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High-protein diet: biochemical mechanisms, metabolic effects and clinical implications – a narrative review

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Abstract

Background: High-protein diets are widely used for weight reduction, body composition improvement, and metabolic health. Although effective, concerns remain regarding their long-term safety. This review summarizes current evidence on their benefits and risks.

Materials and methods: A narrative review of randomized controlled trials, systematic reviews, meta-analyses, and observational studies evaluated the effects of high-protein diets on metabolic health and potential adverse outcomes.

Results: High-protein diets promote weight loss by increasing satiety, thermogenesis, energy expenditure, and preserving fat-free mass. They improve appetite regulation through increased GLP-1 and GIP secretion and reduced ghrelin levels. Benefits are particularly evident in individuals with obesity, insulin resistance, or type 2 diabetes. However, excessive long-term intake, especially from animal sources, may increase renal workload, nephrolithiasis, hyperuricemia, nutritional deficiencies, and possibly cardiovascular risk. Evidence regarding cancer remains inconclusive.

Conclusions: When appropriately planned and individualized, high-protein diets are effective for short- and medium-term weight management. Their long-term safety depends on protein source, dietary quality, and individual health status. Further long-term studies are needed to define their role in clinical practice.

Keywords: High-protein diet; weight loss; diet-induced thermogenesis; GLP-1; ghrelin; satiety; kidney function; hyperuricemia; cardiovascular health; bone health; metabolic health; narrative review.

1.Introduction

High-protein diets have gained significant attention in recent years, both in the scientific community and popular culture, as a potential means to support weight management, muscle development, and overall health. The increasing popularity of such diets, particularly among athletes, bodybuilders, and individuals aiming for weight loss, underscores the need to better understand their health implications. While many studies highlight the potential benefits of high-protein diets, such as enhanced satiety, improved metabolic rate, and better body composition, concerns have also been raised regarding their long-term effects on kidney function, cardiovascular health, and bone density. This review aims to provide a comprehensive overview of the health benefits and risks associated with high-protein diets, critically examining current research to offer a balanced perspective for both clinicians and individuals considering this dietary approach.

2.1 Loss of body weight and enhanced satiety

Protein intake is essential for the proper functioning of the human body. The World Health Organization recommends a minimum daily intake of 0.83 grams per kilogram of body weight [1]. Studies have shown that a high-protein diet may provide additional metabolic benefits. Among these benefits are maintaining proper body mass while preserving lean body mass and reducing body fat [2]. It has been demonstrated that a high-protein diet increases feelings of

fullness. A study was conducted to assess subjective hunger between meals. Using the Visual Analogue Scale (VAS) to measure subjective feelings of hunger and satiety, it was shown that consuming a high-protein meal, compared to a high-fat meal, provided a greater sense of satiety [3]. Improved weight regulation observed during high-protein diets is thought to result, at least in part, from endocrine adaptations that enhance satiety and reduce subsequent energy intake. Protein-rich meals stimulate the secretion of incretin hormones, including GLP-1 and GIP, which contribute to enhanced satiety and improved postprandial glucose regulation [4]. GIP and GLP-1, as incretin hormones, play a role in regulating blood glucose levels through insulin secretion. GLP-1 is also important for maintaining proper body weight, as it delays gastric emptying and slows intestinal motility via the vagus nerve pathway, thereby reducing food intake [5, 6]. Due to their effects on appetite regulation and glycemic control, GLP-1 receptor agonists have become an established therapy for type 2 diabetes and are increasingly used in obesity management [7]. A high-protein diet is also associated with reduced ghrelin secretion, which is a peptide that stimulates growth hormone release and appetite [4, 8]. Ghrelin has orexigenic effects through hypothalamic pathways that regulate appetite and also acts peripherally to promote fat accumulation in the body [9]. These hormonal regulations may result in increased control over body weight. In recent years, the impact of a high-protein diet on thermogenesis has been studied. Diet-Induced Thermogenesis (DIT) is the thermal effect caused by food intake; in other words, it is the metabolic response to food consumption. The transient increase in energy expenditure is due to the multi-step processing of ingested nutrients [4]. In most studies, DIT is quantified as the increase in energy expenditure following meal consumption above baseline energy expenditure. It is, along with the basal metabolic rate and the energy cost of physical activity, one of the three components of daily energy expenditure [10]. It has been demonstrated that compared to a diet with lower protein content, a high-protein diet increases thermogenesis and energy expenditure, with increased thermogenesis having a significant impact on the feeling of fullness [11]. Evidence for this comes from a study conducted on young women aged 19-22 years, who were given a high-protein diet for one day and a high-carbohydrate diet for one day, each separated by either 28 or 56 days. After each diet, various parameters, including body temperature and resting energy expenditure, were measured. Postprandial thermogenesis was approximately twice as high on the high-protein diet compared to the high-carbohydrate diet. Additionally, body temperature was higher after high-protein meals [12]. The proteins in food, by increasing satiety associated with DIT, play an important role in maintaining appropriate body weight [11].

