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Protein supplementation: the double-edged sword

Vishw Patel, MBBS[a], Kanishk Aggarwal, MBBS[b], Ashish Dhawan, MBBS[c], Bhupinder Singh, MBBS[d], Priyanshi Shah, MBBS[e], Aanchal Sawhney, MD[f], and Rohit Jain, MD[g]

[a]Department of Medicine, Pandit Deendayal Upadhyay Government Medical College, Rajkot, India; [b]Department of Medicine, Dayanand Medical College and Hospital, Ludhiana, Punjab, India; [c]Department of Medicine, Gian Sagar Medical College and Hospital, Punjab, India; [d]Department of Medicine, Government Medical College, Amritsar, India; [e]Department of Medicine, Narendra Modi Medical College, Ahmedabad, India; [f]Department of Internal Medicine, Crozer Chester Medical Center, Upland, Pennsylvania, USA; [g]Department of Medicine, Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania, USA

ABSTRACT

Protein supplements are widely consumed by athletes as well as young adults and teenagers going to the gym and are an excellent source to increase protein intake, build muscle mass, and enhance recovery. They are available in the form of powders, gummies, protein bars, and ready-to-drink shakes and have been shown to have effects on almost every system in the body. Subjects consuming whey protein–based supplements regularly show significantly lower systolic blood pressure, while subjects who consume soy-based protein supplements have been reported to show a significant decrease in their systolic and diastolic blood pressures. Favorable effects of soy protein consumption have been observed on the serum lipid profile, with significant decreases in serum low-density lipoprotein and triglyceride levels. Lower postprandial glucose levels have been observed in diabetic subjects as well, which can be attributed to the lower glycemic index of these supplements. This can lead to an indirect decrease in diabetes-related complications. While these supplements affect the body positively, caution has to be exercised while consuming them in excess, as they have been shown to cause hyperfiltration and increased urinary calcium excretion which can, in turn, lead to chronic kidney disease development. This article focuses on the effects of protein supplementation on the human body, with emphasis on the cardiovascular, endocrine, and renal systems.

KEYWORDS Dietary supplements; exercise; soy protein; whey protein

Protein supplements are processed protein formulations that are widely used to supplement or increase protein intake to enhance performance, recovery, and muscle mass.[1] These supplements are popularly used and advertised by athletes, though their consumption is widely seen in young adults and teenagers going to the gym.[1] Protein supplements are available in different formulations such as powders, gummies, protein bars, and ready-to-drink shakes[2] and they can also be categorized based on the source of protein like whey, casein, egg albumin, carnivore (beef), and vegan (pea and soy). The majority of these protein supplements are further classified as concentrate, isolate, and hydrolysate based on the processing and concentration of protein.[3,4] Another very popular category of protein supplements is the amino-acid supplement, which contains individual amino acids or a combination of amino acids like branched-chain amino acids (BCAA) and essential amino acids.[5]

Among the different formulations of protein supplements in the market, protein powders have dominated with a revenue share of 56% in 2021.[6] However, ready-to-drink protein is expected to grow faster with a compound annual growth rate of 8.5%. On the other hand, plant-based protein supplements are expected to grow as an individual niche at a compound annual growth rate of 8.7%.[6] This is due to the increasing popularity of vegan or plant-based diets.

Protein supplements are widely available at supermarkets, retail shops, and e-commerce websites under popular brands such as Optimum Nutrition, MusclePharm, Pure Protein, Dymatize, etc. The growth of the protein supplement industry is mainly due to increasing health awareness and the easy availability of supplements in different formulations.[2] The

Corresponding author: Priyanshi Shah, MBBS, 131, Block 3, LB Avenue, College Road, Nadiad, Ahmedabad 387001, India (e-mail: priyanshishah3010@gmail.com)
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protein supplement industry in the US had a total revenue of $2,069.3 million in 2021, and the industry is expected to grow further with increased acceptance of food supplementation and improved sports and fitness infrastructures. By 2030, it is anticipated that the market for protein supplements will be worth $10.80 billion.[6]

The amount and timing of consumption of protein supplements are considered to play a role in muscle hypertrophy and recovery. Several studies reported that protein consumption after a workout provides greater benefits in increasing protein synthesis and muscle hypertrophy.[7] Therefore, it is a common practice among bodybuilders to consume fast-digesting protein supplements such as whey protein immediately after exercise. In contrast, other studies have suggested that consuming protein before resistance exercise is more beneficial, as it is reported to increase protein synthesis by replenishing amino acids even before a workout session.[8]

According to international consensus, the daily reference intake of protein for the healthy adult population is 0.8 g/kg body weight.[9,10] However, individuals who engage in physical activity may require more protein, ranging from 1.2 to 2 grams per kilogram of body weight.[11] To fulfill these requirements, many athletes and active individuals opt for whey protein (WP) supplements to increase their protein intake. The appropriate amount of WP intake for individuals depends on their objectives, current level of physical activity, and body composition. Research suggests that a dosage of 20 to 25 g/day of WP provides the desired benefits, while amounts >40 g/day may lead to adverse effects on the body.[12,13]

It is also important to consider that a container of protein supplement contains not only protein but also various amounts of sugars, additives, and preservatives, which are added to enhance flavor and increase shelf life. For example, a supplement of WP concentrate may contain more than 25% (up to 80%) of protein by weight. The remaining percentage may comprise fat, lactose, added sugar, and preservatives.[14] This review aims to unfold the effects of protein supplements and their components on the human body.

PATHOPHYSIOLOGY

Protein supplement consumption is known to cause decreased weight gain and fat deposition and improve insulin sensitivity in the human body. WPs are a tremendous source of BCAA, like leucine, isoleucine, valine, lysine, and threonine, which can induce insulin secretion.[15] Enzyme glutamate dehydrogenase in β cells of the pancreas is activated by various amino acids like leucine, leading to increased Krebs cycle activity and oxygen consumption, causing increased insulin production. In addition, these particular amino acids, like leucine, have been found to regulate adenosine monophosphate-activated protein kinase and mammalian target of rapamycin (mTOR), leading to a decrease in the expression of hunger-stimulating neuropeptides and an increase in appetite-reducing neuropeptides, which may improve postprandial hyperglycemia.[16,17] Glutamate, alanine, and cysteine have been observed to enhance insulin secretion by amplifying the effects of glucose stimulation.[15,18] Certain peptides found in dairy protein have the potential to enhance insulin secretion by hindering the activity of dipeptidyl peptidase-4 in the proximal gut, consequently preventing the breakdown of the incretin hormones gastric inhibitory polypeptide and glucagon-like peptide-1 (GLP-1).

