with leucine supplementation on improving muscle quality and quantity in older adults with sarcopenia.

The researchers searched for randomized trials in the PubMed-Medline, Embase, and Cochrane Library databases. Six randomized controlled trials involving 699 participants were selected. The search results showed that protein supplements rich in leucine improved overall muscle strength, mass, and performance compared with the control group (SMD = 0.939; 95% CI, 0.440–1.438; $p < 0.001$). As a primary outcome, muscle strength was significantly improved in the leucine group (SMD = 0.794; 95% CI, 0.104–1.485; $p = 0.024$).

Conclusion. Leucine-rich protein supplements may improve muscle strength in older adults with sarcopenia and may be recommended in the dietary management of sarcopenia [17].

Effects of arginine on metabolic regulation.

There is increasing interest in arginine in the scientific community because it is involved in many metabolic processes that play an important role in a wide range of physiological and pathophysiological conditions. Studies have shown that arginine affects nutrient metabolism, stimulates insulin release, participates in nonspecific immune and antioxidant responses, and increases disease resistance. In particular, arginine may regulate energy homeostasis through modulation of the adenosine 5'-monophosphate-activated protein kinase pathway; arginine may also regulate protein synthesis by activating the target of rapamycin (TOR) signalling pathway.

According to the literature, dietary supplementation with L-arginine reduces white fat mass in diet-induced obese rats and in obese humans. A study was conducted to test the hypothesis that arginine regulates glucose and fatty acid metabolism in insulin-sensitive tissues. Male Sprague-Dawley rats, 4 weeks old, were fed either a low-fat or high-fat diet for 15 weeks. After that, lean or obese rats were given the corresponding diet and water containing 1.51% L-arginine-HCl or 2.55% alanine. After 12 weeks of treatment, the researchers collected tissue samples for biochemical analyses. High-fat feeding increased the size of adipocytes isolated from visceral adipose tissue, whereas arginine treatment reduced their size. The total number of adipocytes in adipose tissue did not differ among the four groups of rats. Glucose oxidation in the extensor digitorum longus muscle, soleus muscle, and adipose tissue was reduced in response to high-fat feeding. In contrast, oleic acid oxidation in adipose tissue was increased in rats fed the high-fat diet. Arginine treatment stimulated both glucose and oleic acid oxidation in the extensor digitorum longus and soleus muscles, without affecting glucose oxidation, oleic acid oxidation, or basal lipolysis of adipocytes in visceral adipose tissue. Taken together, these results suggest that oral arginine supplementation in diet-induced obesity may promote the oxidation of energy substrates in skeletal muscle, thereby reducing white body fat.

Further clinical studies are needed to translate these findings to humans, which will advance our understanding of the effects of amino acids on metabolism and have practical value in the development of obesity treatment approaches [18].

The effect of vitamin D on body mass index in obesity.

Obesity, prediabetes and type 2 diabetes mellitus (T2DM) are global diseases of the population of Ukraine, the incidence of which is increasing annually. Insulin resistance occurs in 90% of obese patients, contributing to the accumulation of white adipose tissue and the risk of further development of prediabetes and type 2 diabetes mellitus. However, other factors also play a negative role in the development of obesity, in particular, cholecalciferol (vitamin D) deficiency. Vitamin D is a steroid hormone, the main function of which is the regulation of calcium and phosphorus metabolism, but this molecule also exhibits various properties, including an effect on carbohydrate metabolism.

The present study was conducted to evaluate the role of vitamin D in obese patients treated with glucagon-like peptide-1 (GLP-1a) agonists in combination with lifestyle changes and to compare its efficacy with that in patients treated with metformin and sodium-glucose cotransporter 2 inhibitors (SGLT2i). The prospective study included 155 obese patients, and follow-up data were available for 49 of them. The study group consisted of 30 patients who received combination therapy with liraglutide GLP-1a at a dose of 1.2–3.0 mg per day. The control group consisted of 19 patients who received combination therapy with metformin at daily doses of 500 to 2000 mg and SGLT2i at daily doses of 10 to 12.5 mg. Vitamin D deficiency was treated with cholecalciferol at a dose of 4000 IU/day.