2.2 Enhancement of mental health

It's well-established that our everyday diet influences our overall well-being and can affect mental health. The rising rates of anxiety and depression appear to be associated with modern lifestyle changes, which often result in insufficient time to follow a balanced and nutritious diet [13, 14].

A high-protein diet may contribute to improved well-being in some individuals. Observational studies have reported an association between total dietary protein intake and a lower risk of depressive symptoms [15]. Protein is essential for the synthesis of neurotransmitters such as

serotonin, dopamine, and norepinephrine, which play a crucial role in mood and emotional regulation. Amino acids, which are the building blocks of proteins, serve as precursors for these neurotransmitters. Adequate dietary amino acid intake may contribute to neurotransmitter synthesis and potentially influence nervous system function [16, 17]. Higher-protein diets may support weight loss, which may indirectly contribute to improved emotional well-being through improvements in metabolic health and body weight. In overweight and obese adults following an energy-restricted diet, improvements in subjective sleep quality were also reported, although these improvements were not specifically attributable to the higher protein intake [18]. A high-protein diet can support the maintenance of a healthy body weight by preserving lean muscle mass and reducing body fat [2]. Weight loss in individuals with overweight or obesity, as well as maintaining a healthy body weight, has a positive impact on well-being [19].

A notable group being studied regarding the impact of a high-protein diet on well-being is women with polycystic ovary syndrome (PCOS). Polycystic ovary syndrome is a heterogeneous metabolic and endocrine disorder. The symptoms are caused by androgen excess and ovarian dysfunction [20]. PCOS is also associated with the presence of comorbid conditions such as infertility and obstetric complications, as well as cardiovascular and metabolic diseases like type 2 diabetes. Women with PCOS also have a higher BMI and are more likely to experience overweight and obesity. PCOS is also characterized by the presence of hyperinsulinemia and insulin resistance [21, 22]. Research indicates that women with polycystic ovary syndrome are also at a higher risk for atherosclerosis, and high blood pressure [21]. Numerous studies have identified a connection between PCOS and chronic low-grade inflammation, with evidence showing that inflammatory markers are often elevated in individuals with this condition [23].

It has been shown that a high-protein meal causes less hyperinsulinemia and smaller fluctuations in blood glucose levels compared to glucose consumption. Compared with a high-protein meal, glucose ingestion has been associated with greater cortisol secretion. Cortisol is a hormone released by the adrenal cortex that increases lipolysis in adipose tissue and raises free fatty acid levels. In the presence of hyperinsulinemia, these fatty acids are stored in intra-abdominal fat depots, leading to central obesity. Free fatty acids are also used to produce triglycerides, which results in hyperlipidemia [24]. Higher protein intake may contribute to improved hormonal and metabolic outcomes in women with PCOS as part of a comprehensive lifestyle intervention [25]. Hyperandrogenism triggers insulin resistance and elevated blood sugar levels, which contribute to the generation of reactive oxygen species, oxidative stress, and the accumulation of abdominal fat [26]. Hyperandrogenism can lead to symptoms such as obesity, excessive hair growth, acne, and androgenetic alopecia. These symptoms can lead to substantial psychological distress for women and contribute to the development of depression [27]. The difficulties with conception and infertility related to PCOS can also contribute to poor mental health. Women with infertility frequently report higher levels of anxiety and depression, demonstrating that infertility is a major source of stress [28]. Considering the common occurrence of overweight, obesity, and insulin resistance, weight loss can substantially enhance conditions like insulin resistance, high androgen levels, reproductive system disorders, and

fertility in these women [29]. A high-protein diet that supports healthy weight management may indirectly contribute to improved mental health in women with PCOS [25,29].

2.3 Prevention of osteoporosis and maintenance of bone mass

Osteoporosis is a health issue related to skeletal disease. It is characterized by reduced bone mass and structural abnormalities in bone architecture. Osteoporotic changes affect 1 in 3 women and 1 in 5 men over the age of 50, highlighting its global significance [30].

