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REVIEW PAPER

ARTYKUŁ PRZEGLĄDOWY

RELATIONSHIP BETWEEN HIGH PROTEIN DIET AND RISK OF KIDNEY DISEASE PROGRESSION AND NEPHROLITHIASIS

ZWIĄZEK POMIĘDZY DIETĄ WYSOKOBIAŁKOWĄ A RYZYKIEM PROGRESJI CHORÓB NEREK I KAMICY NERKOWEJ

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Summary

Chronic kidney disease (CKD) is a condition with increasing incidence worldwide. People suffering from CKD should carefully control the amount of protein they consume and its food

source. They should ensure that most of their protein comes from plant sources. A diet that limits animal protein intake is associated with longer life expectancy. Healthy individuals without diagnosed CKD can consume protein without restrictions. Protein consumption of up to 3.5 g/kg of body weight per day has not been associated with kidney damage. This type of diet offers many benefits to patients, including more effective building of muscle mass, a better feeling of satiety after meals, and a reduction in the amount of body fat. However, people suffering from kidney stones and CKD should limit the consumption of animal protein. The use of the DASH (Dietary Approaches to Stop Hypertension) diet in people at risk of kidney stones is associated with a significant decrease in the risk of developing kidney stones, even reducing the risk of developing the disease by 45%. Therefore, there is no one universal answer to the question whether a high-protein diet is beneficial, because different groups of people with their own predispositions may benefit from it, or it may bring them more negative consequences.

Keywords: whey protein, high protein diet, renal circulation, nephrolithiasis, chronic kidney disease

Streszczenie

Przewlekła choroba nerek (PChN) jest schorzeniem o rosnącej częstości występowania na całym świecie. Osoby cierpiące na PChN powinny starannie kontrolować ilość spożywanego białka oraz jego źródło. Powinny one upewnić się, że większość białka pochodzi ze źródeł roślinnych. Dieta ograniczająca spożycie białka zwierzęcego jest związana z dłuższą oczekiwaną długością życia. Zdrowe osoby bez zdiagnozowanej choroby nerek mogą spożywać białko bez ograniczeń. Spożycie białka w ilości do 3,5 g/kg masy ciała na dobę nie było związane z uszkodzeniem nerek w tej grupie chorych. Tego rodzaju dieta oferuje wiele korzyści, w tym bardziej efektywne budowanie masy mięśniowej, lepsze uczucie sytości po posiłkach oraz redukcję ilości tkanki tłuszczowej. Jednak osoby cierpiące na kamicę nerkową i

PChN powinny ograniczyć spożycie białka zwierzęcego. Stosowanie diety DASH (Dietary Approaches to Stop Hypertension – dietetyczne podejście do zatrzymania nadciśnienia) w grupie osób zagrożonych kamicą nerkową wiąże się ze znacznym zmniejszeniem ryzyka ich wystąpienia, redukując to ryzyko nawet o 45%. Dlatego nie ma jednej uniwersalnej odpowiedzi na pytanie, czy dieta wysokobiałkowa jest korzystna, ponieważ różne grupy osób, z różnymi predyspozycjami, mogą czerpać z niej korzyści lub może ona przynieść im negatywne konsekwencje.

Słowa kluczowe: białko serwatkowe, dieta wysokobiałkowa, krążenie nerkowe, kamica nerkowa, przewlekła choroba nerek

Introduction

A high-protein diet is very popular among professional athletes, but also with people who regularly engage in physical activity to build a muscular figure. Effectively achieving muscle hypertrophy requires a positive protein balance and maintaining it for a relatively long period of time. This is the main motivation for athletes to consume more protein [1]. Another aspect is the increased protein consumption and lower carbohydrate consumption by the people who want to lose weight. There is no universal definition of a high-protein diet. Various publications state that it begins when we consume protein in the amount of 1.2 to 2 g/kg body weight/day [2,3]. The recommended daily dose of protein for people who want to eat a balanced diet is from 0.6 to 0.8 g/kg body weight of protein per day, which constitutes 15-16% of the energy consumed with food. Excessive protein intake leads to accumulation of a large amount of its metabolites in the body, some of which must be removed by the kidneys. Many studies have investigated the impact of high protein intake on kidney function, with ambiguous conclusions. A high-protein diet has been suspected of potentially damaging the kidneys due to

increased glomerular pressure. This article aims to analyze the risk of harmful effects of a high-protein diet on people with normal kidney function and on people with chronic kidney disease (CKD) and the risk of developing kidney stones.

