



Dietary protein intake and obesity-associated cardiometabolic function

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Purpose of review

High-protein intake is commonly recommended to help people manage body weight. However, high-protein intake could have adverse health consequences. Here we review the latest findings concerning the effect of high-protein intake on cardiometabolic health.

Recent findings

Calorie-reduced, high-protein, low-carbohydrate diets lower plasma glucose in people with type 2 diabetes (T2D). However, when carbohydrate intake is not markedly reduced, high-protein intake often does not alter plasma glucose and increases insulin and glucagon concentrations, which are risk factors for T2D and ischemic heart disease. High-protein intake does not alter plasma triglyceride and cholesterol concentrations but promotes atherogenesis in animal models. The effect of high-protein intake on liver fat remains unclear. In population studies, high-protein intake is associated with increased risk for T2D, nonalcoholic fatty liver disease, and possibly cardiovascular diseases.

Summary

The relationship between protein intake and cardiometabolic health is complex and influenced by concomitant changes in body weight and overall diet composition. Although a high-protein, low-carbohydrate, reduced-energy diet can have beneficial effects on body weight and plasma glucose, habitual high-protein intake, without marked carbohydrate and energy restriction, is associated with increased cardiometabolic disease risk, presumably mediated by the changes in the hormonal milieu after high-protein intake.

Keywords

high-protein diet, nutrition intervention, obesity

INTRODUCTION

Weight gain and excess adiposity are often associated with a series of cardiometabolic abnormalities, including insulin resistance, β -cell dysfunction, nonalcoholic fatty liver disease (NAFLD), and atherogenic dyslipidemia (high-plasma triglyceride and low-density lipoprotein-cholesterol [LDL-cholesterol] and low high-density lipoprotein-cholesterol [HDL-cholesterol] concentrations), which are important risk factors for serious complications, such as type 2 diabetes (T2D), cirrhosis, and cardiovascular diseases (CVD) [1]. Preventing weight gain is, therefore, critical to maintain health and prevent premature mortality. In addition, weight loss in people with obesity improves and can even eliminate many of these abnormalities [1–3]. High-protein intake (both absolute amounts and as percentage of total dietary energy intake) is commonly recommended to help people avoid body weight gain and to help people with obesity lose weight

as acutely protein is more satiating and has a greater thermic effect of feeding than carbohydrate and fat [4–6]. However, the results from long-term observational and several randomized controlled diet intervention studies do not demonstrate a beneficial effect of high-protein intake on body weight or metabolic health; on the contrary, high-protein intake is associated with both weight gain and obesity and increased risk for developing cardiometabolic diseases [6,7^{••}]. High-protein intake in the context of a calorie-reduced diet leads to greater

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KEY POINTS

- High-protein intake in the context of a calorie-reduced diet leads to greater weight loss, but the beneficial effect is small and appears to be limited to the first few weeks of diet intervention and to diets that increase protein intake at the expense of carbohydrate intake.
- Calorie-reduced, high-protein, low-carbohydrate diets lower plasma glucose in people with type 2 diabetes, but when carbohydrate and energy intake are not markedly reduced, high-protein intake often does not alter plasma glucose and increases insulin and glucagon concentrations, which are risk factors for type 2 diabetes and ischemic heart disease.
- High-protein intake does not alter plasma triglyceride and cholesterol concentrations but promotes atherogenesis in animal models.
- The effect of high-protein intake on liver fat content remains unclear.
- In population studies, high-protein intake is associated with increased risk for type 2 diabetes, nonalcoholic fatty liver disease, and possibly cardiovascular diseases.

weight loss, but the beneficial effect is small and appears to be limited to the first few weeks of diet intervention and to diets that increase protein intake at the expense of carbohydrate intake [2,6]. Moreover, high-protein intake without marked carbohydrate restriction blunts the beneficial metabolic effects associated with weight loss [8,9]. In this article, we review protein intake guidelines and the latest results (published in the past 2 years; for a detailed review of earlier work see ref. [6]) from studies that evaluated the effect of protein intake on cardiometabolic health. We focus our review on clinical trials, with one exception – the effect of protein intake on atherogenesis, which has to our knowledge only been addressed in animal models.

