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Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

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THE IMPACT OF PROTEIN SUPPLEMENTATION ON HUMAN HEALTH: A LITERATURE REVIEW OF RENAL, HEPATIC, CARDIOVASCULAR AND GASTROINTESTINAL EFFECTS

Bartłomiej Czerwiec *(Corresponding Author, Email: bartek.czerwiec3@onet.pl*
Medical University of Warsaw, Żwirki i Wigury 63A, 02-091 Warsaw, Poland
ORCID ID: 0009-0002-4207-2531

Malwina Wojtas
Medical University of Warsaw, Żwirki i Wigury 63A, 02-091 Warsaw, Poland
ORCID ID: 0009-0008-3859-6168

Julia Skowrońska-Borsuk
Medical University of Warsaw, Żwirki i Wigury 63A, 02-091 Warsaw, Poland
ORCID ID: 0009-0005-4790-9320

Joanna Pergoł
Prof. Witold Orłowski Independent Public Clinical Hospital, CMKP, Czerniakowska 231, 00-416 Warsaw, Poland
ORCID ID: 0009-0002-5662-3082

Martyna Narożniak
Jagiellonian University Medical College Świętej Anny 12, 31-008 Cracow
ORCID ID: 0009-0001-2987-9261

Adam Borsuk
Praski Hospital of the Transfiguration of the Lord, al. "Solidarności" 67, 03-401 Warsaw, Poland
ORCID ID: 0009-0004-6394-1980

Adrianna Ewa Pękacka
Medical University of Warsaw, Żwirki i Wigury 63A, 02-091 Warsaw, Poland
ORCID ID: 0009-0004-3885-1190

Julia Borkowska
Medical University of Warsaw, Żwirki i Wigury 63A, 02-091 Warsaw, Poland
ORCID ID: 0009-0008-1210-0574

Zuzanna Krupa
Medical University of Warsaw, Żwirki i Wigury 63A, 02-091 Warsaw, Poland
ORCID ID: 0009-0003-0113-5599

Julia Sposób
Medical University of Warsaw, Żwirki i Wigury 63A, 02-091 Warsaw, Poland
ORCID ID: 0009-0000-2266-6899

ABSTRACT

Introduction and purpose
Protein is a key nutrient, especially for physically active individuals. The growing popularity of whey protein (WP) supplementation among athletes and fitness enthusiasts is driven by its benefits for muscle regeneration and metabolism. However, concerns arise regarding excessive and unmonitored intake, particularly its effects on kidney and liver function, gut microbiota, and cardiovascular health. This review aims to summarize current knowledge on the health impacts of WP, highlighting both benefits and risks.
Methods
A literature review was conducted using PubMed, Scopus, and Google Scholar with terms such as "whey protein", "adverse effects", "liver toxicity", "kidney function", "gut microbiota", and "cardiovascular health". Priority was given to studies from the last decade, including clinical trials and systematic reviews.
Brief description of the state of knowledge
WP supports muscle growth, insulin sensitivity, and satiety. It may positively affect cardiovascular health by increasing GLP-1 levels, which help reduce blood glucose, blood pressure, and body weight. Nonetheless, excessive intake may strain liver and kidney function, particularly in those with pre-existing conditions. Effects on gut microbiota are mixed while some studies show anti-inflammatory benefits, others suggest dysbiosis. A key issue is the lack of dosage standardization and individual consultation, increasing misuse risk.
Summary
WP supplementation can offer health and performance benefits when used responsibly. Risks, especially for liver and kidneys, must be considered. Individualized guidance and more standardized research are essential to ensure safe and effective use.

KEYWORDS
Activity and Health, Liver Damage, Kidney Failure, Muscle Protein Synthesis

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Introduction.

Protein is an essential nutrient in the human diet. It is crucial for growth, proper metabolism, and overall human development. On a daily basis, we are typically able to supply the body with an adequate amount of this nutrient through regular food intake. Its deficiency in a well-balanced diet is rare. [1] The recommended dietary allowance of protein to avoid protein deficiency in adults is 0.80 g/kg body weight (BW)/day, which translates to about 48–56 g/day and about 10%–15% of the total daily energy expenditure. Exceeding this amount may be defined as a high-protein diet, which can result, for example, from the intake of dietary supplements.[2] In the studies selected for this review, high protein diets are mostly described as providing more than 20-25% of total energy from protein, or over 2.0 g/kg/da**y** with a potential health risk thresholds for protein intake above 3.0 to 3.5 g/kg/day, especially if sustained long-term. Nowadays, increasing attention is being paid to promoting a healthy lifestyle, and dietary supplements are gaining popularity, particularly among athletes seeking to improve performance and support physical recovery.[3] Individuals who engage in sports may have increased physiological demands for protein to maintain proper synthesis and energy production.[4] It is worth emphasizing that protein requirements increase with the intensity of physical activity, therefore, protein intake should be properly balanced. The American Dietetic Association, Dietitians of Canada, and the American College of Sports Medicine recommend a daily intake of 1.2 to 2 g/kg of body weight for endurance and strength athletes.[5] It is estimated that the prevalence of dietary supplement use among athletes may reach up to 100%, depending on several factors, including the level of competition, type of sport, and the definition of supplement use.[6] Currently, many dietary supplement manufacturers aim to produce products that help