Aim of the work

This work aims to organize the latest information on the impact of a high-protein diet on kidney function. The review consists of four chapters. The first chapter discusses the theoretical aspects of the topics – the impact of a high-protein diet on functional changes in the kidneys. The theoretical review covers issues based on both human and animal models (rats). The remaining three chapters discuss the effects of a high-protein diet on individuals with reduced kidney function, individuals with preserved kidney function, and the risk of kidney stone formation. This division is necessary because the conclusions regarding the use of this diet differ for each of the three groups mentioned above.

Methods

This article comprises a literature review based on publications from PubMed, the Google Scholar library and ClinicalKey utilizing keywords such as: nephrolithiasis, whey protein, high protein diet on renal function, renal hyperfiltration, CKD. The main limitation of this research problem is the small amount of research conducted on this topic. The works from which we drew the most knowledge come from the period 2017-2023. Additionally, there are several older publications that provided interesting conclusions included in the article. One article was written only in the Polish language, the other articles were in English.

Literature review results

Theoretical aspect of the impact of a high protein diet

Glomerular hyperfiltration

Increasing protein intake in the diet leads to an increase in serum oncotic pressure, followed by increased flow in the renal glomeruli and vascular resistance, resulting in an increase in hydraulic pressure in the glomerular capillaries. Chronic exposure to renal hyperfiltration may potentially lead to mesangial hyperplasia and increased permeability of the protein filtration barrier. Studies on rats have demonstrated that this mechanism's impact intensifies with a decrease in functional nephrons within the kidney [4]. This suggests that the effect of an unfavorable hyperfiltration mechanism may have a particularly adverse effect among individuals with current kidney disease in which the number of functional nephrons is reduced. Numerous studies conducted among humans show an analogy of the effect of large amounts of protein in plasma on renal hyperfiltration, but there are no clear conclusions as to whether this effect is significant enough to lead to kidney damage in people with normal renal function [5].

Urea production

The consequence of consuming large amounts of protein is a greater accumulation of its final metabolites, including urea and nitrogen compounds. In a study conducted on an animal model, Liu et al. [6] demonstrated that in rats receiving a diet consisting of 40% protein, the concentration of urea and the osmolality of the produced urine were 17-fold (2600 mmol/L)

and 4-fold (3000 mOsm/kg H_2O) higher, respectively, compared to the control group. It was shown that the increased concentration of urea led to changes in the biological signaling pathways in the urinary tract urothelium. In the high-protein diet group, a significant increase in the expression of genes associated with inflammatory response (e.g., MCTP2, MCTP9, EPHX2, SRGN) was detected, which is linked to the local intensification of inflammation. There was an increased expression of genes (CDKN1C and BAX) promoting cell apoptosis and decreased expression of genes (CDK6, CCNB1, and PCNA) promoting the cell cycle. All the aforementioned aspects contribute to the deterioration of the bladder urothelium condition. High concentrations of urea can lead to genome destabilization and an increased risk of urinary tract cancer development. A study by Martin et al. [7] on a group of five men who consumed diets with increasing protein content over 12 weeks, with each phase lasting 4 weeks, drew the following conclusions: with the increase in protein consumption, the urine specific gravity (USG) and blood urea nitrogen (BUN) concentration increased. Comparing high-protein and low-protein diets, these values were respectively: (1.021±0.001 vs 1.018±0.001, $p<0.10$) for USG and (21.26±1.71 vs 11.96±0.84 mg/dL, $p<0.05$) for BUN concentration. However, plasma osmolality remained within the normal range, suggesting maintenance of water and electrolyte balance. Nevertheless, the authors suggest that the increase in USG and BUN may be early indicators of renal stress.

Satiety provided by high protein diet

Meals containing a lot of protein provide a better feeling of satiety and have a beneficial effect on reducing body fat in people. Understanding the mechanism of action of a high-protein diet on the regulation of satiety is complex and is based on different signals at different levels of the body. The regulation of these processes is carried out by counter-rotating effector systems

that integrate signals from both the periphery and from various areas of the brain [8]. After eating a high-protein meal, the intestine releases various hormones, such as cholecystokinin, PYY and GLP-1, which stimulate the vagus nerve, transmitting impulses mainly to the vestibular-apical nucleus area [9].