Providing the right nutrients through diet is essential for maintaining proper bone mass, so adequate intake of protein, calcium, and vitamin D is necessary to reduce the risk of osteoporosis and related fractures. Calcium plays a structural role and is essential for the proper development of bones and teeth, so sufficient intake is also important during the growth period. Calcium supplementation has been shown to reduce bone turnover and may contribute to the prevention of osteopenia and osteoporosis. Protein-rich foods such as milk and other dairy products are important dietary sources of both protein and calcium. Adequate protein intake has been associated with enhanced intestinal calcium absorption and may support bone remodeling [2, 30, 31]. In elderly patients, low protein intake is commonly seen in those with hip fractures. Studies show that following orthopedic treatment, supplementation with casein protein can help reduce bone loss, improve muscle strength, lessen medical complications, and decrease the duration of hospital stays [32].

Maintaining bone health requires a well-balanced diet that includes adequate energy, sufficient protein from both plant and animal sources, and adequate calcium and vitamin D intake, combined with regular physical activity. While adequate protein intake supports bone health, excessively high protein intake without sufficient calcium intake may increase urinary calcium excretion. However, current evidence indicates that this does not necessarily translate into adverse effects on bone health when calcium intake is adequate [2,30–33].

2.4 Cancer prevention

Recent studies have explored the relationship between high-protein diets and cancer, yielding mixed results. A study conducted as part of the Swedish Västerbotten Intervention Programme (VIP) in 2013 aimed to assess the association between a low-carbohydrate, high-protein (LCHP) diet and cancer risk in the Swedish population. Participants were categorized into groups based on their LCHP diet scores, and their health was monitored for an average of 9.7 years. Data on macronutrient intake, including carbohydrates, proteins, and fats, as well as their sources (animal vs. plant-based), were analyzed. Overall, no statistically significant associations were found between a low-carbohydrate, high-protein (LCHP) diet and cancer risk in the studied population. However, an increased risk of respiratory system cancers was observed in men with moderate LCHP scores. The study accounted for numerous potential confounding factors such as age, obesity, lifestyle, education, smoking, alcohol consumption, and saturated fat intake, allowing for a more precise analysis of the results. The study highlights

the importance of further research to better understand the impact of diet on health and cancer risk [34].

In another study, a low-carbohydrate, high-protein diet demonstrated the ability to reduce tumor growth and cancer initiation in mice. This was attributed to lower blood glucose, insulin, and lactate levels. The observed reduction in insulin and glucose levels may contribute to reduced cancer cell proliferation, as many tumor cells rely heavily on glucose metabolism. The expression of genes related to metabolism was also altered, reinforcing pathways that limit energy availability to cancer cells. In this mouse model, the LCHP diet slowed the growth of existing tumors and reduced the incidence of newly developing tumors. Although preclinical studies have produced encouraging findings, robust clinical evidence confirming comparable effects in humans is still lacking [35].

A recent cohort study investigated the relationship between a high-protein diet and breast cancer risk. The study found that a high-protein diet may be associated with a reduced risk of breast cancer. The findings suggest that replacing refined carbohydrates and fats with plant-derived protein may be associated with a lower risk of breast cancer; however, further prospective and interventional studies are needed to confirm these findings [36].

Overall, current evidence suggests that high-protein diets may provide several health benefits beyond weight management, including favorable effects on satiety, metabolic regulation, bone health, and selected aspects of mental well-being. However, many of these effects depend on protein source, overall dietary quality, and individual health status, while evidence regarding cancer prevention remains limited and inconclusive [2,4,15,25,33–36].

3.1 Effect on kidneys and hyperuricemia

The high-protein diet, despite its growing popularity, has significant health implications, particularly for individuals predisposed to certain conditions. Early research highlighting the adverse effects of high-protein diets on kidney function dates back to the early 20th century. Autopsies revealed that animals fed large amounts of protein exhibited dilated renal tubules with urine casts and tubular epithelial degeneration. In rabbits fed exclusively soybeans, blood urea levels were three times higher than in the control group. Although James Miller's work from the Department of Pathology at Harvard University Medical School on albino rabbits did not provide definitive evidence of kidney damage, aside from progressive hypertrophy, it was concluded that patients with kidney disease should limit protein intake as much as possible [37]. To this day, numerous studies continue to investigate the impact of high-protein diets on kidney function. It has been shown that increased concentrations of amino acids in the blood lead to increased renal blood flow, resulting in elevated glomerular filtration rate (GFR), a marker of glomerular filtration [38].

