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THE IMPACT OF HIGH-PROTEIN DIETS ON RENAL FUNCTION: A COMPREHENSIVE REVIEW

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ABSTRACT

Introduction and purpose: Protein is one of the key macronutrients in the diet, playing an irreplaceable role in tissue construction and repair, as well as enzyme and hormone production. While it is widely recognised that a high-protein diet can be harmful to those with pre-existing kidney issues, there is limited evidence to suggest that high protein consumption poses a risk to healthy individuals. High-protein diets, defined as those in which protein intake exceeds standard recommendations (typically >1.2-2.2 g protein per kilogram of body weight per day), are frequently employed in medical and sporting contexts. The present article aims to investigate the effects of a high-protein diet on renal filtration function.

Materials and methods: To write this article, data bases such as PubMed and Google Scholar were searched using the following terms: high protein diet, protein intake, renal function, renal failure, chronic kidney disease, nutrition, glomerular filtration rate, GFR

Description of the state of knowledge: A high-protein diet constitutes a significant component in the therapeutic management of various conditions, including, but not limited to, chronic illness, cachexia (particularly in cancer), and the aftermath of orthopaedic and surgical interventions, as well as extensive burns. Notably, high protein intake is frequently employed by individuals of sound health to achieve weight reduction (through fat loss), enhance muscle mass, prolong satiety, and regulate appetite. The kidneys are responsible for the removal of excess protein from the organism, a process that involves the filtration of urea and other nitrogenous products from the blood and their subsequent excretion in the urine.

Summary: A review of studies demonstrated that short-term (up to several months) high-protein diets induced glomerular hyperfiltration, while long-term studies revealed decreased renal filtration function, particularly in individuals with cardiovascular disease and diabetes mellitus. However, there is an absence of compelling evidence associating increased protein intake with renal damage in healthy individuals. The necessity for large, long-term randomised trials in this population is underscored. For individuals with chronic kidney disease (CKD), studies have indicated that a high-protein diet may accelerate the deterioration of renal function, leading to an increase in creatinine levels and other indicators of kidney damage. Excessive protein supply may further increase glomerular filtration rate (GFR) burden, which may lead to faster progression of kidney disease.

KEYWORDS

High Protein Diet, Protein Intake, Renal Function, Glomerular Filtration Rate, GFR

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Introduction

In the context of a balanced diet, three fundamental macronutrients are identified: proteins, fats and carbohydrates. In contrast to carbohydrates and fats, protein ingestion through food is converted into body protein, which can be categorised into various functions, including the development of bodily structures, the enhancement of immune systems, the regulation of enzymes, and the production of hormones. The liver and kidneys are responsible for the removal of excess proteins and amino acids through metabolic processes.

The protein content of a diet can be assessed basing on the total amount consumed, the percentage of overall energy intake, or the amount of protein relative to body weight. The World Health Organization advises that adults need at least 0.83 g/day of protein per kg of ideal body weight, but it does not specify a maximum tolerable limit [1]. A high-protein diet is defined as one where the daily protein intake exceeds the standard recommendations, typically ranging from 1.2 to 2.2 grams per kilogram of body weight. The Institute of Medicine defines the acceptable macronutrient distribution range (AMDR) for protein as 10–35% of total energy intake. Diets with protein intake exceeding 35% should be regarded as high-protein diets [2].

Following a high-protein diet can have many benefits. Athletes and physically active people may take advantage of this type of diet to induce greater muscle hypertrophy during resistance training [3], increase or maintain muscle mass [4], recover faster or achieve better sports result [5]. Moreover, it may help overweight

or obese people reduce weight and achieve satiety feeling [4, 6]. It also prevents sarcopenia in the aging process [7] and improves tissue sensitivity to insulin [8] – this consequence may be particularly important in type 2 diabetes. However, there are clinical conditions in which excessive protein supply is contraindicated. The diet in question is unsuitable for people with chronic kidney disease [9] or metabolic disorders (for example, phenylketonuria [10] or cystinuria [11]).