Modification of the urine composition

A high-protein diet may change the composition of urine produced in the kidneys. Studies conducted on rats have demonstrated the impact of a protein-rich diet (with casein being the most significant) on an increase in the excretion of calcium and phosphates along with reduced excretion of citrates. The elevated level of calcium ions in urine resulting from a casein-rich diet raises the risk of its crystallization in the urinary tract. The appropriate concentration of citrates in urine serves as a specific mechanism to prevent the formation of kidney stones containing calcium [10]. Hypocitraturia abolishes this mechanism for kidney stones composed of calcium oxalate (67.3%) and calcium phosphate (16.1%), which together constitute 83.4% of the types of kidney stones. The incidence of kidney stones is increasing worldwide. A high-protein diet may be one of the factors responsible for this increase [11] (Figure 1).

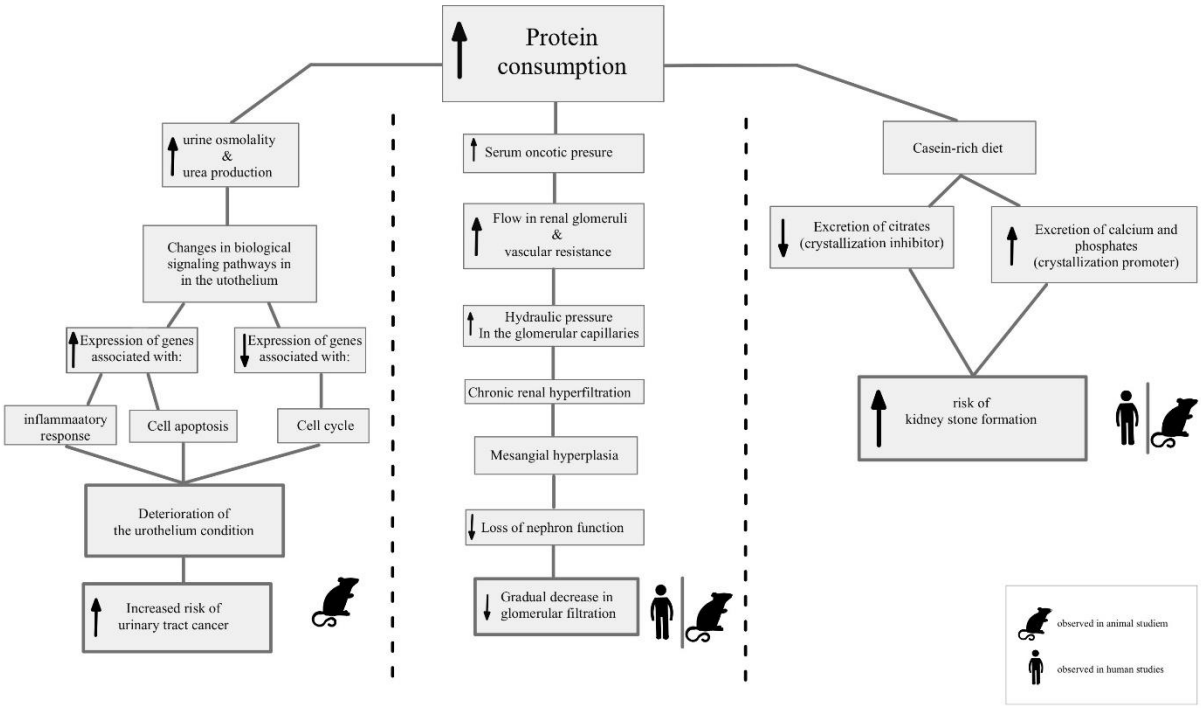

Figure 1. Summary of the potential impact of a high-protein diet [4-7,10,11]

Impact of a high-protein diet on people with reduced kidney filtration capacity

The increase in the incidence of CKD is rising worldwide. CKD may affect up to 850 million people around the world (Table 1). Between 1988–1994, the mortality rate was 11.8%, and in the USA in 2015–2016 it increased to 14.2%. This disease particularly affects individuals with diabetes (24.5% among diabetics). The risk of developing CKD in individuals with hypertension was 35.5%, whereas in individuals without hypertension, the risk was 10.2% [12]. In the Polish population, the most common cause is CKD due to diabetic nephropathy (27.16%), followed by glomerulonephritis (18.57%). The estimated number of people suffering from CKD in Poland is 6.2 million people [13].