PROTEIN REQUIREMENTS AND RECOMMENDED AND HABITUAL PROTEIN INTAKES

Protein is a critical component of the diet as it provides essential amino acids. The Institute of Medicine recommended daily intake (RDI) – set to meet the requirement of 97.5% of adults to avoid loss of body nitrogen – is 0.8 g/kg/day, which corresponds to 10–13% of total daily energy requirements. Most adults (~85%) in developed countries consume at least the RDI of protein and many (~50%) consume significantly more than the RDI [10,11,12[•]]. Median protein intakes in the first, second, third, and fourth quartiles

of protein intake are 0.8, 1.1, 1.3, and 1.8 g/kg/day, respectively, accounting for 10–22% of total energy intake across all body mass index (BMI) categories and energy intakes [10,11,12[•],13,14]. Accordingly, high-protein intake (more than the RDI of 0.8 g/kg/day) is common and often occurs when carbohydrate and/or fat intake are not restricted. Most popular high-protein diets, such as the Atkins Diet, the Zone Diet, or the Protein Power Diet, are intended for weight loss (i.e. calorie restriction) and focus on the relative amount of protein in the diet ($\geq 20\%$ of total energy); total protein intake when consuming these diets, therefore depends on total energy intake and often far exceeds the RDI even when energy intake is markedly restricted.

HIGH-PROTEIN INTAKE AND PLASMA GLUCOSE HOMEOSTASIS

Plasma glucose concentration is determined by the balance between the rate of glucose appearance (from hepatic glucose production and meals) in and the rate of glucose disappearance (uptake by tissues) from the circulation. Glucagon and insulin are the primary regulators of glucose production and tissue glucose uptake [15,16]. Glucagon stimulates hepatic glucose production whereas insulin inhibits hepatic glucose production and stimulates glucose uptake into skeletal muscles and adipose tissue [15–17]. Hyperglycemia in prediabetes and T2D results from increased glucagon secretion combined with both impaired insulin action and impaired insulin secretion [15–17].

Acutely, protein ingestion stimulates both glucagon and insulin secretion [18^{••}] and impairs insulin action on glucose metabolism [19]. This coordinated metabolic response prevents hypoglycaemia after protein ingestion. The cellular mechanisms involved in protein-mediated insulin secretion differ from those involved in glucose-stimulated insulin secretion [20]. Therefore, the effects of glucose ingestion and protein ingestion on insulin secretion are additive, and protein–carbohydrate co-ingestion can (i.e. when the protein-induced insulin response is sufficient to overcome the protein-induced increase in glucagon secretion and insulin resistance) [6], but does not always [21,22], result in lower plasma glucose concentration than glucose ingestion alone. Moreover, in people with T2D, protein ingestion-induced insulin secretion can compensate for impaired glucose-stimulated insulin secretion [22]. Accordingly, protein ingestion can have favourable effects on plasma glucose, especially when combined with reduced carbohydrate intake [23], but may adversely affect the plasma hormone profile by increasing plasma

glucagon and insulin, which are risk factors for T2D and ischemic heart disease [6,24,25[¶]].

In the following sections, we review the results from the most recent studies (published in the last 2 years) that evaluated the effect of high-protein intake on basal plasma glucose and insulin concentrations and the metabolic response to meal ingestion that add new insights into the complex relationship between protein intake and postprandial glucose homeostasis. We pay particular attention to the source of protein as the amino acid composition and digestibility of proteins in foods, which can affect the metabolic response to protein ingestion, varies greatly. In addition, bioactive factors that are found in different protein-rich foods, particularly those from plant vs. animal sources (e.g. fiber, saturated fats), could also affect the metabolic response.