Materials and Methods

This narrative review was based on a literature search conducted in electronic databases, including PubMed and Google Scholar. The search strategy used the following keywords and their combinations: high protein diet, protein intake, renal function, glomerular filtration rate, GFR.

Diagnostic criteria

The most important biomarkers for assessing kidney function are the evaluation of GFR and albuminuria (or proteinuria).

The estimation of Glomerular Filtration Rate (GFR) is based on the measurement of serum creatinine levels, which are filtered by the kidneys. Calculation is based on commonly accessible clinical parameters, including age, weight, sex, race, and levels of serum creatinine. [19]

The assessment of albuminuria and the estimation of glomerular filtration rate can be conducted through two methods: the collection of a 24-hour urine sample or the measurement of the urine albumin/creatinine ratio (UACR) in a random spot urine sample. For the purposes of prevention and screening, the measurement of UACR emerges as the optimal approach, given its cost-effectiveness and minimal inconvenience, while maintaining a high degree of accuracy. [20]

The normal range for urine albumin excretion is considered to be less than 30 mg/g creatinine, moderately elevated albuminuria is classified as 30–300 mg/g creatinine, and severely elevated albuminuria is defined as 300 mg/g creatinine or higher. [21]

A glomerular filtration rate of >90 ml/min/1.73 m² (category G1) is considered normal, but taking into account factors such as age, a level of 60–89 ml/min/1.73 m² (category G2) is also considered a variant of normal [22].

Pathophysiology

The nephron is the fundamental structural and functional unit of the kidney. The average number of nephrons in the human kidney is approximately 1.5 million, formed during fetal life. Each nephron consists of a glomerulus and a connected system of tubules. As part of the ageing process, almost half of the nephrons are lost from early adulthood to old age. [12].

Urea is the primary by-product of protein metabolism, which the organism eliminates through the process of renal filtration [13].

Evidence from both animal and human studies indicates that the ingestion of protein by mouth and the infusion of amino acids result in increased renal blood flow and glomerular filtration rate (GFR) [14].

The chronic consumption of high amounts of protein has been demonstrated to be associated with glomerular hyperfiltration, congestion and increased pressure, resulting in dilatation of the ductus arteriosus and consequent morphological changes in the glomeruli [15].

However, the ability to boost GFR in response to protein consumption, referred to as kidney functional reserve, is a normal adaptive mechanism that helps the kidney enhance solute clearance when there is an increase in solute (i.e., nitrogen) load. This adaptive function is not considered a risk factor for the onset of CKD [16].

Moreover, renal hyperfiltration is a physiological mechanism associated with pregnancy [17], in which eGFR increases by up to 65%, but does not increase the risk of chronic kidney disease [18].

Chronic kidney disease

Chronic kidney disease is prevalent among the general adult population. A study of data from the United States has estimated a prevalence of 13.1% among adults, with an upward trend over time [23]. A diagnosis of chronic kidney disease (CKD) in an adult is made when the individual has a glomerular filtration rate (GFR) below 60 ml/min/1.73 m² for three months or longer, or when the GFR is above 60 ml/min/1.73 m² but accompanied by signs of kidney damage. [24] The primary factors contributing to chronic kidney disease (CKD) are diabetes, high blood pressure, chronic glomerulonephritis [23]

The classification of CKD is based on the underlying cause, the glomerular filtration rate (GFR) category (G1-G5), and the albuminuria category (A1-A3). Collectively, these categories are referred to as CGA. [Figure 1] [25]

KDIGO: Prognosis of CKD by GFR and albuminuria categories				Persistent albuminuria categories		
				Description and range		
				A1	A2	A3
				Normal to mildly increased <30 mg/g <3 mg/mmol	Moderately increased 30–300 mg/g 3–30 mg/mmol	Severely increased >300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m ²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk. GFR, glomerular filtration rate.