Table 1. Estimated number of CKD cases

Study	Population	Population prevalence
Kovesdy [1]	Worldwide	843.6 mln
Król, Rutkowski [13]	Poland	6.2 mln

For our review, people with glomerulonephritis are the most important, as it often affects relatively young individuals, and the disease itself remains asymptomatic for a long time until the kidney function significantly deteriorates [14]. People with CKD or people without one kidney, i.e., those with a reduced number of active nephrons, should be cautious about consuming excessive amounts of protein. It has been proven that high protein intake can lead to glomerular hyperfiltration, which in turn may cause structural and functional damage to the kidneys by increasing the interstitial pressure in the renal glomeruli and inducing the growth of mesangial cells. Such people should start following a low-protein diet, as it is associated with slowing down the progression of CKD [15]. The 11-year observational study conducted by Knight et al. [16] on a cohort of women (n=1624) with preserved and reduced renal function demonstrated that in women with mildly reduced GFR (range 80–55 ml/min per 1.73 m²), each 10 g increase in protein intake was associated with a mean change of -1.69 ml/min per 1.73 m² in estimated GFR (CI, -2.93 to -0.45 ml/min per 1.73 m²). Specifically, this decline was attributed to animal-derived protein. For every 10 g increase in non-dairy animal protein intake, the decline was -1.21 ml/min per 1.73 m² (CI, -2.34 to -0.33 ml/min per 1.73 m²), whereas dairy protein intake showed a decline of -0.05 ml/min per 1.73 m² (CI, -1.48 to 1.38 ml/min per 1.73 m²). A diet completely excluding animal protein did not correlate with a decline in GFR. Cirillo et al. [17] conducted an observational study on a group of patients (n=1522), where they subjected the association of protein intake with GFR to a 12-year observation in middle-aged individuals consuming an average of 1.34 ± 0.57 g of protein per day. After the observation

period, it was established that a 1 g/day higher protein intake was related to a −4.1 mL/min × 1.73 m² more negative eGFR change (95% CI=−5.1/−3.1) and to a 1.78 risk for incidence of eGFR < 60 mL/min×1.73 m² (95% CI=1.15/2.78).

We suggest to pay attention to the source of the protein. Plant based protein is associated with a lower risk of CKD. Kim et al. [18] found in their study that a diet dominated by plant protein is associated with a lower incidence of CKD and lower mortality in this group of patients. It reduces the risk of hyperphosphatemia occurring in patients with CKD. Such a diet should be based mainly on fresh fruit and vegetables, whole grain products, nuts and legumes. The authors emphasize that fruit juices and highly processed cereal products lose the properties that produce the above-mentioned positive effects.

All the aspects mentioned above are applicable to individuals already diagnosed with kidney disease. Not only should such individuals closely monitor their protein intake, but they would also benefit more from a low-protein diet, which has been proven to reduce glomerular pressure and mitigate the risk of metabolic acidosis in people with CKD. Despite the increased protein excretion in their urine, it might seem counterintuitive for individuals with CKD to limit their protein intake. However, research clearly indicates that a protein intake of 0.6–0.8 g/kg body weight/day is sufficient to meet their nutritional needs without excessively burdening the kidneys. The authors of this article emphasize the importance of including high-quality animal protein sources such as meat, fish, eggs, and dairy products [19] (Table 2).

Table 2. Summary of the impact of a high-protein diet on people with reduced kidney filtration

Study	Sample size	Investigation	Follow-up period	Results
Knight et al. [16]	1,624 normal renal function: 1,135 mild renal insufficiency: 489	determining whether protein intake influences the rate of renal function change in women	11 years	- no changes in kidney function in individuals with GFR > 80 ml/min per 1.73 m² - a decline of -1.69 ml/min per 1.73 m² (CI[1], -2.93 to -0.45) in the group with eGFR 55–80 ml/min per 1.73 m² per 10 g increase in protein intake
Cirillo et al. [17]	1,522	association of protein intake with GFR, indexed by estimated GFR (eGFR) in long term observation	12 years	- high protein intake associated with higher decrease of GFR over time in middle-aged adults
Kim et al. [18]	14,686	investigating the relationship between plant-based diets and the risk of developing chronic kidney disease (CKD), as well as changes in kidney function, over a period of 20 years in the general population	24 years	- individuals with a healthy plant-based diet having a 14% lower risk of developing CKD (HR=0.86; 95% CI, 0.78–0.96; *p*=0.001) - a plant-based diet rich in healthy plant foods and low in animal foods being a preventive measure for CKD

Notes: [1] CI – Confidence Interval, [2] HR – Hazard Ratio.