Metabolic response to high-protein meal ingestion

Three studies evaluated the metabolic response to high-protein meal ingestion. The additional protein in these studies was derived from predominantly animal-rich foods (eggs, meat, and dairy). In one study, participants with T2D received either isocaloric (2500 kcal per day) high-protein carbohydrate-reduced (30% energy from protein, 30% from carbohydrate, 40% from fat) or standard-protein (15% protein, 55% carbohydrate, 30% fat) meals for 2 days in a randomized cross-over study design [26]. The postprandial metabolic responses to breakfast and lunch were evaluated on day 2 and were characterized by lower plasma glucose and insulin and higher glucagon concentrations after the high-protein reduced-carbohydrate than the standard meals [26]. In another study, participants who were overweight consumed either a high-protein low-fat (30% protein, 51% carbohydrate, 19% fat), an isocaloric standard-protein, high-carbohydrate, low-fat (14% protein, 65% carbohydrate, 21% fat), or an isocaloric standard-protein, high-fat (15% protein, 39% carbohydrate, 46% fat) breakfast and then a standard meal 4 hours later [27]. The postprandial plasma glucose and insulin concentrations after the three breakfasts were not different [27]. In a third study, participants who had previously (on average 6 years earlier) undergone Roux-en-Y gastric bypass surgery and continued to have hypoglycemic episodes, each consumed a breakfast and lunch that were either high-protein carbohydrate-reduced (30% protein, 30% carbohydrate, 40% fat) or contained standard amounts of protein (15% protein, 55% carbohydrate, 30% fat) [28]. Postprandial plasma glucose concentration was not different after

the high-protein carbohydrate-reduced and the standard-protein breakfast but was lower after the high-protein carbohydrate-reduced than the standard-protein lunch whereas postprandial insulin was lower and glucagon was higher after both the high-protein carbohydrate-reduced than the standard breakfast and lunch [28].

Metabolic response to high animal and plant protein meal ingestion

A study that evaluated the postprandial plasma metabolic profile after consuming high-protein meals that contained proteins from predominantly plant (pea) or animal (casein, whey, egg white) sources in people with T2D found a greater increase in plasma glucagon and insulin after the high plant than the high animal protein meal intake whereas plasma glucose was not different after the animal and plant protein meals [29^{¶¶}]. This study did not compare the metabolic response of these meals to a standard-protein meal.

Isocaloric high-protein diet interventions

Two studies evaluated the effect of a high-protein (1.4–1.6 g/kg body weight per day) compared with a standard-protein (0.8 g/kg body weight per day) diet (both from mixed sources of protein) for 10–12 weeks on fasting plasma glucose and insulin concentrations in older adults and found no difference [30,31]. Increased protein intake in these studies occurred at the expense of a small (~10%) reduction in carbohydrate intake [30,31]. Another study evaluated the effect of consuming a high-protein carbohydrate-reduced (30% protein, 30% carbohydrate, 40% fat) compared with an isocaloric standard-protein (17% protein, 50% carbohydrate, 33% fat) diet for 6 weeks on glucose homeostasis in people with T2D [32]. Fasting and postprandial plasma glucose concentrations, postprandial insulin concentration, and HbA1c were markedly (~20%) lower after the high-protein carbohydrate-reduced than the standard-protein diet [32]. These data suggest a high-protein reduced-carbohydrate diet has beneficial effects on plasma glucose homeostasis; however, the results are difficult to interpret as both diets caused weight loss, which itself could have caused these effects [1,3]. Moreover, weight loss was almost twice as great in the high-protein than the standard-protein diet.

Hypercaloric high-protein diet interventions

A carefully controlled, randomized-crossover study evaluated the effect of a hypercaloric high-sucrose

high-protein, compared with a hypercaloric high-sucrose high-fat diet for 6 days on plasma glucose and insulin concentrations in healthy lean men and women. The amount of sucrose and total carbohydrate content were the same in the two diets. Both the hypercaloric high-protein and the hypercaloric high-fat diets increased fasting plasma glucose and insulin and postprandial glucose concentrations with no difference after the two diets whereas the postprandial increase in insulin was markedly (~25%) greater after the high-protein than the high-fat diet, even though the meal glucose content and blood glucose concentration were the same in the two groups; fasting plasma glucagon increased in the high-protein but not the high-fat diet [33²²].

Dietary protein intake and type 2 diabetes risk

The results from several longitudinal population studies suggest an independent adverse effect of high-protein intake on the risk of developing T2D [6,12²³]. In some, but not all of these studies, the association between high-protein intake and the risk of developing T2D was related to the source of protein (increased risk with proteins from animal, but not plant, sources). Often the trend was the same for both animal and plant protein sources but the association with plant protein did not reach statistical significance.

