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Dietary protein intake and obesity-associated cardiometabolic function

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Abstract

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, non-alcoholic fatty liver disease, and possibly cardiovascular diseases.

Summary and conclusion: 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, non-alcoholic fatty liver disease (NAFLD), and atherogenic dyslipidemia (high plasma triglyceride and LDL-cholesterol and low HDL-cholesterol concentrations), which are important risk factors for serious complications, such as type 2 diabetes (T2D), cirrhosis, and cardiovascular diseases

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Conflict of interest

None

(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 percent of total dietary energy intake) is commonly recommended to help people avoid body weight gain and to help people with obesity lose weight, because 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 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 paper, 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 because 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/d, 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 [10-12*]. Median protein intakes in the 1st, 2nd, 3rd and 4th quartiles of protein intake are 0.8, 1.1, 1.3 and 1.8 g/kg/d, respectively, accounting for 10%−22% of total energy intake across all body mass index (BMI) categories and energy intakes [10–14]. Accordingly, high-protein intake (more than the RDI of 0.8 g/kg/d) 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 (≥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 two 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 because 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 (2,500 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 two days in a randomized cross-over study design [26]. The postprandial metabolic responses to breakfast and lunch were evaluated on day two 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 four 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 six 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 to 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 six 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 because 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 six 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 [33**].

Dietary protein intake and T2D risk

The results from several longitudinal population studies suggest an independent adverse effect of high-protein intake on the risk of developing T2D [6, 12*]. 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 because 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 [25*].

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 to 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 grams) 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 T2D

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 six 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 [33**].

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, 41**]. Furthermore, they demonstrate that this adverse effect is caused by protein derived amino acids, which activate mTOR in plaque macrophages [41**]. 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 to 16 y 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 NAFLD

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 six 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/m^2) and prediabetes were randomized to a high-protein or standard-protein diet for two 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 six months and two years. After two 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 two 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 six 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 six-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 due to the high-protein content or the reduction in energy intake or both.

High-protein hypercaloric diet and liver fat

In a carefully controlled, six-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 six-fold whereas a hypercaloric high-carbohydrate, high-protein (fat-reduced) diet had a much smaller effect (2-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 g/kg/d vs 0.8 g/kg/d in the control group), which limits the applicability of these results to the general population and clinical practice.

High-protein intake and NAFLD 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/m^2 [49**]. In another study, which included liver biopsies, high-protein intake (≥17.3% of total energy) was associated with a 5-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.

Summary and 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 due to 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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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest

** of outstanding interest

[1]. Jensen MD, Ryan DH, Apovian CM et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. J Am Coll Cardiol 2014; 63:2985–3023. [PubMed: 24239920]

[2]. Thom G, Lean M. Is there an optimal diet for weight management and metabolic health? Gastroenterology 2017; 152:1739–1751. [PubMed: 28214525]

[3]. Magkos F, Fraterrigo G, Yoshino J et al. Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity. Cell Metab 2016; 23:591–601. [PubMed: 26916363]

[4]. Quatela A, Callister R, Patterson A, MacDonald-Wicks L. The energy content and composition of meals consumed after an overnight fast and their effects on diet induced thermogenesis: a systematic review, meta-analyses and meta-regressions. Nutrients 2016; 8.

[5]. Sutton EF, Bray GA, Burton JH et al. No evidence for metabolic adaptation in thermic effect of food by dietary protein. Obesity 2016; 24:1639–1642. [PubMed: 27356102]

[6]. Mittendorfer B, Klein S, Fontana L. A word of caution against excessive protein intake. Nat Rev Endocrinol 2020; 16:59–66. [PubMed: 31728051]

[7]. Lang S, Martin A, Farowski F et al. High protein intake is associated with histological disease activity in patients with NAFLD. Hepatol Commun 2020; 4:681–695. [PubMed: 32363319] ** This study shows that high-protein intake is associated with a 5-times greater risk of Non-alcoholic fatty liver disease (NAFLD, assessed by liver biopsy histology) and a 3.75 times greater risk of liver fibrosis.

[8]. Smith GI, Yoshino J, Kelly SC et al. High-protein intake during weight loss therapy eliminates the weight-loss-induced improvement in insulin action in obese postmenopausal women. Cell Rep 2016; 17:849–861. [PubMed: 27732859]

[9]. Te Morenga L, Docherty P, Williams S, Mann J. The effect of a diet moderately high in protein and fiber on insulin sensitivity measured using the dynamic insulin sensitivity and secretion test (DISST). Nutrients 2017; 9.

[10]. Berryman CE, Lieberman HR, Fulgoni VL 3rd, Pasiakos SM. Protein Intake Trends and Conformity with the Dietary Reference Intakes in the United States: Analysis of the National Health and Nutrition Examination Survey, 2001–2014. Am J Clin Nutr 2018; 108:405–413. [PubMed: 29931213]

[11]. Mangano KM, Sahni S, Kiel DP et al. Dietary protein is associated with musculoskeletal health independently of dietary pattern: the Framingham Third Generation Study. Am J Clin Nutr 2017; 105:714–722. [PubMed: 28179224]

[12]. Chen Z, Franco OH, Lamballais S et al. Associations of specific dietary protein with longitudinal insulin resistance, prediabetes and type 2 diabetes: The Rotterdam Study. Clin Nutr 2020; 39:242–249. [PubMed: 30739809] * This is the most recent of a series of papers that find habitual high protein intake in the general population and describe an associations between protein intake and risk of obesity, insulin resistance and type 2 diabetes.