athletes maintain both good performance and well-being, for example, by introducing branched-chain amino acid supplementation to reduce muscle soreness after intense exercise and to improve training performance.[7] For many individuals who practice sports, quick visual results are important, which is why rapidly digested and absorbed supplements, such as whey proteins, are highly desirable and are becoming increasingly popular.[8] Milk protein consists primarily of two main components: whey protein (WP) and casein.[9] Among them, WP is often consumed as a dietary supplement to support muscle hypertrophy and myogenesis.[10] Therefore, it can be inferred that WP has a beneficial impact on human body composition.[11] Whey proteins can vary significantly depending on several factors, including the method used to precipitate casein, storage conditions, heat treatment, and other variables.[12] Currently, the main issue is the lack of standardization across various studies that would clearly define WP's nutritional and physiological properties.[13] Little is known about the side effects and potential long-term harmful consequences of WP supplementation, particularly its effects on the liver and kidneys.[14,15] WP is believed to have a beneficial impact on human health.[16,17] However, the lack of guidelines and monitoring for supplement use may lead to overconsumption, which in turn may cause health problems.[18,19] One modifiable factor through increased protein intake is the gut microbiota, which may have both positive and negative effects on host health. This aspect also warrants further scientific investigation.[20] Research is also focusing on the potential role of WP in triggering allergic reactions and in the context of type 2 diabetes mellitus (T2DM).[21,22] WP may ultimately interfere with glucose homeostasis at the molecular level and may be responsible for increasing the body's demand for insulin.[23-26] As such, nutrient supplementation, as outlined above, is associated with various consequences, not all of which are beneficial.

Health concerns related to WP consumption highlight the need for a comprehensive review of its health effects. This review, through the analysis of existing scientific literature, aims to present the relationship between WP supplementation and its impact on selected human organs. This is particularly important as such dietary supplements continue to gain popularity among the general population. The aim of this study is to examine the impact of dietary supplements on human health, with a particular focus on the additional intake of protein in the diet.

Methods

A literature review was conducted using PubMed, Scopus, and Google Scholar with terms such as "whey protein", "adverse effects", "liver toxicity", "kidney function", "gut microbiota", and "cardiovascular health". Priority was given to studies from the last decade, including clinical trials and systematic reviews.

Discussion

The growing popularity and trend of going to the gym is driving the demand for dietary supplements.[27] Thanks to the development of the industry, companies producing dietary supplements now offer a wide range of products aimed at, among other things, increasing muscle mass and promoting fat loss.[28] Since oral whey supplements improve athletic performance, their use has recently become very common in both professional and amateur sports.[29] These supplements are easily accessible, however, their side effects have not been fully elucidated. It is very important to emphasize the appropriate dosage and timing of WP intake, as improper use may lead to adverse effects. Unfortunately, people often take protein supplements regularly without any consultation with a specialist.

Kidney Function

The kidneys are paired organs of the urinary system, located on both sides of the spine in the posterior part of the abdominal cavity. Their primary function is to filter blood and remove unnecessary metabolic waste products in the form of urine. Nitrogenous compounds are produced as a result of protein degradation. With increased protein intake, the kidneys must enhance filtration to eliminate the excess supplied substance, which may be associated with damage.[30] Studies suggest that short-term increases in creatinine levels likely do not indicate deterioration of kidney function.[31] A potentially harmful effect of a high-protein diet on kidney function in the general population has been suggested.[32] This is confirmed by a cohort study, which demonstrated a strong association between high-protein diets, renal hyperfiltration, and a faster decline in kidney function.[33] Such a diet may lead to a prolonged increase in creatinine levels. Blood creatinine levels and estimated creatinine clearance are key parameters in assessing whether protein intake affects kidney function.[34] However, these tests have limitations, therefore, the estimated glomerular filtration rate (eGFR), which includes age, sex, and creatinine, is used to provide a more comprehensive assessment.[35] The growing interest in dietary supplements leads to an increased need to promote their proper use and raise awareness