Summary

The new (last few years) data from diet intervention studies confirm the results from previous studies [23,34] that found beneficial effects of high-protein reduced-carbohydrate diets on plasma glucose concentration in people with T2D who lose weight. However, when carbohydrate intake is not markedly reduced, high-protein intake often does not alter plasma glucose and increases insulin and glucagon concentrations. The changes in the hormonal milieu after high-protein intake, especially in the context of carbohydrate and energy excesses, can have potentially detrimental health consequences and provide a physiological mechanism for the association between high-protein intake and increased risk for developing T2D. High insulin secretion and plasma insulin concentration are associated with increased risk of developing T2D, presumably as chronic high insulin secretion can cause insulin resistance and lead to β -cell exhaustion [6,24]. Furthermore, high glucagon has recently been associated with increased risk for developing ischemic heart disease [25²⁴].

HIGH-PROTEIN INTAKE AND ATHEROGENIC DYSLIPIDEMIA

Atherogenic dyslipidemia is characterized by high plasma triglyceride and LDL-cholesterol and low HDL-cholesterol concentrations. It is well established that obesity and a hypercaloric, Western-type diet are involved in the pathogenesis of atherosclerosis but the underlying mechanisms and specific nutrients responsible for the adverse effect are still unclear, because of the complex interaction among not only the types but also sources of macronutrient intake. Saturated, but not unsaturated, fat intake is associated with increased LDL-cholesterol and high carbohydrate intake raises plasma triglycerides and reduces HDL-cholesterol [2,35]. High-protein intake often occurs at the expense of carbohydrate intake and is often accompanied by high saturated fatty acid intake, which can confound the interpretation of results from studies that sought to evaluate the effect of protein intake on plasma lipids.

High-protein intake and plasma lipids in people with overweight or obesity

Four studies recently evaluated the effect of high-protein diets in people with overweight or obesity. One of them found a high-protein (1.6 g/kg body weight per day) compared with a standard-protein (0.8 g/kg body weight per day) diet, in which the increased protein intake occurred at the expense of a small (~10%) reduction in carbohydrate intake, for 10–12 weeks did not affect plasma triglyceride and HDL-cholesterol concentration but increased LDL-cholesterol [31]. The others found daily whey protein (35 g) supplementation [36] or consuming a high-protein (1.2–1.3 g/kg per day) compared with a standard-protein (0.8 g/kg per day) weight loss diet [37,38] did not alter plasma triglyceride, LDL-cholesterol, and HDL-cholesterol concentrations in older women engaged in an exercise training program [36] and in people with obesity and metabolic syndrome enrolled in a weight loss program [37,38], respectively.

High-protein intake and plasma lipids in people with type 2 diabetes

Two studies recently evaluated the effect of high-protein intake on plasma triglyceride concentration in people with T2D. One found that acutely, a high-protein carbohydrate-reduced (29% protein, 31% carbohydrate, 40% fat), compared with a standard-protein (16% protein, 54% carbohydrate, 30% fat) meal increased plasma triglycerides after breakfast but not after lunch, with an overall (from

before breakfast until 2.5 h after lunch) neutral effect on plasma triglycerides [39]. The other found that consuming a high-protein carbohydrate-reduced (30% protein, 30% carbohydrate, 40% fat) compared with an isocaloric standard-protein (17% protein, 50% carbohydrate, 33% fat) diet for 6 weeks decreased plasma triglyceride concentration [32]. However, both diets caused weight loss, and weight loss was almost twice as great in the high-protein than the standard-protein diet (1.4 vs. 0.8 kg), which could have confounded the results.

High-protein intake and plasma lipids in the context of overfeeding in lean people

In a carefully controlled study, conducted in healthy lean men and women, it was found that both a hypercaloric high-carbohydrate high-fat diet and a hypercaloric high-carbohydrate high-protein (reduced fat) diet increased fasting and postprandial plasma triglyceride concentrations without a difference between groups [33²²].

Protein intake and atherogenesis

Studies conducted in animal models suggest high dietary protein intake is involved in the pathogenesis of atherogenic plaques, especially complex plaques that are prone to rupture [40,41²²]. Furthermore, they demonstrate that this adverse effect is caused by protein-derived amino acids, which activate mTOR in plaque macrophages [41²²]. The effect of high-protein intake on vascular health in people is unknown.

Protein intake and cardiovascular disease risk and mortality

The authors of a meta-analysis published in 2013 concluded that a high-protein low-carbohydrate diet score was associated with a ~30% increased risk of all-cause mortality and a trend for increased CVD incident and mortality during an average 6–16-year follow-up period [42]. More recently, a secondary analysis of data collected in the PREDIMED trial confirmed these findings [43].