Impact of a high-protein diet on people with preserved kidney function

Protein intake above the recommended level may be beneficial to health in people who have normal kidney function. Studies conducted so far on healthy people following a high-protein diet, despite an increase in glomerular filtration rate (GFR), have not shown any impact on kidney damage [20]. Numerous studies indicate that such a diet does not have any negative

consequences for the functioning of the kidneys and liver. Both studies lasting from several days up to 1 year clearly state that this type of diet has not been proved to have a negative impact on human health [21,22]. These conclusions are also supported by the World Health Organization, which stated that there is no evidence suggesting that healthy people need to limit protein intake [23].

A follow-up investigation provided by Antonio et al. [24] showed that protein intake of 2.3 to even 3.4 g/kg of body weight per day was associated with better percentage reduction of body fat. Athletes on a high-protein diet also achieved better results during strength training. Campos-Nonato et al. [25] examined the effectiveness of a protein-rich diet for weight loss in obese individuals. This diet was shown to be effective in reducing body weight, supporting the loss of fat tissue while maintaining muscle mass. The presence of a large amount of protein in the diet improved the feeling of satiety after meals. The benefits of this for obese people include a lower risk of metabolic diseases, such as hypertension, cardiovascular diseases and diabetes.

When it comes to the timing of consumption of high-protein meals, this is particularly important for physically active people. Consuming 20–30 g of high-quality protein before or after exercise stimulates muscle protein synthesis [26]. Trommelen et al. [27] conducted a study on a group of men (n=36). The test group were administered 30 g of protein before sleep following muscle stimulation through exercise. The study found that casein protein consumption before sleep resulted in the release of 55% of its volume into the bloodstream, which translated into a better overnight whole-body protein balance. However, this did not transfer into an increase in muscle mass over the 7.5-hour sleep period. Nevertheless, this effect is observed with longer-term supplementation. Kouw et al. [28] conducted a study on a group of 48 men, approximately 72 years old, to evaluate the effect of nocturnal protein supplementation on preventing age-related muscle mass loss. For 8 months, participants were supplemented with 20-40 g of casein before sleep. Muscle protein synthesis rates were assessed

during supplementation. In the placebo group, the synthesis rate was 0.033%/h, while in the supplementation group, it increased to 0.044%/h, which was statistically significant. The authors concluded that such supplementation could be an effective dietary strategy to help prevent muscle mass loss in older individuals.

Protein supplementation may have additional benefits such as lowering blood pressure and improving the lipid profile. A study conducted on 55 participants with stage 1 hypertension or high normal blood pressure showed that consuming 2 servings of 15 g of daily led to an average reduction in body fat of 1.25 kg over 12 weeks and contributed to a reduction in blood pressure by approximately 4%. The best results were achieved by obese people, for whom protein supplementation was associated with the greatest reduction in body weight [29]. Protein supplements may also be used in the treatment of patients suffering from cancer cachexia. Leucine supplementation may help reduce the loss of muscle mass and reduce the activation of proteolysis pathways in muscles. Leucine affects cellular metabolism by modulating ketone and butyrate metabolism, which brings benefits in the case of limited glucose availability in cancer patients. The study also suggests that leucine can modulate the immune response and reduce inflammation, which is important for patients with cancer cachexia [30].

Table 3. Summary of the impact of a high-protein diet on population with preserved kidney function

Study	Sample size	Investigation	Protein intake[1]	Follow-up period	Results
Stephen et al. [20]	164	effect of a high-protein diet on kidney GFR in healthy adults	no data (25% of calories intake per day)	3 diets (each last for 6 weeks with 2-4 washout period)	- average GFR value increase: 3.81 mL/min/1.73 m^2 (p<0.001)
Antonio et al. [21]	14	determining the effects of a high protein diet over a one-year period	2.51±0.69 – 3.32±0.87	12 years 6/6 months of high and normal protein diet	- average GFR value: normal diet: 101±17 high Protein: 98±16 no harmful effect on any measured parameter

Poortmans et al. [22]	38	determining the effect of high protein diet on kidney function and potential health risk in athletes	1.35±0.12 – 1.94±0.13	7 days	- GFR reduced by 3-4% no major plasma differences for variables associated with protein metabolism and renal impairment
Antonio et al. [24]	48	determining the effect of a high-protein diet on performance, body mass composition of physically active people	2.1±0.7 3.4±0.6	8 weeks	- fat mass reduction: • HP: 1.6 kg (-2.4%) • NP: 0.3 kg (0.3%) - significant (p<0.05) increase in weight-bearing exercise: • squat • bench press
Campos-Nonato [25]	118	determining the effect of increased protein intake on weight loss and biomarkers of metabolic syndrome	1.34	6 months	- average weight loss in the group: HP: –7.0±3.7 (7.6±0.7%) NP: –5.1±3.6 (5.5±0.6%) - increase in BUN by 0.9 mg/dL in the HP group, no change in creatinine levels

Notes: [1] – gram of protein/kilogram of body weight/day, [2] – HP – high protein diet, [3] – NP – normal protein diet.