Whey is a source of bioactive compounds like immunoglobulins, lactoferrin, α-lactalbumin, and glutamine, which have been proven to boost the levels of incretin hormones and restrict the activity of dipeptidyl peptidase-4, ultimately resulting in increased sensitivity of β-cells to glucose, promoting β-cell growth, and safeguarding against apoptosis.[17,19,20] In addition, GLP-1 also slows down the emptying of the stomach by relaxing the upper part of the stomach, decreasing movement of the antrum, and increasing the tone of the pylorus. This helps regulate energy intake and prevent glucagon secretion, improving glycemia after a meal. Whey consumption has been shown to upregulate gut peptide hormones such as cholecystokinin, polypeptide YY, GLP-1, and glycosylphosphatidylinositol, decreasing appetite and significantly impacting satiety. Consuming high-protein meals has been suggested to increase the production of polypeptide YY and provide a greater feeling of fullness in both overweight and normal-weight people. Ghrelin, a peptide that stimulates appetite, decreases after consuming protein, contributing to the feeling of fullness.

Various mechanisms come into play after consuming high-protein meals that stimulate the central nervous system directly through the bloodstream at the level of the hypothalamus or indirectly through the vagus nerve, resulting in reduced weight gain and fat buildup and improved insulin sensitivity in the body.[17,21–23] Studies have shown that whey-derived peptides have antihypertensive properties that primarily work by inhibiting the angiotensin-converting enzyme (ACE) found on the surface of vascular endothelial cells.[24,25] ACE converts angiotensin I to angiotensin II, which is a potent vasoconstrictor. By inhibiting ACE, WP increases the concentration of bradykinin, a potent vasodilator, leading to a more significant vasodilatory effect.[26] Some whey-derived peptides may also enhance nitric oxide production, improving vascular function. Leucine, an amino acid found in various protein supplements, stimulates insulin production, affecting vasodilation and vasoconstriction through its impact on nitric oxide production and bioavailability. Insulin triggers the phosphatidylinositol-3-kinase/protein kinase B pathway, increasing nitric oxide production, leading to vasodilation and improved vascular function.[24,27,28]

WP contain high levels of cysteine (2.2 g per 100 g of amino acid), providing potential antioxidant properties. Cystine, produced from the oxidation of cysteine, is also essential for producing the antioxidant glutathione.[29] This contribution to glutathione synthesis can alleviate liver damage and ameliorate oxidative stress. Patients with nonalcoholic steatohepatitis who took oral WP isolate supplements experienced improved liver biochemistries, increased plasma glutathione, and reduced hepatic macrovesicular steatosis.[30] Recent studies have also suggested that WP components can positively affect patients suffering from hepatitis C and B, so that it may be used as supplemental therapy. In patients suffering from hepatitis B, lactoferrin is thought to exert its effect on the modification of hepatitis B virus and hepatitis C virus infections by interacting with host cell molecules, preventing the virus from adhering to and entering the cells. Thus, lactoferrin may be considered a reagent that could effectively treat patients with chronic hepatitis.[31]

In addition, WP components like α-lactalbumin and β-lactoglobulin have a preeminent ability to reduce markers of the inflammatory response, such as monocyte chemotactic protein-1 and chemokine ligand-5, and suppress the production of the inflammatory cytokine interleukin-6, thus inhibiting the significant monocyte migration across the endothelial lumen, a crucial early step in atherosclerotic plaque formation.[24,32] Several studies have shown the potential benefits of protein supplementation in treating cancer-related cachexia, which causes progressive muscle and adipose tissue atrophy; thus, protein supplementation is often recommended for these patients.[33] WP, in particular, contains high levels of leucine and other essential amino acids, crucial for muscle protein synthesis and preservation of lean body mass.[34] Leucine stimulates the production of insulin, a hormone related to the activation of the mTOR pathway, which is essential for myofibrillar protein synthesis and subsequent signaling. In cancer cells, mTOR exhibits a heightened activation as a result of the pathophysiological process, thereby fostering a favorable environment for cellular growth, proliferation, and cell survival.[33] WP is a promising treatment for patients with immunity-related diseases because it can help regulate the immune system by significantly increasing lymphocyte proliferation and human neutrophil responses.[31,35] WP can modulate the immune system and has antibacterial, antiviral, and antifungal properties. Even though there are obvious documented advantages of adding WP to the diet, its excessive use can adversely affect long-term health, including increased acne, dysfunction of microbiota, and changes to kidney and metabolism.[13]

Dietary protein intake plays a significant role in determining the workload of the kidneys, affecting glomerular filtration. Several experimental and clinical studies have confirmed that protein intake impairs renal function due to the hyperfiltration response after protein intake.[36] Intake of high amounts of protein brings about a sudden increase in glomerular filtration rate (GFR) and renal blood flow, up to 100% from the baseline. Some studies have shown that GFR and renal blood flow are directly proportional to the protein consumed, often causing glomerular injury by increasing intraglomerular pressures and flow, leading to progressive glomerular injury and sclerosis in preexisting diseased or damaged kidneys.[37] However, the long-term effects of chronic protein intake on healthy kidneys are poorly understood.