Fig. 1. Prognosis of CKD by GFR and albuminuria categories [25]

It has been estimated that in excess of 90% of cases of type 2 diabetes and 65% of cases of hypertension, two major causes of kidney disease, could be prevented if all US adults adopted a healthy lifestyle and diet. [26, 27].

Metanalysis of studies – kidney damage

It is widely accepted that high protein intake may be harmful to individuals with chronic kidney disease (CKD). However, hyperfiltration might simply be an adaptive response to increased protein consumption and may not directly lead to a decline in kidney function in people with normal kidney function.

A randomised, controlled trial was conducted to investigate the association between increased protein intake and hydration indices [28]. Participants followed eucaloric diets for a period of four weeks, with each diet containing 3.6 (high protein), 1.8 (moderate protein) and 0.8 (low protein) g / kg / day of protein. The following assessments were performed: blood urea nitrogen, plasma osmolality, urine specific gravity and fluid balance estimates. Baseline plasma osmolality was found to be elevated in the high protein group in comparison to the low and moderate protein groups. The study concluded that the effect of elevated dietary protein intake on fluid status was minimal [28, 29]. In 1928, Watzadse's research utilised a frog model to demonstrate that amino acids and peptides could enhance renal blood flow [30]. Subsequent animal studies yielded analogous results [31, 32, 33].

Short-term effects of a high-protein diet on kidney function

The findings of short-term studies conducted on healthy subjects have been found to lack clarity. In a prospective study lasting a minimum of four months on a group of 88 subjects with normal renal function (32 vegetarians, 12 bodybuilders without supplementary protein concentrates, 28 bodybuilders with supplementary protein concentrates and 16 subjects without a special diet), a significant correlation was observed between albumin excretion rate and endogenous creatinine clearance. However, no significant correlation was found between albumin excretion rate and nitrogen excretion rate. These alterations are indicative of structural changes in glomeruli and tubules resulting from prolonged protein intake [34].

A study in a group of healthy young men showed that high-protein diets in healthy young men lead to significant changes in GFR, filtration fraction, albuminuria, serum uric acid levels and urine pH, while other markers of renal function remained stable. Although the clinical relevance of these results is uncertain, close monitoring of renal function is recommended in people on high-protein diets, as potential long-term effects have not yet been ruled out [35].

In the OmniHeart Trial, 164 healthy adults with prehypertension or stage 1 hypertension were fed three distinct diets for a period of six weeks. The results demonstrated that the protein diet, as compared with diets comprising carbohydrates and unsaturated fats, resulted in a significant increase in cystatin C-based eGFR by approximately 4 ml/min/1.73 m² ($P < 0.001$). No substantial difference was observed between diets containing carbohydrates and unsaturated fats [36].

In the early stages, glomerular hyperfiltration is characterised by an increase in GFR, proteinuria, or both. However, it can result in kidney function deterioration over time, especially in individuals with chronic kidney disease, risk factors for kidney disease, or both. A high-protein diet may have a detrimental effect on kidney health in the general population, particularly in those with pre-existing hyperfiltration or additional risk factors like cardiovascular disease or a history of type 2 diabetes [37].

Long-term effects of a high-protein diet on kidney function

In the Nurses' Health Study [38], an 11-year observational study involving women with mild renal insufficiency (defined as eGFR between 55 and 80 ml/min per 1.73 m²), each 10-gram increase in protein intake was found to be significantly associated with a decline in eGFR by -1.69 ml/min per 1.73 m² (95% CI, -2.93 to -0.45 ml/min per 1.73 m²). This association was not observed in subjects with normal kidney function [38, 39].