High protein diet and risk of kidney stone disease

The incidence of kidney stones has been increasing gradually since the 1960s. In a study by Romero et al. [31] analyzing the situation in the United States, Germany, Italy and Scotland, it was observed that men are more likely to suffer from it than women in a ratio of 2.5:1 to 1.15:1, depending on the country in which the research was conducted. The peak age of occurrence of urolithiasis is between 40 to 59 years, varying depending on the country from which the data were collected [31]. Consumption of large amounts of protein may be one of the risk factors for kidney stones in the population due to a greater decrease in pH, a decrease in

the release of citrates into urine and an increase in calcium excreted in urine. All three aspects mentioned above are risk factors for the formation of calcium stones in the urinary tract [32].

In the case of kidney stones, the source of protein we consume is crucial. Consumption of animal protein is associated with an increase in oxalate excretion, which elevates the risk of oxalate stone formation. However, the results regarding the effect of plant-based protein suggest a lower risk. Therefore, an important recommendation is to limit animal protein in the diet for people suffering from kidney stones, as reducing its consumption may be linked to a decreased risk of kidney stones [33]. To further reduce the risk of kidney stones, the DASH (Dietary Approaches to Stop Hypertension) diet is highly recommended. It is characterized by: high consumption of fruit, vegetables, nuts, legumes and low-fat dairy products and low consumption of meat, sweetened drinks and sodium. Taylor et al. [34] conducted a prospective follow-up study on a very large group of a total of 241,766 participants, which they divided into 3 groups: men (45,821), older women (94,108) and young women (101,837). The relative risk ratios for those following the DASH diet regularly were as follows: for men, 0.55 (CI, 0.46 to 0.65); for older women, 0.58 (95% CI, 0.49 to 0.68); and for younger women, 0.60 (95% CI, 0.52 to 0.70), indicating that adherence to this diet can reduce the risk of developing kidney stones by 45% (Table 4).

Table 4. Summary of the impact of a high-protein diet on kidney stone formation risk

Study	Sample size	Investigation	Follow-up period	Results
Nguyen et al. [33]	33 20 people with ICSFs[1] (12 with MMH and 8 without MMH) 13 healthy individuals in the control group	comparison of the impact of a protein-rich meat diet on urinary oxalate excretion in three groups: healthy volunteers, kidney stone patients with MMH,[2] and kidney stone patients without MMH	5 months	- a significant increase in urinary oxalate excretion observed in one-third of patients with ICSF (4 with MMH and 3 without MMH) - no changes observed in urine in the control group
Taylor et al. [34]	Three cohorts: 1. Health Professionals Follow-up Study (HPFS): 45,821 men 2. Nurses' Health Study I (NHS I): 94,108 older women 3. Nurses' Health Study II (NHS II): 101,837 younger women	association between a DASH-style diet and the risk of kidney stones.	HPFS: 18 years NHS I: 18 years NHS II: 14 years	- the highest quintile of the DASH score compared to the lowest quintile having a lower risk of developing kidney stones: Men: RR=0.55 (95% CI, 0.46 to 0.65) Older women: RR=0.58 (95% CI, 0.49 to 0.68) Younger women: RR=0.60 (95% CI, 0.52 to 0.70)

Notes: [1] idiopathic calcium stone formers (ICFS), [2] mild metabolic hyperoxaluria (MMH).

Conclusions

A high-protein diet in healthy people has shown benefits such as supporting the reduction of body weight and fat tissue and reducing the risk of lifestyle diseases. People with CKD should limit their protein intake – especially animal protein. Limiting the consumption of animal protein reduces the risk of kidney stones by up to 45%. During the preparation of the study, the authors noted the limited availability of research investigating the impact of a high-protein diet on individuals with CKD. This topic is not sufficiently understood to determine whether a high-protein diet unequivocally presents a favorable balance of benefits and risks in

this population. However, due to the growing trend of increasing protein intake in diets, research addressing this issue is expected to grow over time.

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