Long-term high-protein intake may accelerate renal function decline in those with preexisting chronic kidney disease (CKD) who consume at least 90 g/day of protein. A study showed that a diet supplemented with short-term WP increased plasma urea, urinary volume, and calcium excretion while decreasing pH and urinary citrate. Low urinary pH, hypocitraturia, and hypercalcemia increase the risk of nephrolithiasis.[13,38] Therefore, for those suffering from CKD, reducing protein intake can help reduce hyperfiltration and slow the progression of chronic nephropathies. In addition to decreasing hyperfiltration, decreasing protein intake lowers uremic toxins and alleviates uremic symptoms.[39]

Supplementation with a high-protein plant-based diet has been observed to decrease mortality in patients suffering from CKD.[40] The difference in their effects on kidney function can be attributed to a difference in the amino acid composition of the plant vs. animal-based protein supplement. Individuals who consumed plant protein had increased proportions of cysteine, proline, glutamic acid, phenylalanine, and serine compared to individuals consuming animal-based protein.[41] In addition to different amino acid compositions, plant-based proteins also affect cholesterol metabolism. High plant-based protein intake lowers serum low-density lipoprotein (LDL), triacylglycerol, and uric acid.[42] Similarly, soy protein intake significantly reduces serum total cholesterol, LDL, and triglycerides.[43] Reduced levels of these lipids can help to attenuate oxidized lipoprotein-induced glomerular damage and progression of CKD.[44]

Another factor affecting CKD progression in patients taking animal-based proteins is the predominance of acid precursors in them, leading to a higher estimated net endogenous acid production associated with a net loss of GFR.[44] On the contrary, plant-based proteins predominantly have base precursors,[45] showing a decreased risk of a composite of dialysis, death, or a GFR event.[46] Uremic toxins have been implicated in CKD progression, cardiovascular disease, and mortality in patients with kidney disease, and plant-based proteins are associated with a decreased production of uremic toxins like p-cresyl sulfate and indoxyl sulfate. Several studies have been conducted to determine the effectiveness of soy protein in treating kidney disease, with conflicting results. Some studies show that a soy protein diet reduces proteinuria. In contrast, others show no difference between soy and meat diets.

Soy protein is the only high-quality plant-based protein widely available, and it contains essential amino acids. Various studies have found that soy protein consumption can reduce serum creatinine, serum phosphorus, and triglyceride concentrations compared to animal protein. In addition, consuming at least 25 g/day of soy protein decreased total cholesterol and LDL cholesterol in nephrotic patients with proteinuria. In contrast, Anderson et al found that a soy diet increased urine protein excretion compared to an animal protein diet in patients with type 2 diabetes. Isoflavones may play a key role, as shown by Texeira et al, who found that urinary albumin-creatinine ratios were inversely correlated with plasma isoflavone concentrations. Overall, soy diets are safe for the kidneys and could potentially reduce the decline of glomerular filtrate and the progression of proteinuria in the long term.[47]

Despite convincing research showing the importance of plant-based proteins in CKD patients, caution needs to be exercised when interpreting these results, as it is difficult to establish if the results can be attributed to the plant protein itself or to the higher polyunsaturated and lower saturated fatty acid, or higher fiber levels. Thus, additional interventional studies need to be carried out to fully understand plant proteins' effects in patients suffering from CKD. According to the nutritional guidelines in CKD (K-DOQI 2020), to reduce the risk of end-stage kidney disease in adults with CKD 3–5 (who are not on dialysis) and are metabolically stable, it is recommended to follow a low-protein diet that provides 0.55 to 0.60 g of dietary protein per kilogram of body weight per day. Alternatively, a very low-protein diet can be followed, providing 0.28 to 0.43 g of dietary protein per kilogram of body weight per day with additional keto acid/amino acid. For adults with CKD 3–5 who have diabetes, it is reasonable to maintain a stable nutritional status and optimize glycemic control by prescribing a dietary protein intake of 0.6 to 0.8 g per kilogram of body weight per day under close clinical supervision.[48]

Research has shown that chronic protein supplementation may increase the expression of anger and acne in athletes. Studies have shown that BCAAs in WP compete with tryptophan and reduce serotonin synthesis, a neurotransmitter linked to impulsivity and depression, potentially causing anger-related symptoms. WP containing insulin-like growth factor-1, associated with promoting cell growth and division, sebum production, and increased estrogen factors, could explain the association between the high consumption of WP products and acne.[13,39] While WP is generally considered easily digestible and beneficial, it contains components like beta-lactoglobulin that can cause allergies, particularly in children who are intolerant to cow's milk. Symptoms of WP allergy may include atopic dermatitis, respiratory problems such as asthma and coughing, gastrointestinal discomfort, and even life-threatening anaphylactic reactions in infants. Fortunately, specific processing methods, like heat treatment above 90°C and enzymatic hydrolysis, have been found to reduce the allergenicity of WP.[31,49]

High-protein diets can significantly influence the composition and function of the microbiota by causing amino acid fermentation in the colon. This fermentation process leads to the production of potentially harmful metabolites, including ammonia, amines, phenols, and sulfides. These metabolites can have detrimental effects on the overall health and metabolism of the host.[50,51] Specifically, compounds like P-cresol, phenols, and hydrogen sulfide are known to play roles in conditions such as irritable bowel disease, colon cancer, increased intestinal permeability, inflammation, and DNA damage.[52]

DISCUSSION

Protein supplements were initially designed to provide athletes and bodybuilders with an extra source of protein, but they are now being used in the dietary management of patients with various medical conditions, such that researchers have been studying the effects of protein supplementation on health *(Figure 1)*. An increase in the muscle protein synthesis and an improvement in the net protein balance are observed in patients who exercise regularly and consume protein supplements. In addition to muscle growth, a meta-analysis also determined that the supplements have a small to moderate effect on muscle recovery.[53] Soy protein supplements, a type of plant protein, have come on the market, and their efficacy in stimulating myofibrillar protein synthesis has been compared to animal protein supplements. The myofibrillar protein synthesis rates demonstrated by soy proteins were lower than those demonstrated by milk, beef, or WP. The proposed decreased anabolic capacity of the plant-based protein is thought to be due to either a difference in amino acid composition or differing amino acid absorption/kinetics.[34] However, additional research remains necessary to compare the effects of other plant and animal proteins.