Results. In the GLP-1a study group, 25 (83.3%) patients had vitamin D deficiency, which was statistically similar to the control group ($p > 0.05$) – 17 (89.5%) cases. All patients with vitamin D deficiency received 4000 IU of cholecalciferol daily during the observation period. In the GLP-1a study group, the average body weight before treatment was 104.6 kg, after treatment – 96.36 kg ($p = 0.000007$), and the average body weight loss was 7.8% (range 1–23.71%) from baseline. The mean body mass index (BMI) before treatment was 37.1 kg/m2, after treatment – 34.11 kg/m2 ($p = 0.000006$). In the control group, the mean body weight before treatment was 99.4 kg, after treatment – 91.74 kg ($p = 0.000196$), and the mean body weight loss was 7.73% (range 0–

16.9%) from baseline. The mean BMI before treatment was 35.6 kg/m2, after treatment – 34.11 kg/m2 (p = 0.000196). Analysis of carbohydrate metabolism indicators showed a significantly lower blood glucose level – 5.75 mmol/l in the GLP-1a study group compared to 8.42 mmol/l in the control group (p = 0.00024). It should be noted that a similar clinical picture was observed after treatment, despite the compensation of type 2 diabetes in all patients: a significantly lower blood glucose level – 5.03 mmol/l in the GLP-1a study group compared to 5.99 mmol/l in the control group (p = 0.002453). However, in the GLP-1a study group before treatment, significantly higher insulin levels were found – 27.02 mU/l compared to 18.59 mU/l in patients in the control group (p = 0.003286). After treatment, a similar situation was observed with significantly higher insulin levels: 19.41 mU/l in patients in the GLP-1a study group compared to 14.42 mU/l in the control group (p = 0.0024). Corresponding changes were also observed for the HOMA index.

Conclusion. The results obtained indicate the high effectiveness of increasing vitamin D levels in cases of vitamin D deficiency as part of the treatment of obese patients with liraglutide, metformin, or SGLT2i [19-40].

The effect of vitamin D on metabolic processes and body weight indicators.

Vitamin D is known for its role in regulating calcium and phosphorus metabolism, but it also has an important effect on metabolic processes. Studies show that vitamin D deficiency may be associated with increased fat accumulation and the development of obesity.

The study below aims to study the effect of vitamin D on metabolic processes and body weight indicators. The study included patients with different levels of vitamin D and different body weight indicators. Body mass index (BMI), waist circumference and other anthropometric measurements were used to assess fat accumulation. Fat metabolism indicators were assessed by triglyceride and cholesterol levels.

Results. The analysis showed that patients with low vitamin D levels tend to have a higher body mass index compared to those with normal vitamin D levels. It has also been found that vitamin D deficiency may be accompanied by increased levels of triglycerides and other indicators of dyslipidemia, indicating a possible impact on fat metabolism.

Conclusion. The results obtained indicate a possible relationship between vitamin D deficiency, fat accumulation and the development of obesity. The results provide grounds for additional clinical studies to reveal the mechanisms of this relationship and develop treatment strategies [19-40].

The relationship between vitamin D and metabolic syndrome: Data from meta-analysis and In Silico studies.

The study of the effects of amino acids and vitamin D on the treatment of obesity opens new perspectives for the development of effective therapeutic strategies. According to the literature, there is a close relationship between obesity, metabolic syndrome (MS) and vitamin D deficiency. MS is a set of metabolic conditions that increases the risk of cardiovascular disease and type 2 diabetes. Components of MS have been defined in various guidelines and consensus agreements and currently include central (intra-abdominal) obesity, hypertension, insulin resistance, and dyslipidemia.

Vitamin D deficiency may affect extraskeletal functions associated with MS risk factors. However, the precise effects and mechanisms of vitamin D on dyslipidemia and insulin resistance in subjects with MS remain controversial. To explore potential therapeutic targets, pathways, and mechanisms of vitamin D effects on MS parameters, the investigators conducted a systematic literature search in various databases, including PubMed, Web of Science, Embase, Cochrane Library, Ovid, Scopus, and ProQuest.

According to various studies analyzed in this review, vitamin D supplementation has beneficial effects in treating components of metabolic syndrome, such as lipid profile, insulin resistance and hyperglycemia, obesity, and hypertension. These effects may be related to the ability of vitamin D to influence various physiological parameters, including reducing arterial stiffness, decreasing the activity of the renin-angiotensin-aldosterone system, decreasing the level of parathormone, inflammatory cytokines, increasing the activity of lipoprotein lipase, improving phospholipid metabolism, and mitochondrial oxidation.

Effects of vitamin D on obesity.

According to two meta-analyses, vitamin D supplementation may help reduce body mass index (BMI) and waist circumference, but not weight [41]. In this vein, a meta-analysis of 22 observational studies found that, despite an inverse relationship between per cent fat mass and serum vitamin D levels, vitamin D supplementation was not found to significantly reduce per cent fat mass compared to placebo groups [42]. In contrast, Lotfi-Dizaji et al. observed a reduction in weight and fat mass in vitamin D-deficient subjects who took 50,000 IU of vitamin D for 12 weeks [43]. However, there are studies that show the opposite results, finding no positive effect of vitamin D supplementation on parameters such as BMI, weight, hip circumference, or per cent fat [44]. Similarly, studies in 6–14-year-olds have shown that vitamin D supplementation has no effect on BMI, waist circumference, waist-to-hip ratio, and body fat percentage [17, 45, 46].