Persistent intraglomerular hypertension and glomerular hyperfiltration may increase glomerular permeability and, over time, contribute to structural glomerular injury, particularly in individuals with pre-existing kidney disease [39]. Several long-term studies have demonstrated

that high protein intake may accelerate the decline in kidney function among patients with chronic kidney disease (CKD). The source of dietary protein also appears to play an important role. Higher consumption of red meat has been associated with an increased risk of CKD progression, whereas plant-based protein sources appear to exert less adverse effects on kidney function. Furthermore, animal-based protein intake may alter the composition of the gut microbiota and increase the production of metabolites associated with inflammation and renal dysfunction. High protein intake may also contribute to albuminuria, defined as increased urinary albumin excretion, particularly in susceptible individuals. Although some studies suggest that similar mechanisms may occur in the general population, current evidence remains inconsistent, and most available studies have relatively short follow-up periods, making the long-term effects of high-protein diets difficult to establish conclusively [38].

A prospective study involving approximately 45,000 adult men reported an association between higher intake of animal protein and an increased risk of symptomatic kidney stones [40]. High animal-protein intake may increase urinary calcium and uric acid excretion, both of which are recognized risk factors for kidney stone formation [41]. In addition, animal protein contributes to an increased dietary acid load, reflected by a higher Potential Renal Acid Load (PRAL), which lowers urinary pH and promotes the formation of poorly soluble uric acid [42]. Consequently, high consumption of animal protein may contribute to kidney stone formation, particularly in individuals with pre-existing metabolic disorders or a family history of nephrolithiasis, although additional dietary and metabolic factors also influence this risk [43].

Uric acid is the final product of purine metabolism, and purines are particularly abundant in meat and seafood, which are frequently consumed in high-protein diets. Hyperuricemia is a well-established risk factor for gout, an inflammatory arthritis caused by the deposition of monosodium urate crystals in joints. In addition to impaired renal excretion, increased dietary intake of purine-rich foods may contribute to elevated serum uric acid concentrations [44]. Prospective studies have demonstrated that higher consumption of meat and seafood is associated with an increased risk of gout, whereas dairy products are associated with a lower risk. In contrast, protein derived from plant sources has not been consistently associated with an increased risk of gout [45]. Experimental studies have also shown that a high-protein diet can increase serum uric acid concentrations in animal models. In a chicken model, prolonged hyperuricemia resulted in urate crystal deposition in joint tissues, producing pathological features resembling human gout [44].

The increased serum concentration of urea and other nitrogenous wastes resulting from a high-protein diet also has additional health implications. To excrete these compounds, the body requires increased fluid elimination, which raises the risk of dehydration. This concern is particularly significant for older adults, who may not consistently consume adequate fluids, and for athletes, as intense physical activity leads to heightened sweat production and water loss [46]. Elevated concentrations of uremic toxins have also been hypothesized to contribute to systemic inflammation and endothelial dysfunction, although the underlying mechanisms remain incompletely understood [38].

3.2 Cardiovascular disease

Studies showing the relationship between a high-protein diet and the cardiovascular system are quite controversial, and the results are often contradictory. Of note, however, are researchers from Washington University School of Medicine study from 2020. Besides demonstrating that mice on a high-protein-high-fat diet developed 30% more atherosclerotic plaques than mice on a high-lipid low-protein diet, they also noticed that these plaques are more abundant in dead macrophages than the regular ones. This feature makes a plaque extremely unstable and more prone to rupture. They also took a closer look on how exactly amino-acids lead to the development of unstable atherosclerotic plaque. By following the path amino acid takes after being digested, they came to the conclusion that excess of them activate a protein called mTOR. The signal from mTOR stops macrophages from cleaning up the toxic waste from plaque, which leads to cell death and its accumulation in the plaque [47].

Fifteen years of observation of over 43,000 Swedish women brought quite clear results regarding the risk of cardiovascular diseases depending on diet. The study covered women aged 30-49 - the group that most often seeks effective methods of weight loss and is encouraged to try HPLC (high protein low carbohydrate) diets. When dividing participants into study groups, other risk factors for cardiovascular diseases were taken into account, such as smoking, BMI, alcohol consumption, and physical activity. 5 different cardiovascular outcomes were studied - ischemic heart disease, ischemic stroke, haemorrhagic stroke, subarachnoid haemorrhage, and peripheral arterial disease. Overall, a higher incidence of cardiovascular events was observed among women with higher adherence to low-carbohydrate, high-protein dietary patterns. The results generally did not differ statistically depending on whether the dietary protein was animal or plant-based. It is worth emphasizing that three other studies conducted in Europe also showed an association between HPLC diets and the higher risk of cardiovascular events. Studies conducted in the US, on the other hand, have found no such link. Differences in dietary protein sources and the prevalence of obesity are believed to be the reason for the discrepancies between studies [48].