Supplementation with protein has been shown to yield beneficial outcomes for both cardiovascular and metabolic risk factors. Studies analyzing the effect of WP on hypertension reported significantly lower systolic blood pressure readings in prehypertensive and mildly hypertensive overweight individuals than the control group (126.5 ± 6.9 mm Hg vs. 128.8 ± 7.4 mm Hg, $P = 0.033$).[54] A similar effect was seen with soy protein consumption, with a mean decrease of 2.21 mm Hg for systolic blood pressure (95% confidence interval [CI] − 4.10 to −0.33; $P = 0.021$) and 1.44 mm Hg (95% CI −2.56 to −0.31; $P = 0.012$) for diastolic blood pressure.[55] Also, investigations into soy proteins have revealed reductions in serum LDL by 4.76 mg/dL (95% CI −6.71 to −2.80 mg/dL; $P < 0.0001$) and total cholesterol levels by 6.41 mg/dL (95% CI −9.30 to −3.52 mg/dL; $P < 0.0001$).[56] Another meta-analysis of WP supplementation in the diabetic population revealed significantly lower postprandial glucose levels at 60 minutes (weighted mean deviation −2.67 mmol/L; 95% CI −3.62 to −1.72 mmol/L) and 120 minutes (−1.59 mmol/L; 95% CI −2.91 to −0.28 mmol/L). The incremental area under the insulin curve was significantly higher in the WP group (24.66 nmol/L × min, 1.65–47.66 nmol/L × min) than in the placebo group.[57] Thus, adding protein supplements can improve cardiovascular health by positively impacting blood pressure, lipid levels, and glycemic control. Additionally, the better glycemic control leads to a decrease in diabetes-related complications and mortality rates.

Studies have shown that WP can positively reduce oxidative stress and may play a role in the treatment of hepatitis. For example, 12-week supplementation with 20 g/day of WP isolate in individuals with nonalcoholic steatohepatitis increased glutathione and overall antioxidant capacities. Consuming

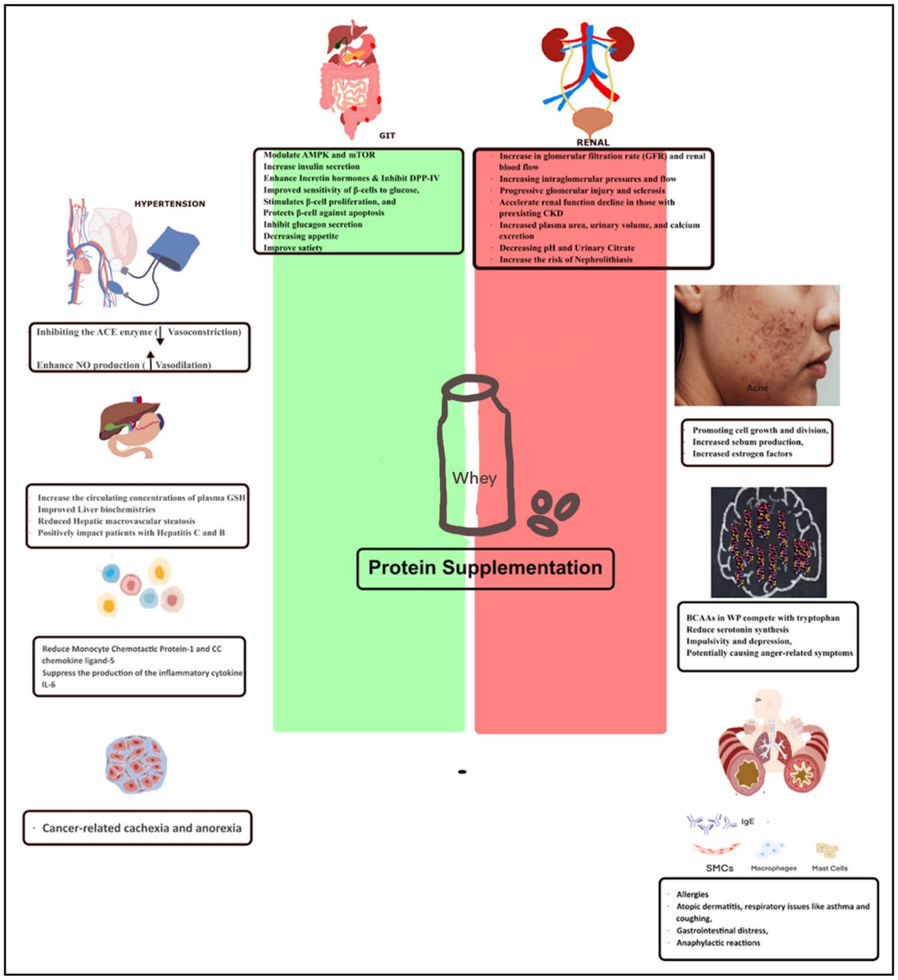

Figure 1. Effects of protein supplementation.

45 g/day of WP in bar format for 14 days in healthy subjects increased lymphocyte glutathione levels. Additionally, feeding patients with ischemic stroke a diet containing WP via a nasogastric tube reduced interleukin-6 and increased glutathione levels after 5 days of supplementation.[58]

In a study carried out by Moreno et al investigating the effect of protein supplementation on athletes' gut microbiota, no significant alterations in microbiota diversity were noted, but there was an observed increase in the abundance of *Bacteroidetes* phylum, linked to proteolytic activity. Conversely, health-related taxa such as *Roseburia, Blautia,* and *Bifidobacterium longum* showed a decreased presence. This suggests that prolonged protein supplementation may have an adverse effect on the composition of the gut microbiota.[59] In contrast, in an observational study involving rugby players whose protein intake accounted for 22% of their total energy intake, a decrease in the *Bacteroidetes* phylum was observed when compared to the microbiota of healthy controls, whose protein consumption accounted for 15% of their total energy intake.[52] These results depict a potential role of quantity and source of protein supplement as important variables in observing the impact on intestinal microbiota as well. However, a small study set makes it difficult to make any generalized conclusions, and large studies are required to bolster these findings.