The Gubbio study [40], which involved 1522 participants aged 45–64 years, found that higher protein intake was associated with a lower eGFR after 12 years, both in individuals with and without chronic kidney disease (CKD). In this study, CKD was defined as an eGFR <90 ml/min per 1.73 m². A multivariable regression analysis revealed that for every additional gram of protein consumed per day, there was a more negative change in eGFR of -4.1 ml/min per 1.73 m² (95% CI, -5.1 to -3.1) and a significantly greater risk of developing an eGFR <60 ml/min per 1.73 m² (odds ratio, 1.78; 95% CI, 1.15 to 2.78) [40, 41].

A study involving young, healthy men and women [42] demonstrated that consuming a high-protein diet (3.4 g/kg/d) in conjunction with intensive resistance training can yield favourable outcomes in terms of body composition. Furthermore, no alterations were observed in any of the blood parameters, including a decline in renal filtration function.

A body of research has indicated a correlation between high-protein diets and an elevated risk of kidney stone formation. A substantial prospective study in humans has identified a positive association between the consumption of animal protein and the development of kidney stones [43]. Consequently, high protein intake may pose a risk for individuals with genetic or latent conditions associated with kidney disease and stone formation [44]. These findings suggest that higher protein intake could be an independent risk factor for kidney stone development in those who are predisposed. Nephrolithiasis is associated with increased risk of chronic and end stage kidney disease [45].

A Systematic Review

In their comprehensive study, Devries and colleagues [46] selected a total of 28 studies meeting the criteria after analyzing 2144 abstracts. The inclusion criteria for studies were as follows: randomized controlled trials (RCTs) investigating the impact of high-protein (HP) intake (moderate – greater than the recommended dietary allowance (RDA) but lower than HP intake, or lower-protein (RDA or less)) on glomerular filtration rate (GFR) in adults aged 18 years or older. The studies had to involve participants who were healthy, obese, had type 2 diabetes, and/or hypertension. Studies were excluded if they included individuals with type 1 diabetes, chronic kidney disease (CKD), or any other signs of kidney dysfunction (such as proteinuria or a history of kidney stones) or if participants had recently undergone any surgical procedures [46].

In summary, the results of this meta-analysis indicate that high-protein (HP) intake exerts minimal or no effect on GFR in individuals with normal renal function. Furthermore, there is an absence of evidence that a high-protein diet can lead to deterioration of renal function in healthy individuals. Moreover, the analysis demonstrates that even in groups at increased risk of deterioration of renal function, such as people with type 2 diabetes, no such association was observed [46].

In a prospective study, Schwingshackl and Hoffmann [47] created a meta-analysis based on 14 observational studies involving a total of 105,872 participants, and found that a high-protein diet increases the risk of all-cause mortality [48]. Rather than being a pathological response, changes in kidney function induced by high protein intake, such as the increase in GFR, may actually reflect a normal physiological adaptation [49]. The kidney's ability to enhance its function with protein consumption indicates the presence of a renal functional reserve[50].

Conclusions

The view that high protein intake may be detrimental to people with CKD is widely accepted and seems obvious. However, hyperfiltration may simply be an adaptive response to high protein intake and may not necessarily be associated with a decline in renal function in individuals with normal renal function.

Dietary practices alone are unlikely to induce kidney damage in most individuals because the kidneys possess a redundant set of nephrons, their functional units. For the general population, based on the results of the aforementioned studies and meta-analyses, consuming a high-protein diet appears to be more beneficial than harmful.

However, the relationship between high-protein diets and incident CKD may be largely mediated by insulin resistance and the development of metabolic syndrome, diabetes, and hypertension.

In the general population, long-term cohort studies will continue to provide valuable insights as the follow-up periods lengthen. Specifically, large community-based studies, which will include regular screening for diet and renal function, are likely to enhance our understanding of the potentially negative effects of high-protein diets and some of their sources.

For patients with comorbidities, such as type 2 diabetes and obesity- both of which increase the risk of developing chronic kidney disease- there is an urgent need for long-term, carefully designed randomized controlled trials focusing on various aspects of dietary protein intake.

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