Summary

Together, the results from diet intervention studies in people suggest that high-protein intake does not alter plasma triglyceride and cholesterol concentrations but the results from studies conducted in animals suggest intake could have detrimental consequences on vascular health by promoting atherogenic plaque formation and deterioration. These

observations in animals are supported by the results from observational studies in people.

HIGH-PROTEIN INTAKE AND NONALCOHOLIC FATTY LIVER DISEASE

NAFLD is a common complication of obesity and is tightly linked to insulin resistance [44,45]. The results from several, but not all, randomized controlled studies suggest high-protein intake has beneficial effects on liver fat content. However, the results are confounded by poor compliance and/or simultaneous decreases in carbohydrate intake or body weight or both, which are important determinants of liver fat content [46]. Following are the results from the most recent studies that evaluated the effect of protein intake on liver fat content.

High-protein isocaloric diets and liver fat

In one study, liver fat content decreased more when participants with T2D were randomized to a high-protein, carbohydrate-reduced (30% protein, 30% carbohydrate, 40% fat) than a standard-protein (17% protein, 50% carbohydrate, 33% fat) for 6 weeks each [32]. However, both diets caused weight loss, and weight loss was almost twice as great in the high-protein than the standard-protein diet (1.4 vs. 0.8 kg). In another study [47], men and women with overweight/obesity (BMI ~31 kg/m²) and prediabetes were randomized to a high-protein or standard-protein diet for 2 years after a short (8 week) period of low-calorie diet-induced weight loss; liver fat content was evaluated before the weight loss intervention and after 6 months and 2 years. After 2 years, liver fat content was significantly decreased from baseline without a difference between groups; however, diet compliance was poor and protein intake was not different in the 2 groups.

Effect of high animal and plant protein diets on liver fat

A study that compared the effect of diets that were enriched (~30% of total energy) in either animal or plant proteins on changes in liver fat content in people with T2D found liver fat declined by about 40% after 6 weeks in both the animal and plant protein groups with no difference between groups [48]. Although the diets were designed to be isocaloric, both groups lost about 1–2 kg of body weight during the 6-week diet intervention. In addition, the study did not include a control group that consumed a standard-protein diet. Therefore, it is unclear whether the beneficial effect of the diets

were because of the high-protein content or the reduction in energy intake or both.

High-protein hypercaloric diet and liver fat

In a carefully controlled, 6-day diet intervention study in young, healthy, lean men and women, it was found that a hypercaloric high-carbohydrate high-fat diet increased liver fat content 6-fold whereas a hypercaloric high-carbohydrate, high-protein (fat-reduced) diet had a much smaller effect (two-fold increase) on liver fat [33^{***}]. These findings suggest high-protein intake can mitigate the adverse effect of high-energy intake on liver fat, even when carbohydrate intake is high. However, the protein content of the high-protein diet was very high (2.7 vs. 0.8 g/kg/day in the control group), which limits the applicability of these results to the general population and clinical practice.

High-protein intake and nonalcoholic fatty liver disease risk

High-protein intake has been linked to the development of NAFLD. Among over 3,500 participants in the Rotterdam study, habitual high-protein intake was an independent risk factor for NAFLD (assessed by ultrasound) in people with a BMI >25 kg/m² [49^{**}]. In another study, which included liver biopsies, high-protein intake (≥17.3% of total energy) was associated with a five times greater risk of NAFLD and a 3.75 times greater risk of liver fibrosis [7^{**}].

Summary

Numerous diet intervention studies have evaluated the effect of high-protein intake on liver fat but the results continue to be difficult to interpret because of concomitant changes in body weight and/or marked reductions in carbohydrate intake. The results from long-term observational studies suggest high-protein intake has adverse effects on liver fat content.

CONCLUSION

The relationship between protein intake and cardiometabolic health is complex and influenced by concomitant changes in body weight and overall diet composition. Many of the purported beneficial effects of high-protein diets are because of markedly reduced carbohydrate and energy intake whereas habitual high-protein intake, which occurs without marked reductions in carbohydrate and energy intake, is associated with increased cardiometabolic

disease risk, presumably mediated by the changes in the hormonal milieu after high-protein intake. Accordingly, increasing protein intake especially by consuming protein-enriched foods, as is popular, should be considered with caution.

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Conflicts of interest

There are no conflicts of interest.

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