WP is a promising treatment for patients with cancer-related cachexia causing progressive muscle and adipose tissue atrophy; thus, protein supplementation is often recommended for patients suffering from cancer-related cachexia. Various studies have shown promising results when patients were supplemented with dietary protein. A study conducted by May et al with patients with solid tumors demonstrated weight loss of >5% supplemented with β-hydroxy-β-methylbutyrate (3 g/day), L-arginine (14 g/day), and L-glutamine (14 g/day [HMB/Arg/Gln]). Compared with controls, over 4 weeks patients who supplemented with HMB/Arg/Gln gained 0.95 ± 0.66 kg of body mass, while the control group lost 0.26 ± 0.78 kg. The HMB/Arg/Gln–supplemented group significantly increased fat-free mass (1.12 ± 0.68 kg). The effect of HMB/Arg/Gln was maintained over 24 weeks (1.60 ± 0.98 kg; $P < 0.05$). No adverse effects of negative effects on quality-of-life measures were observed.[60]

Cancer cachexia is associated with high catabolism, and supplementation with leucine has been proposed due to its significant effect on mTORC1 pathway activation, leading to increased protein synthesis and decreased protein degradation. Multiple preclinical studies on rodents have explored the impact of leucine supplementation in cachectic tumor-bearing hosts. A review of the preclinical literature by Beaudry and Law showed that out of the 14 preclinical studies on cancer cachexia, 13 suggested that leucine-rich feeding can be an effective additive treatment for cancer cachexia. The current preclinical research indicates that leucine supplementation may help reduce skeletal muscle loss by preserving protein synthesis and decreasing protein degradation, attenuating cardiac dysfunction, improving immune competence, preserving energy production capacity, and decreasing inflammation.[61]

Lactoferrin is believed to positively impact the treatment of hepatitis B virus and hepatitis C virus infections. Lactoferrin could be a potential anti-hepatitis agent that effectively treats patients with chronic hepatitis, as shown in a pilot study conducted by Tanaka et al, suggesting that lactoferrin inhibits hepatitis C viremia in patients with chronic hepatitis C. Eleven patients with chronic hepatitis C received an 8-week course of bovine lactoferrin (1.8 or 3.6 g/day). At the end of lactoferrin treatment, a decrease in serum alanine transaminase and hepatitis C virus RNA concentrations was observed in 3 of 4 patients (75%) with low pretreatment serum concentrations of hepatitis C virus RNA. However, seven patients with high pretreatment concentrations showed no significant changes in these indices. This pilot study suggests that lactoferrin is one of the potential candidates for an anti–hepatitis C virus reagent that may be effective in treating patients with chronic hepatitis.[62] Similarly, a study by Koji Hara et al suggests that the interaction of lactoferrin with cells was crucial for its inhibitory effect. Lactoferrin may be a candidate for an anti–hepatitis B virus reagent that could be effective in treating patients with chronic hepatitis.[63]

Some studies have shown that WP supplementation does not adversely affect renal function in healthy individuals.[64] However, it is essential to be cautious, as excessive protein consumption may lead to hyperfiltration (mean deviation 7.18 mL/min/1.73 m^2; 95% CI 4.45 to 9.91; $P < 0.001$) and increased urinary calcium excretion (mean deviation 25.43 mg/24 h; 95% CI 13.62 to 37.24; $P < 0.001$) compared to low protein consumption.[65] This has been associated with a higher risk of proteinuria and CKD in healthy individuals (risk ratio 1.644; 95% CI 1.064 to 2.541).[66] Clinical trials investigating the relationship between protein intake and kidney disease rarely consider the type of protein consumed, whether of animal or plant origin. However, this difference is crucial, as demonstrated by a study from China, which found that a higher intake of red meat was associated with a greater risk of end-stage renal disease.[67] A study conducted by Barsotti et al showed that as patients with nondiabetic nephrosis transitioned from an animal-vegetable diet (1.0–1.3 g/kg/day of protein) to a vegan diet (0.7 g/kg/day), there was a significant decrease in proteinuria.[68] A recent study conducted in Taipei analyzed the relationship between vegetarian diets and CKD prevalence. The study included 55,113 participants, of which 4,236 were vegans, 11,809 were ovo-lacto vegetarians, and 39,068 were omnivores. The study discovered that a vegetarian diet was significantly linked to a lower prevalence of CKD with a lower prevalence of proteinuria.[47] The 2020 update of the Kidney Disease Quality Outcomes Initiative stated that, in order to reduce the risk for end-stage kidney disease, adults with CKD should restrict protein in their diet, with or without keto acid analogues, further bolstering this claim.[48]

In spite of these guidelines, the role of protein restriction in patients with CKD has been debated for decades, with mixed results,[69] since reducing protein intake can also contribute to protein-energy wasting. Furthermore, supplementation of a very low protein diet (VLPD) with ketoanalogues, which are organic compounds that contain groups of carboxylic acid and ketones and can form amino acids after undergoing transamination, is seen to have significant advantages in CKD patients over patients who are on a VLPD only (risk ratio 0.57; 95% CI 0.38 to 0.85).[70] When comparing patients on a low-protein diet with patients on VLPD supplemented with ketoanalogues, a pooling of multiple studies demonstrated a significantly lower relative risk (relative risk 0.63; 95% CI 0.47 to 0.86). The lower risk may not be solely due to the addition of ketoanalogues, as an additional decrease in protein intake in patients on VLPD or a difference in the quality of proteins used in both groups may also affect the outcome.[71] Therefore, the impact of protein and protein supplements on individuals with CKD is a multifaceted issue influenced by several factors, and reducing protein intake may not offer a simple solution for enhancing CKD management.

In addition to these effects on the physiologic processes in the body, use of protein supplements has also been linked to the development of acne.[72] While talking about the effects of protein supplementation, we also need to consider the amount of physical activity carried out by these subjects, since those who consume these supplements regularly are also thought to have a higher activity level than those who do not. For example, there have been established benefits of exercise in the elderly and overweight patients with heart failure with reduced ejection fraction, whereas the effects of protein supplementation in these patients have not been clearly understood and may thus act as a confounding factor when determining the actual role of the supplements.[73] Hence, despite the existing body of literature that substantiates the impacts of protein supplementation on the body, there is a research void concerning its long-term effects and the consideration of various other factors that may also exert an influence on these physiological functions. Consequently, it is crucial to initiate further research that specifically delves into these facets to fully elucidate the comprehensive spectrum of effects these supplements induce in individuals.