about potential risks associated with their consumption. Currently, the development of kidney damage due to supplement use remains controversial, mainly because athletes often combine various supplements that may negatively impact kidney function. Such substances include anabolic-androgenic steroids and excessively high doses of vitamins A, D, and E.[10,32] It should be emphasized that monitoring kidney function is very important in individuals with specific dietary preferences or medical conditions, such as athletes, especially those who consume protein supplements.[36,37] People with preserved kidney function may not experience adverse effects from a high-protein diet, whereas those with impaired kidney function should exercise caution when consuming the same amount of protein.[38] This approach aims to protect at-risk individuals from worsening kidney function due to dietary mistakes. Scientific studies highlight correlations between high-protein diets and kidney function problems, especially with long-term supplementation.[39] It has been observed that a sedentary lifestyle may exacerbate the negative effects of prolonged high-protein diets, such as increased kidney mass and calcium excretion in urine, which may be early signs of renal insufficiency. Evidence supporting this includes the increased risk of kidney stones due to higher urine production and calcium excretion.[40,41] To date, nutritional guidelines recommend reducing protein intake, especially animal proteins, in cases of diagnosed kidney stones. Therefore, excessive protein consumption may be contraindicated in individuals with kidney failure, and supplementation of this nutrient should be discussed with a specialist.

Liver Function

The liver is one of the largest and most important organs in the human body. It performs many vital functions, among which key roles include nutrient metabolism and detoxification of harmful substances. The liver plays a crucial role in protein metabolism, serving as the main receptor of amino acids introduced exogenously and produced endogenously by our body. A byproduct of amino acid degradation is urea, which is then filtered by the kidneys and subsequently excreted. It has been observed that excessive protein supplementation may lead to adverse changes in liver function. However, this effect appears to be less pronounced in physically active individuals.[42] Currently, there is limited research in humans that conclusively confirms the harmful impact of excessive protein supplementation on liver function. The influence of whey protein (WP) on liver function thus seems to vary across studies. It has been shown that products intended for bodybuilders are the most common cause of liver damage among individuals using dietary supplements. A slight increase in ALT and AST levels has also been observed, particularly noticeable in young men. The proportion of liver injury cases attributed to dietary supplements has significantly increased in recent years.[43] Studies on the effects of WP on rat livers were conducted, among others, by Deminice et al., who observed an increase in oxidative stress, while Gürgen et al. reported liver toxicity and increased inflammatory markers in mice.[44,45] In human studies, Chitapanarux et al. observed beneficial effects, including reduced liver steatosis and oxidative stress in patients with NASH.[46] Scientific research suggests that physical exercise may reduce the harmful effects of proteins on the liver because, during exercise, protein is utilized for muscle synthesis, thereby preventing liver damage.[47] The results of these studies indicate significant discrepancies regarding the conclusions about how protein supplementation may affect liver function. Although WP may be beneficial in certain conditions, its uncontrolled use may pose risks to liver health. The importance of physical activity as a protective factor for the liver is emphasized here.

Intestinal Function and Microbiota

Dietary protein and its metabolites, amino acids, are essential nutrients for humans and animals. Nutritional products for athletes are developed and targeted primarily to improve nutrient intake, performance, and muscle growth. In high-protein diets, more undigested protein-derived components reach the large intestine compared to moderate or low-protein diets, resulting in increased bacterial amino acid metabolism in the colon, which has both positive and negative systemic and metabolic effects on the host.[48] The human microbiota consists of both symbiotic and potentially pathogenic bacteria.[49-51] The main bacterial types detected in feces are Bacteroides and Firmicutes, followed by Proteobacteria, Actinobacteria, and Verrucomicrobia.[52,53] The gut microbiome and its metabolism vary according to ethnicity, age, diet, physical activity, geographic location, and individual physiological characteristics of the host.[4] Scientific studies suggest that protein consumption may be associated with both improvement and deterioration of intestinal function. Changes have been observed in the gut microbiome of cross-country runners, including an increase in Bacteroidetes and a decrease in beneficial bacteria such as Roseburia and Blautia.[54] Some bacteria within the gut flora can utilize amino acid fermentation to produce energy.[55] Bacterial fermentation of amino acids can result in the production of end products with systemic effects. These products may influence immunomodulatory, neurological, cardiovascular, and intestinal functions.[56-58] They may also be linked to the

development of colorectal cancer and various metabolic diseases, including diabetes and obesity.[59] Therefore, it can be hypothesized that a high-protein diet may correlate with the development of these conditions. One study described a 10-week observation period that showed no changes in microbial diversity or fermentation-derived metabolites in athletes supplementing with high-protein products but noted a reduction in certain bacterial groups, including Roseburia, Blautia, and Bifidobacterium longum.[54] Other studies suggest that protein supplementation is associated with improved concentrations of gut bacteria (increased Lactobacillus and reduced Helicobacter), decreased oxidative stress, and potential slowing of aging processes.[60] Additionally, whey protein appears to aid in the proper development of the infant microbiota.[61] Further research on this topic is needed. Nevertheless, a study by Moreno-Perez et al. suggests that long-term protein supplementation may negatively affect the gut microbiota of athletes and consequently adversely impact their health.[54] Despite the presented studies, the relationship between microbiota diversity and health status remains unclear.[62] These studies indicate a complex interdependence between whey protein supplementation and gut health.