[13]. National Center for Health Statistics. NCHS nutrition data In: Statistics National Center for Health 2017.

[14]. Anderson JJ, Celis-Morales CA, Mackay DF et al. Adiposity among 132 479 UK Biobank participants; contribution of sugar intake vs other macronutrients. Int J Epidemiol 2017; 46:492–501. [PubMed: 27407038]

[15]. Petersen MC, Shulman GI. Mechanisms of insulin action and insulin resistance. Physiol Rev 2018; 98:2133–2223. [PubMed: 30067154]

[16]. Roden M, Shulman GI. The integrative biology of type 2 diabetes. Nature 2019; 576:51–60. [PubMed: 31802013]

[17]. Petersen MC, Vatner DF, Shulman GI. Regulation of hepatic glucose metabolism in health and disease. Nat Rev Endocrinol 2017; 13:572–587. [PubMed: 28731034]

[18]. Ang T, Bruce CR, Kowalski GM. Postprandial aminogenic insulin and glucagon secretion can stimulate glucose flux in humans. Diabetes 2019; 68:939–946. [PubMed: 30833465] ** This study describes the metabolic response to protein ingestion, which is characterized by hyperinsulinemia and hyperglucagonemia.

[19]. Smith GI, Yoshino J, Stromsdorfer KL et al. Protein Ingestion Induces Muscle Insulin Resistance Independent of Leucine-Mediated mTOR Activation. Diabetes 2015; 64:1555–1563. [PubMed: 25475435]

[20]. Newsholme P, Gaudel C, McClenaghan NH. Nutrient regulation of insulin secretion and beta-cell functional integrity. Adv Exp Med Biol 2010; 654:91–114. [PubMed: 20217496]

[21]. Manders RJ, Praet SF, Vikstrom MH et al. Protein hydrolysate co-ingestion does not modulate 24 h glycemic control in long-standing type 2 diabetes patients. Eur J Clin Nutr 2009; 63:121–126. [PubMed: 17717533]

[22]. Ang M, Muller AS, Wagenlehner F et al. Combining protein and carbohydrate increases postprandial insulin levels but does not improve glucose response in patients with type 2 diabetes. Metabolism 2012; 61:1696–1702. [PubMed: 22705093]

[23]. Busetto L, Marangon M, De Stefano F. High-protein low-carbohydrate diets: what is the rationale? Diabetes Metab Res Rev 2011; 27:230–232. [PubMed: 21309052]

[24]. Trico D, Natali A, Arslanian S et al. Identification, pathophysiology, and clinical implications of primary insulin hypersecretion in nondiabetic adults and adolescents. JCI Insight 2018; 3.

[25]. Ng JCM, Schooling CM. Effect of glucagon on ischemic heart disease and its risk factors: a Mendelian Randomization study. J Clin Endocrinol Metab 2020; 105.* This paper describes an independent effect of high glucagon secretion on ischemic heart disease risk.

[26]. Samkani A, Skytte MJ, Kandel D et al. A carbohydrate-reduced high-protein diet acutely decreases postprandial and diurnal glucose excursions in type 2 diabetes patients. Br J Nutr 2018; 119:910–917. [PubMed: 29644957]

[27]. Meng H, Matthan NR, Ausman LM, Lichtenstein AH. Effect of prior meal macronutrient composition on postprandial glycemic responses and glycemic index and glycemic load value determinations. Am J Clin Nutr 2017; 106:1246–1256. [PubMed: 28903959]

[28]. Kandel D, Bojsen-Moller KN, Svane MS et al. Mechanisms of action of a carbohydrate-reduced, high-protein diet in reducing the risk of postprandial hypoglycemia after Roux-en-Y gastric bypass surgery. Am J Clin Nutr 2019; 110:296–304. [PubMed: 30624666]

[29]. Markova M, Hornemann S, Sucher S et al. Rate of appearance of amino acids after a meal regulates insulin and glucagon secretion in patients with type 2 diabetes: a randomized clinical trial. Am J Clin Nutr 2018; 108:279–291. [PubMed: 29982277] ** 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 type 2 diabetes and found a greater increase in plasma glucagon, insulin, and glucose after the high plant than the high animal protein meal.

[30]. Wright CS, Zhou J, Sayer RD et al. Effects of a high-protein diet including whole eggs on muscle composition and indices of cardiometabolic health and systemic inflammation in older adults with overweight or obesity: a randomized controlled trial. Nutrients 2018; 10.

[31]. Mitchell SM, Milan AM, Mitchell CJ et al. Protein intake at twice the RDA in older men increases circulatory concentrations of the microbiome metabolite trimethylamine-N-oxide (TMAO). Nutrients 2019; 11.