CONCLUSION

Protein supplements are commonly used to boost protein intake and enhance performance, recovery, and muscle mass. These supplements are marketed toward athletes but are also frequently consumed by young adults and teenagers who work out. Protein supplementation has positive effects on metabolic and cardiovascular risk factors and better glycemic control in diabetic populations. However, caution is advised regarding potential risks, such as hyperfiltration and increased urinary calcium excretion. Overall, protein supplementation offers several health benefits, but should be approached with a balanced perspective, considering its advantages and potential risks. Continued research will be essential to better comprehend its effects on various health aspects and guide its appropriate use in different populations.

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ORCID

Priyanshi Shah http://orcid.org/0000-0002-1537-2726
Rohit Jain http://orcid.org/0000-0002-9101-2351

1. Samal JRK, Samal IR. Protein supplements: pros and cons. *J Diet Suppl*. 2018;15(3):365–371. doi:10.1080/19390211.2017.1353567.
2. Kårlund A, Gómez-Gallego C, Turpeinen AM, Palo-Oja OM, El-Nezami H, Kolehmainen M. Protein supplements and their relation with nutrition, microbiota composition and health: Is more protein always better for sportspeople? *Nutrients*. 2019;11(4):829. doi:10.3390/nu11040829.
3. Carter BG, Drake MA. Invited review: the effects of processing parameters on the flavor of whey protein ingredients. *J Dairy Sci*. 2018;101(8):6691–6702. doi:10.3168/jds.2018-14571.
4. Lagrange V, Whitsett D, Burris C. Global market for dairy proteins. *J Food Sci*. 2015;80(S1):A16–A22. doi:10.1111/1750-3841.12801.
5. Martinho DV, Nobari H, Faria A, Field A, Duarte D, Sarmento H. Oral branched-chain amino acids supplementation in athletes: a systematic review. *Nutrients*. 2022;14(19):4002. doi:10.3390/nu14194002.
6. Grand View Research. Protein Supplements Market Size, Share Industry Trends Report, 2025. Grandviewresearch.com. Published 2019. https://www.grandviewresearch.com/industry-analysis/protein-supplements-market.
7. Buckley JD, Thomson RL, Coates AM, Howe PR, DeNichilo MO, Rowney MK. Supplementation with a whey protein hydrolysate enhances recovery of muscle force-generating capacity following eccentric exercise. *J Sci Med Sport*. 2010;13(1):178–181. doi:10.1016/j.jsams.2008.06.007.
8. Witard OC, Tieland M, Beelen M, Tipton KD, van Loon LJ, Koopman R. Resistance exercise increases postprandial muscle protein synthesis in humans. *Med Sci Sports Exerc*. 2009;41(1):144–154. doi:10.1249/MSS.0b013e3181844e79.
9. Wu G. Dietary protein intake and human health. *Food Funct*. 2016;7(3):1251–1265. doi:10.1039/c5fo01530h.
10. Phillips SM, Van Loon LJ. Dietary protein for athletes: from requirements to optimum adaptation. *J Sports Sci*. 2011;29(Suppl 1):S29–S38. doi:10.1080/02640414.2011.619204.
11. Thomas DT, Erdman KA, Burke LM. Nutrition and athletic performance. *Med Sci Sports Exerc*. 2016;48(3):543–568.
12. Witard OC, Jackman SR, Breen L, Smith K, Selby A, Tipton KD. Myofibrillar muscle protein synthesis rates subsequent to a meal in response to increasing doses of whey protein at rest and after resistance exercise. *Am J Clin Nutr*. 2014;99(1):86–95. doi:10.3945/ajcn.112.055517.
13. Vasconcelos QDJS, Bachur TPR, Aragão GF. Whey protein supplementation and its potentially adverse effects on health: a systematic review. *Appl Physiol Nutr Metab*. 2021;46(1):27–33. doi:10.1139/apnm-2020-0370.
14. Patel AS, Yeung CK, Brennan C, Zheng H. Ingredients and Formulation. ScienceDirect. Published January 1, 2022. https://www.sciencedirect.com/science/article/abs/pii/B9780128187661001616?via%3Dihub. Accessed July 25, 2023.
15. Newsholme P, Bender K, Kiely A, Brennan L. Amino acid metabolism, insulin secretion and diabetes. *Biochem Soc Trans*. 2007;35(Pt 5):1180–1186. doi:10.1042/BST0351180.
16. Potier M, Darcel N, Tomé D. Protein, amino acids and the control of food intake. *Curr Opin Clin Nutr Metab Care*. 2009;12(1):54–58. doi:10.1097/MCO.0b013e32831b9e01.
17. Lesgards JF. Benefits of whey proteins on type 2 diabetes mellitus parameters and prevention of cardiovascular diseases. *Nutrients*. 2023;15(5):1294. doi:10.3390/nu15051294.
18. Jain SK. L-cysteine supplementation as an adjuvant therapy for type-2 diabetes. *Can J Physiol Pharmacol*. 2012;90(8):1061–1064. doi:10.1139/y2012-087.
19. Bjørnshave A, Hermansen K. Effects of dairy protein and fat on metabolic syndrome and type 2 diabetes. *Rev Diabet Stud*. 2014;11(2):153–166. doi:10.1900/RDS.2014.11.153.
20. Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. *Cell Metab*. 2013;17(6):819–837. doi:10.1016/j.cmet.2013.04.008.
21. Marathe CS, Rayner CK, Jones KL, Horowitz M. Relationships between gastric emptying, postprandial glycemia, and incretin hormones. *Diabetes Care*. 2013;36(5):1396–1405. doi:10.2337/dc12-1609.
22. Nguyen NQ, Fraser RJ, Bryant LK, et al. The relationship between gastric emptying, plasma cholecystokinin, and peptide YY in critically ill patients. *Crit Care*. 2007;11(6):R132. doi:10.1186/cc6205.
23. Fromentin G, Darcel N, Chaumontet C, Marsset-Baglieri A, Nadkarni N, Tomé D. Peripheral and central mechanisms involved in the control of food intake by dietary amino acids and proteins. *Nutr Res Rev*. 2012;25(1):29–39. doi:10.1017/S0954422411000175.
24. Price D, Jackson KG, Lovegrove JA, Givens DI. The effects of whey proteins, their peptides and amino acids on vascular function. *Nutr Bull*. 2022;47(1):9–26. doi:10.1111/nbu.12543.
25. Fekete AA, Givens DI, Lovegrove JA. The impact of milk proteins and peptides on blood pressure and vascular function: a review of evidence from human intervention studies. *Nutr Res Rev*. 2013;26(2):177–190. doi:10.1017/S0954422413000139.
26. Taddei S, Bortolotto L. Unraveling the pivotal role of bradykinin in ACE inhibitor activity. *Am J Cardiovasc Drugs*. 2016;16(5):309–321. doi:10.1007/s40256-016-0173-4.
27. Adams RL, Broughton KS. Insulinotropic effects of whey: mechanisms of action, recent clinical trials, and clinical applications. *Ann Nutr Metab*. 2016;69(1):56–63. doi:10.1159/000448665.
28. De Nigris V, Pujadas G, La Sala L, Testa R, Genovese S, Ceriello A. Short-term high glucose exposure impairs insulin signaling in endothelial cells. *Cardiovasc Diabetol*. 2015;14(1):114. doi:10.1186/s12933-015-0278-0.
29. Yu X, Long YC. Crosstalk between cystine and glutathione is critical for the regulation of amino acid signaling pathways and ferroptosis. *Sci Rep*. 2016;6(1):30033. doi:10.1038/srep30033.
30. Chitapanarux T, Tienboon P, Pojchamarnwiputh S, Leelarungrayub D. Open-labeled pilot study of cysteine-rich whey protein isolate supplementation for nonalcoholic steatohepatitis patients. *J Gastroenterol Hepatol*. 2009;24(6):1045–1050. doi:10.1111/j.1440-1746.2009.05865.x.
31. Ng TB, Cheung RC, Wong JH, et al. Antiviral activities of whey proteins. *Appl Microbiol Biotechnol*. 2015;99(17):6997–7008. doi:10.1007/s00253-015-6818-4.