Cardiovascular system

Cardiovascular diseases (CVD) are the number one cause of death globally.[63] These chronic diseases develop silently over the years on the basis of atherosclerosis. Predisposing factors are type 2 diabetes, obesity, dyslipidemia, lack of physical activity, tobacco use, and elevated blood pressure.[64] Primary prevention includes modification of the patient's diet and lifestyle habits. One of the recommendations for weight loss is high high-protein and low-carb diet. This dietary pattern not only reduces body weight but also the appetite by increasing anorexigenic hormone levels.[65] An additional benefit of high high-protein diet is the elevation of the GLP-1 factor that decreases blood pressure, glycemia, and body weight, thus mitigating the risk of cardiovascular events.[66] Meta-analysis by Zhou et al. (2020) on CVD risk factors concluded that high-quality protein supplementation, including soy protein, milk protein and casein, lowers systolic blood pressure in patients with metabolic syndrome, showing a beneficial role of high-protein diet in reducing CVD risk factors.[67] High high-protein diet composed of plant-based proteins decreases the risk of CVD.[68] However, a study from 2020 shows that elevated amino acid levels in blood may result in macrophage apoptosis, leading to atherosclerotic progression[69]

Conclusions

Protein supplementation is becoming increasingly common, both among athletes and individuals leading less active lifestyles. However, it is crucial that the use of dietary supplements is approached thoughtfully and ideally preceded by consultation with a specialist who can tailor the supplementation appropriately and, if necessary, introduce a suitable physical exercise program. Based on available scientific research, it can be concluded that protein supplementation offers numerous benefits, including supporting muscle growth, improving metabolic functions, and potentially having a positive impact on the cardiovascular system, such as enhancing lipid profiles and reducing inflammation. Nevertheless, it is important to remember that excessive or uncontrolled protein intake may also carry risks to health. The kidneys and liver, organs that play key roles in protein metabolism and the elimination of their byproducts, are particularly vulnerable to adverse effects. Individuals beginning protein supplementation, especially those who already show signs of kidney or liver impairment, should exercise caution and seek medical supervision. While the functions of these organs are certainly challenged by increased protein consumption, it remains unclear to what extent this may lead to lasting damage and what the safe upper limits of protein intake are. It is also worth emphasizing that whey protein (WP) appears to positively influence the composition and functionality of the gut microbiota, which may translate into improved digestive health and overall well-being. Given the growing popularity and easy availability of protein supplements, further extensive scientific studies are necessary to more precisely evaluate both their benefits and potential negative health effects. Only through such research will it be possible to develop effective and safe guidelines for protein supplementation.

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Authors Contribution:

Conceptualization: Bartłomiej Czerwiec, Julia Skowrońska- Borsuk; Methodology: Bartłomiej Czerwiec, Julia Skowrońska- Borsuk, Martyna Narożniak, Adam Borsuk, Malwina Wojtas; Software: Bartłomiej Czerwiec, Martyna Narożniak, Adam Borsuk; Check: Julia Skowrońska- Borsuk, Adrianna Ewa Pękacka, Joanna Pergoł, Bartłomiej Czerwiec, Julia Sposób; Formal Analysis: Bartłomiej Czerwiec, Julia Skowrońska- Borsuk, Joanna Pergoł, Malwina Wojtas, Julia Borkowska, Zuzanna Krupa; Investigation: Bartłomiej Czerwiec, Julia Skowrońska- Borsuk, Martyna Narożniak, Julia Borkowska, Julia Sposób; Resources: Bartłomiej Czerwiec, Julia Skowrońska- Borsuk, Adrianna Ewa Pękacka; Writing-rough preparation: Bartłomiej Czerwiec, Joanna Pergoł, Malwina Wojtas, Adrianna Ewa Pękacka, Zuzanna Krupa; Writing-review and editing: Adam Borsuk, Joanna Pergoł, Adam Borsuk; Visualization: Bartłomiej Czerwiec, Adam Borsuk, Julia Sposób; Supervision: Bartłomiej Czerwiec, Julia Skowrońska- Borsuk

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