However, the combined effect of calcium supplementation with vitamin D3 appears to increase weight loss and improve some metabolic blood profiles in obese women [47].

Vitamin D deficiency has been associated with various components of MS, and vitamin D supplementation may be a relevant strategy for the treatment and prevention of MS. However, it is not possible to draw a clear conclusion about this association because published data are conflicting, and it is unclear whether vitamin D deficiency is a cause or a consequence of MS or any of its components. Therefore, further studies are needed to determine the real role of vitamin D deficiency in the development of MS [21, 48–54].

Vitamin D doses in the treatment of obesity may vary depending on various factors, such as the degree of vitamin D deficiency, age, weight, degree of obesity, and other individual characteristics of the patient. The optimal dose should be determined by the doctor based on the results of the tests and the specific needs of the individual patient. However, there are general recommendations.

Doses for correction of vitamin D deficiency.

In cases of identified vitamin D deficiency, the doctor may prescribe high doses of vitamin D for a short period (for example, 50,000 IU per week for 8 weeks).

After the deficiency is corrected, maintenance doses are recommended, which usually vary between 1000-2000 IU per day or higher, depending on the patient's needs and the doctor's recommendations.

Consideration of risk factors.

In patients at risk, such as the elderly, especially those with limited access to sunlight, or those with a high body mass index, vitamin D doses may be higher. Regular monitoring of vitamin D blood levels allows for individual needs to be considered and dosages adjusted accordingly.

Vitamin D treatment should be under the supervision of a physician, and doses should be individualized, taking into account the specific conditions and needs of each patient [55–58].

CONCLUSIONS

The results obtained indicate the effectiveness of the amino acids leucine and arginine in a comprehensive approach to the treatment of obesity. According to the literature, leucine can affect the activation of key enzymes in protein synthesis after physical activity. These results make an important contribution to the understanding of the molecular mechanisms that support the role of branched-chain amino acids in muscle physiology during physical activity.

Dietary correction can alter several metabolic pathways and modify the metabolic syndrome, acting at the systemic level, according to the study presented in this review, leucine has potential effects at different levels of metabolism, and increasing leucine intake in the diet may be an adjunct in the treatment of insulin resistance associated with obesity.

Also important is that protein supplements rich in leucine can improve muscle strength in older adults with sarcopenia and can be offered as dietary support for such patients.

According to the various studies analyzed in this review, vitamin D supplementation has beneficial effects in the treatment of components of the metabolic syndrome, such as lipid profile, insulin resistance and hyperglycemia, obesity and arterial hypertension.

Vitamin D deficiency is associated with various components of MS, and vitamin D supplementation may be a relevant strategy for the treatment and prevention of MS. However, it is not possible to draw a clear conclusion about this relationship, as the published data are contradictory, and it is unclear whether vitamin D deficiency is a cause or a consequence of MS or any of its components. Further studies are needed to determine the real role of vitamin D deficiency in the development of MS.

Therefore, based on the literature, we can conclude that the integration of the amino acids arginine and leucine, as well as vitamin D3, into the diet may be one of the key strategies in the comprehensive treatment of obesity. For more definitive evidence, additional clinical studies are needed to determine the optimal doses, durations, and effective routes of administration of these amino acids and vitamin D3 for maximum benefit and safety.

AUTHOR CONTRIBUTIONS

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Received 18.04.2025

Accepted 28.10.2025

INFORMATION ABOUT THE AUTHORS

Anna Garnytska, PhD, Assistant of the diabetology department of the Shupic National Healthcare University of Ukraine: work concept and design, data collection and analysis, responsibility for statistical analysis, writing (not revising) sections of the manuscript, final approval of the article.

Olga Orlyk, PhD, leading researcher of the Department of Diagnostics and Treatment of Metabolic Diseases State Scientific Institution “Center for innovative medical technologies of the NAS of Ukraine”: work concept and design, writing (not revising) sections of the manuscript, data collection and analysis, critical review, final approval of the article.

Maryna Kochuieva, Doctor of Medical Sciences, MD, PhD, Professor of the Shupyk National Healthcare University of Ukraine: collection of data, writing (not revising) sections of the manuscript.

Valentyna Psarova, Doctor of Medical Sciences, MD, PhD, Professor of the Sumy State University: data collection and analysis, writing (not revising) sections of the manuscript.