32. Holmer-Jensen J, Karhu T, Mortensen LS, Pedersen SB, Herzig KH, Hermansen K. Differential effects of dietary protein sources on postprandial low-grade inflammation after a single high fat meal in obese non-diabetic subjects. *Nutr J*. 2011;10(1):115. doi:10.1186/1475-2891-10-115.
33. Teixeira FJ, Santos HO, Howell SL, Pimentel GD. Whey protein in cancer therapy: a narrative review. *Pharmacol Res*. 2019;144:245–256. doi:10.1016/j.phrs.2019.04.019.
34. van Vliet S, Burd NA, van Loon LJ. The skeletal muscle anabolic response to plant-versus animal-based protein consumption. *J Nutr*. 2015;145(9):1981–1991. doi:10.3945/jn.114.204305.
35. Shute M. 2004. *Effect of Whey Protein Isolate on Oxidative Stress, Exercise Performance, and Immunity* (Doctoral dissertation), Virginia Tech.
36. Carrero JJ, González-Ortiz A, Avesani CM, et al. Plant-based diets to manage the risks and complications of chronic kidney disease. *Nat Rev Nephrol*. 2020;16(9):525–542. doi:10.1038/s41581-020-0297-2.
37. Friedman AN. High-protein diets: potential effects on the kidney in renal health and disease. *Am J Kidney Dis*. 2004;44(6):950–962. doi:10.1053/j.ajkd.2004.08.020.
38. Aparicio VA, Nebot E, Porres JM, et al. Effects of high-whey-protein intake and resistance training on renal, bone and metabolic parameters in rats. *Br J Nutr*. 2011;105(6):836–845. doi:10.1017/S0007114510004393.
39. Melnik BC. Evidence for acne-promoting effects of milk and other insulinotropic dairy products. *Nestle Nutr Workshop Ser Pediatr Program*. 2011;67:131–145. doi:10.1159/000325580.
40. Kelemen LE, Kushi LH, Jacobs DR Jr, Cerhan JR. Associations of dietary protein with disease and mortality in a prospective study of postmenopausal women. *Am J Epidemiol*. 2005;161(3):239–249. doi:10.1093/aje/kwi038.
41. Elliott P, Stamler J, Dyer AR, et al. Association between protein intake and blood pressure: the INTERMAP Study. *Arch Intern Med*. 2006;166(1):79–87. doi:10.1001/archinte.166.1.79.
42. Jenkins DJ, Kendall CW, Vidgen E, et al. High-protein diets in hyperlipidemia: effect of wheat gluten on serum lipids, uric acid, and renal function. *Am J Clin Nutr*. 2001;74(1):57–63. doi:10.1093/ajcn/74.1.57.
43. Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med*. 1995;333(5):276–282. doi:10.1056/NEJM199508033330502.
44. Scialla JJ, Appel LJ, Astor BC, et al. Net endogenous acid production is associated with a faster decline in GFR in African Americans. *Kidney Int*. 2012;82(1):106–112. doi:10.1038/ki.2012.82.
45. Raphael KL, Wei G, Baird BC, Greene T, Beddhu S. Higher serum bicarbonate levels within the normal range are associated with better survival and renal outcomes in African Americans. *Kidney Int*. 2011;79(3):356–362. doi:10.1038/ki.2010.388.
46. Knight EL, Stampfer MJ, Hankinson SE, Spiegelman D, Curhan GC. The impact of protein intake on renal function decline in women with normal renal function or mild renal insufficiency. *Ann Intern Med*. 2003;138(6):460–467. doi:10.7326/0003-4819-138-6-200303180-00009.
47. Ria P, De Pascalis A, Zito A, et al. Diet and proteinuria: state of art. *Int J Mol Sci*. 2022;24(1):44. doi:10.3390/ijms24010044.
48. Ikizler TA, Burrowes JD, Byham-Gray LD, et al. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. *Am J Kidney Dis*. 2020;76(3 Suppl 1):S1–S107. doi:10.1053/j.ajkd.2020.05.006.
49. Botteman M, Detzel P. Cost-effectiveness of partially hydrolyzed whey protein formula in the primary prevention of atopic dermatitis in high-risk urban infants in Southeast Asia. *Ann Nutr Metab*. 2015;66(Suppl. 1):26–32. doi:10.1159/000370222.
50. Portune KJ, Beaumont M, Davila A-M, Tomé D, Blachier F, Sanz Y. Gut microbiota role in dietary protein metabolism and health-related outcomes: the two sides of the coin. *Trends in Food Science & Technology*. 2016;57:213–232. doi:10.1016/j.tifs.2016.08.011.
51. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*. 2014;505(7484):559–563. doi:10.1038/nature12820.
52. Clarke SF, Murphy EF, O'Sullivan O, et al. Exercise and associated dietary extremes impact on gut microbial diversity. *Gut*. 2014;63(12):1913–1920. doi:10.1136/gutjnl-2013-306541.
53. Saracino PG, Saylor HE, Hanna BR, Hickner RC, Kim JS, Ormsbee MJ. Effects of pre-sleep whey vs. plant-based protein consumption on muscle recovery following damaging morning exercise. *Nutrients*. 2020;12(7):2049. doi:10.3390/nu12072049.
54. Yang J, Wang HP, Tong X, et al. Effect of whey protein on blood pressure in pre- and mildly hypertensive adults: a randomized controlled study. *Food Sci Nutr*. 2019;7(5):1857–1864. doi:10.1002/fsn3.1040.
55. Dong JY, Tong X, Wu ZW, Xun PC, He K, Qin LQ. Effect of soya protein on blood pressure: a meta-analysis of randomised controlled trials. *Br J Nutr*. 2011;106(3):317–326. doi:10.1017/S0007114511000262.
56. Blanco Mejia S, Messina M, Li SS, et al. A meta-analysis of 46 studies identified by the FDA demonstrates that soy protein decreases circulating LDL and total cholesterol concentrations in adults. *J Nutr*. 2019;149(6):968–981. doi:10.1093/jn/nxz020.
57. Chiang SW, Liu HW, Loh EW, et al. Whey protein supplementation improves postprandial glycemia in persons with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *Nutr Res*. 2022;104:44–54. doi:10.1016/j.nutres.2022.04.002.
58. Sousa GT, Lira FS, Rosa JC, et al. Dietary whey protein lessens several risk factors for metabolic diseases: a review. *Lipids Health Dis*. 2012;11(1):67. doi:10.1186/1476-511X-11-67.
59. Moreno-Pérez D, Bressa C, Bailén M, et al. Effect of a protein supplement on the gut microbiota of endurance athletes: a randomized, controlled, double-blind pilot study. *Nutrients*. 2018;10(3):337. 10 doi:10.3390/nu10030337.
60. May PE, Barber A, D'Olimpio JT, Hourihane A, Abumrad NN. Reversal of cancer-related wasting using oral supplementation with a combination of β-hydroxy-β-methylbutyrate, arginine, and glutamine. *Am J Surg*. 2002;183(4):471–479. doi:10.1016/s0002-9610(02)00823-1.
61. Beaudry AG, Law ML. Leucine supplementation in cancer cachexia: mechanisms and a review of the pre-clinical literature. *Nutrients*. 2022;14(14):2824. doi:10.3390/nu14142824.
62. Tanaka K, Ikeda M, Nozaki A, et al. Lactoferrin inhibits hepatitis C virus viremia in patients with chronic hepatitis C: a pilot study. *Jpn J Cancer Res*. 1999;90(4):367–371. doi:10.1111/j.1349-7006.1999.tb00756.x.
63. Hara K, Ikeda M, Saito S, et al. Lactoferrin inhibits hepatitis B virus infection in cultured human hepatocytes. *Hepatol Res*. 2002;24(3):228–235. doi:10.1016/s1386-6346(02)00088-8.
64. Santesso N, Akl EA, Bianchi M, et al. Effects of higher- versus lower-protein diets on health outcomes: a systematic review and meta-analysis. *Eur J Clin Nutr*. 2012;66(7):780–788. doi:10.1038/ejcn.2012.37.
65. Schwingshackl L, Hoffmann G. Comparison of high vs. normal/low protein diets on renal function in subjects without chronic kidney disease: a systematic review and meta-analysis. *PLoS One*. 2014;9(5):e97656. doi:10.1371/journal.pone.0097656.
66. Oh SW, Yang JH, Kim MG, Cho WY, Jo SK. Renal hyperfiltration as a risk factor for chronic kidney disease: a health checkup cohort study. *PLoS One*. 2020;15(9):e0238177. doi:10.1371/journal.pone.0238177.
67. Lew QJ, Jafar TH, Koh HW, et al. Red meat intake and risk of ESRD. *J Am Soc Nephrol*. 2017;28(1):304–312. doi:10.1681/ASN.2016030248.
68. Barsotti G, Morelli E, Cupisti A, Meola M, Dani L, Giovannetti S. A low-nitrogen low-phosphorous vegan diet for patients with chronic renal failure. *Nephron*. 1996;74(2):390–394. doi:10.1159/000189341.