[32]. Skytte MJ, Samkani A, Petersen AD et al. A carbohydrate-reduced high-protein diet improves HbA1c and liver fat content in weight stable participants with type 2 diabetes: a randomised controlled trial. Diabetologia 2019; 62:2066–2078. [PubMed: 31338545]

[33]. Surowska A, Jegatheesan P, Campos V et al. Effects of dietary protein and fat content on intrahepatocellular and intramyocellular lipids during a 6-day hypercaloric, high sucrose diet: a randomized controlled trial in normal weight healthy subjects. Nutrients 2019; 11.** This paper describes the effects of a hypercaloric high-sucrose high-protein, compared with a hypercaloric high-sucrose high-fat diet for six days on plasma glucose and insulin concentrations, lipids and liver fat in healthy lean men and women.

[34]. Schwingshackl L, Chaimani A, Hoffmann G et al. A network meta-analysis on the comparative efficacy of different dietary approaches on glycaemic control in patients with type 2 diabetes mellitus. Eur J Epidemiol 2018; 33:157–170. [PubMed: 29302846]

[35]. Bergeron N, Chiu S, Williams PT et al. Effects of red meat, white meat, and nonmeat protein sources on atherogenic lipoprotein measures in the context of low compared with high saturated fat intake: a randomized controlled trial. Am J Clin Nutr 2019; 110:24–33. [PubMed: 31161217]

[36]. Fernandes RR, Nabuco HCG, Sugihara Junior P et al. Effect of protein intake beyond habitual intakes following resistance training on cardiometabolic risk disease parameters in pre-conditioned older women. Exp Gerontol 2018; 110:9–14. [PubMed: 29752998]

[37]. Campos-Nonato I, Hernandez L, Barquera S. Effect of a high-protein diet versus standard-protein diet on weight loss and biomarkers of metabolic syndrome: a randomized clinical trial. Obes Facts 2017; 10:238–251. [PubMed: 28601864]

[38]. Porter Starr KN, Connelly MA, Orenduff MC et al. Impact on cardiometabolic risk of a weight loss intervention with higher protein from lean red meat: Combined results of 2 randomized controlled trials in obese middle-aged and older adults. J Clin Lipidol 2019; 13:920–931. [PubMed: 31771921]

[39]. Samkani A, Skytte MJ, Anholm C et al. The acute effects of dietary carbohydrate reduction on postprandial responses of non-esterified fatty acids and triglycerides: a randomized trial. Lipids Health Dis 2018; 17:295. [PubMed: 30591062]

[40]. Foo SY, Heller ER, Wykrzykowska J et al. Vascular effects of a low-carbohydrate high-protein diet. Proc Natl Acad Sci U S A 2009; 106:15418–15423. [PubMed: 19706393]

[41]. Zhang X, Sergin I, Evans TD et al. High-protein diets increase cardiovascular risk by activating macrophage mTOR to suppress mitophagy. Nat Metab 2020; 2:110–125. [PubMed: 32128508] ** This paper describes the mechanisms by which high protein intake causes atherogenic plaque formation.

[42]. Noto H, Goto A, Tsujimoto T, Noda M. Low-carbohydrate diets and all-cause mortality: a systematic review and meta-analysis of observational studies. PLoS One 2013; 8:e55030.

[43]. Hernandez-Alonso P, Salas-Salvado J, Ruiz-Canela M et al. High dietary protein intake is associated with an increased body weight and total death risk. Clin Nutr 2016; 35:496–506. [PubMed: 25886710]

[44]. Smith GI, Shankaran M, Yoshino M et al. Insulin resistance drives hepatic de novo lipogenesis in nonalcoholic fatty liver disease. J Clin Invest 2020; 130:1453–1460. [PubMed: 31805015]

[45]. Zaharia OP, Kuss O, Strassburger K et al. Diabetes clusters and risk of diabetes-associated diseases. Lancet Diabetes Endocrinol 2019; 7:684–694. [PubMed: 31345776]

[46]. Kirk E, Reeds DN, Finck BN et al. Dietary fat and carbohydrates differentially alter insulin sensitivity during caloric restriction. Gastroenterology 2009; 136:1552–1560. [PubMed: 19208352]

[47]. Drummen M, Dorenbos E, Vreugdenhil ACE et al. Long-term effects of increased protein intake after weight loss on intrahepatic lipid content and implications for insulin sensitivity: a PREVIEW study. Am J Physiol Endocrinol Metab 2018; 315:E885–E891. [PubMed: 30086649]

[48]. Markova M, Pivovarova O, Hornemann S et al. Isocaloric diets high in animal or plant protein reduce liver fat and inflammation in individuals with type 2 diabetes. Gastroenterology 2017; 152:571–585 e578.

[49]. Alferink LJ, Kiefte-de Jong JC, Erler NS et al. Association of dietary macronutrient composition and non-alcoholic fatty liver disease in an ageing population: the Rotterdam Study. Gut 2019; 68:1088–1098. [PubMed: 30064987] ** This large population-based study shows that high-protein intake is associated with increased risk for non-alcoholic fatty liver disease in men and women with obesity.

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, non-alcoholic fatty liver disease, and possibly cardiovascular diseases