A recent review published in "Proceedings of the Nutrition Society" by Cambridge University Press summarizes the potential role of high-protein diets in cardiac rehabilitation. The review suggests that high-protein diets may support weight loss and improvements in body composition, which could help reduce the risk of recurrent cardiovascular events and improve physical function, particularly in patients with sarcopenia. Additionally, the reviewed evidence indicates that such diets may contribute to improved glycemic control and blood pressure management in selected patient populations. The authors emphasize that although high-protein diets have potential benefits, they should be appropriately balanced and individually tailored to maximize their benefits while minimizing potential adverse effects [49].

3.3 Ketosis and Ketoacidosis

The increasing popularity of high-protein diets may contribute to dietary imbalance, particularly in populations that already consume protein above the recommended intake [50]. Some high-protein dietary patterns, especially those combined with carbohydrate restriction, may also result in inadequate consumption of fruits, vegetables, and other carbohydrate-rich foods [50, 51].

When carbohydrate intake is substantially reduced, the body shifts from glucose to fatty acids as its primary energy source. Consequently, the liver produces ketone bodies (KBs), including β -hydroxybutyrate, acetoacetate, and acetone, which serve as an alternative energy substrate for many tissues. In healthy individuals, this metabolic adaptation, known as nutritional ketosis, is generally well regulated and does not lead to clinically significant disturbances in acid-base balance [52, 53].

Ketoacidosis is a pathological condition characterized by excessive accumulation of ketone bodies and metabolic acidosis. It develops when ketone body production exceeds the body's buffering capacity and is most commonly associated with severe insulin deficiency, prolonged fasting, alcohol misuse, or other metabolic disturbances rather than with high-protein intake alone [53, 54].

Beyond their role as alternative energy substrates, ketone bodies also function as signaling molecules involved in the regulation of cellular metabolism. β -Hydroxybutyrate has been shown to influence several metabolic pathways and may contribute to appetite suppression observed during ketogenic diets, although the underlying mechanisms remain incompletely understood [55, 56].

For healthy individuals, the risk of developing severe ketoacidosis during dietary carbohydrate restriction is considered very low. However, individuals with diabetes mellitus, insulin deficiency, severe infections, prolonged fasting, perioperative stress, or other metabolic disorders may be at increased risk and therefore should undertake restrictive low-carbohydrate dietary interventions only under appropriate medical supervision [52-54, 57, 58].

3.4 Nutritional deficiencies

High-protein diets are widely used for weight loss and the preservation of muscle mass. However, poorly balanced high-protein diets may increase the risk of nutritional deficiencies and adversely affect bone health. High protein intake has been shown to increase urinary calcium excretion, although this does not necessarily indicate calcium loss from bone tissue. The overall effect of dietary protein on bone health depends on multiple factors, including calcium intake, vitamin D status, dietary acid load, and the source of dietary protein. Restrictive dietary patterns that limit the intake of dairy products, fruits, or vegetables may also lead to inadequate intake of vitamin D, magnesium, and other nutrients important for maintaining bone health [2, 59-61].

Summary

High-protein diets have been shown to provide a range of health benefits, including enhanced muscle hypertrophy and improved weight management through increased satiety and diet-induced thermogenesis. Protein plays a critical role in muscle protein synthesis, repair, and

maintenance, making adequate protein intake particularly beneficial for physically active individuals and those engaged in resistance training [2,11,62]. Additionally, higher protein intake may facilitate fat loss by promoting thermogenesis and improving appetite regulation [4,11].

Nevertheless, excessive protein intake may also pose certain health risks. High protein consumption, particularly from animal sources, may increase renal workload and potentially accelerate the progression of chronic kidney disease in susceptible individuals, especially those with pre-existing renal impairment. However, current evidence regarding clinically significant long-term kidney damage in otherwise healthy individuals remains inconclusive [38].

To optimize the health benefits of a high-protein diet while minimizing potential risks, dietary recommendations should be individualized according to age, health status, physical activity, and metabolic requirements. Protein should be obtained from a variety of animal and plant sources as part of a balanced dietary pattern that also provides adequate dietary fiber, healthy fats, vitamins, and minerals to support overall metabolic health [2,38,49,50].

Overall, current evidence suggests that appropriately planned high-protein diets can be an effective nutritional strategy for improving body composition and supporting metabolic health. Their long-term safety and effectiveness depend on protein source, overall dietary quality, adequate hydration, and individual health status. A balanced dietary pattern that includes diverse protein sources and sufficient intake of other essential nutrients may contribute to long-term health and well-being [2,33,38,49].

Disclosure

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