69. Obeid W, Hiremath S, Topf JM. Protein restriction for CKD: time to move on. *Kidney360*. 2022;3(9):1611–1615. doi:10.34067/KID.0001002022.

70. Hahn D, Hodson EM, Fouque D. Low protein diets for chronic kidney disease in non diabetic adults. *Cochrane Database Syst Rev*. 2020;10(10):CD001892. doi:10.1002/14651858.CD001892.pub3.

71. Garneata L, Stancu A, Dragomir D, Stefan G, Mircescu G. Ketoanalogue-supplemented vegetarian very low-protein diet and CKD progression. *J Am Soc Nephrol*. 2016;27(7):2164–2176. doi:10.1681/ASN.2015040369.

72. Cengiz FP, Cevirgen Cemil B, Emiroglu N, Gulsel Bahali A, Onsun N. Acne located on the trunk, whey protein supplementation: Is there any association? *Health Promot Perspect*. 2017;7(2):106–108. doi:10.15171/hpp.2017.19.

73. Azhar G, Raza S, Pangle A, et al. Potential beneficial effects of dietary protein supplementation and exercise on functional capacity in a pilot study of individuals with heart failure with preserved ejection fraction. *Gerontol Geriatr Med*. 2020;6:2333721420982808. doi:10.1177/2333721420982808.