

Protein in optimal health: heart disease and type 2 diabetes¹⁻⁴

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ABSTRACT

Diets with increased protein and reduced carbohydrates have been shown to improve body composition, lipid and lipoprotein profiles, and glycemic regulations associated with treatment of obesity and weight loss. Derived from these outcomes, high-protein, low-carbohydrate diets are also being examined for treatment of heart disease, metabolic syndrome, and type 2 diabetes. High-protein, low-carbohydrate diets have been found to have positive effects on reducing risk factors for heart disease, including reducing serum triacylglycerol, increasing HDL cholesterol, increasing LDL particle size, and reducing blood pressure. These diets appear particularly attractive for use with individuals exhibiting the atherogenic dyslipidemia of metabolic syndrome. High-protein, low-carbohydrate diets have also been investigated for treatment of type 2 diabetes with positive effects on glycemic regulation, including reducing fasting blood glucose, postprandial glucose and insulin responses, and the percentage of glycated hemoglobin. Specific effects of increasing protein compared with reducing carbohydrates have not been extensively investigated. Additional research is needed to determine specific levels of protein, carbohydrate, and fat for optimum health of individuals who differ in age, physical activity, and metabolic phenotypes. *Am J Clin Nutr* 2008;87(suppl):1571S–5S.

INTRODUCTION

Does a high-protein (HP) diet have advantages for treatment or prevention of coronary heart disease (CHD) or diabetes? The impacts of dietary protein on heart disease and diabetes are not fully understood. Early population surveys reported statistical associations of total dietary fat, cholesterol, and saturated fatty acids (SFA) with risk of CHD that were often interpreted as associations with protein intake (1, 2). These studies suggested that consumption of the so-called Western diet, which is high in animal products and low in vegetables and whole grains, had a significant correlation with CHD. Dietary protein became a risk factor largely through guilt by association with cholesterol and SFA.

Subsequent epidemiologic studies evaluated health risks across the range of protein intakes and found that subjects in the highest quartile of protein intakes had the highest quality diets and the lowest risk for CHD (2–4). These findings suggest that earlier associations of dietary protein or protein foods with CHD may have been due to coincidental relations with other modern lifestyle factors, including total energy intake, daily physical activity, stress, inconsistent meal patterns, and convenience foods. Many aspects of the interactions of dietary protein with CHD risk factors such as lipids, lipoproteins, and glucose and insulin metabolism have not been extensively studied.

Concepts about the ideal diet for prevention or treatment of type 2 diabetes (T2D) have continued to evolve. High-carbohydrate (HC) diets (55–60% of energy) have been standard recommendations for management of T2D (5). It has been argued that HC diets enhance insulin sensitivity (6, 7) and are beneficial to reduce risks of CHD because of lowering of fat intake (ie, SFA and cholesterol) (8). Further, HP diets were of concern for their potential to produce hyperinsulinemia (9), increase intake of SFA (8), and accelerate nephropathy (8). These views are being reevaluated with emerging recognition that diets with reduced carbohydrate and increased protein are better for glycemic control and weight management than are HC, low-fat (LF) diets (10). Continued research is necessary to fully understand the impact of dietary protein on heart disease and T2D.

DIETARY PROTEIN INTERACTIONS WITH BLOOD LIPIDS AND HEART DISEASE

A consequence of increasing dietary protein is a reduction in the proportions of carbohydrates and/or fats in the diet. Central questions in evaluating the significance of dietary protein on blood lipids and CHD risk include:

- Does an HP diet have a metabolic advantage over low-protein (LP), HC diets for improvement of plasma lipids and lipoprotein profiles or blood pressure?
- Are the benefits of an HP diet the result of the increase in protein or, rather, a reduction in carbohydrates or fats?

Diets with increased protein have been extensively evaluated for treatment of obesity (11). In conjunction with weight loss, diets in which carbohydrates are replaced by protein (with or without fat) result in improvements in body composition (11) and in plasma lipids and lipoproteins (12–27).

As is the case with all weight loss regimens, the most consistent effect of HP weight-loss diets on blood lipids is reduction in

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serum triacylglycerols (TAG). In randomized clinical trials with normolipidemic subjects, serum TAG were reduced by 30% to 55% from prestudy values (16–18). Changes in TAG levels appear to be maintained long term; however, the magnitude of the differences diminishes as subjects depart from diet compliance (17–19). Interpretation of protein-specific effects within clinical trials is often difficult because of limitations with monitoring food intake and determining actual protein intake.

However, the randomized clinical trials are further supported by short-term weight-loss studies with controlled food intake (12, 14, 20). In studies with meals provided (12, 14) or highly defined meal patterns (20), TAG were reduced by 20% to 55% from baseline. In these studies daily protein intake ranged from 100 to 130 g/d ($\approx 30\%$ of energy intake) with carbohydrates restricted to ≈ 140 g/d ($\approx 40\%$ of energy) and fat consumption at $\approx 30\%$ of energy. Similar results have also been reported for weight-loss studies that reduced carbohydrate intake to <50 g/d ($<20\%$ of daily energy) and increased fat intake to >100 g/d ($\approx 45\%$ of energy) (15, 21).

Other lipoprotein responses to changes in protein and carbohydrate intakes are more complex and reflect diverse genetic and metabolic differences among individuals. Factors that influence lipoprotein responses include baseline lipoprotein patterns (ie, genetic phenotype), dietary fat content of the diets, insulin responsiveness of subjects, and total energy intake (ie, body weight changes). Despite these differences across studies, lipoprotein changes associated with consumption of HP, low-carbohydrate (LC) diets usually include increases in HDL cholesterol concentrations and increases in LDL particle size (13, 15, 22, 23).

Weight-loss studies with normolipidemic, nondiabetic subjects consuming HP/LC diets report inconsistent effects on total cholesterol (TC) or LDL cholesterol concentrations but generally report increases in HDL cholesterol concentrations and decreases in ratios of LDL:HDL and TAG:HDL. For studies comparing HP/LC diets with diets reflecting more standard carbohydrate:protein ratios, TC and LDL cholesterol concentrations have been reported to decrease (12, 24), increase (17), or remain unchanged (14, 20, 25). Short-term studies (<6 mo) during periods of active weight loss report larger decreases in TC and LDL cholesterol for subjects consuming HC/LF diets (14, 15, 17, 22, 26), whereas long-term studies (>6 mo) report that TC and LDL cholesterol tend to be reduced from initial baselines for both HP/LC and LP/HC diets, but there are no differences between diet treatments (17–19). During weight loss, HDL cholesterol concentrations tend to increase with HP diets (12–14, 26) but decrease with HC/LF diets (28). The net differences between the diets result in significant decreases in LDL/HDL and TAG/HDL. Similar findings have been reported by Volek and Sharnan (27) through the use of very-low-carbohydrate diets, which consistently resulted in lower TAG and increased HDL cholesterol with variable effects on TC and LDL cholesterol concentrations.

Determination of specific effects of changes in protein, carbohydrate, or fat intakes in the studies reviewed above is confounded by weight loss, which Datillo and Kris-Etherton (28) reported is an independent factor in altering LDL and HDL values. Krauss et al (22) controlled for diet compared with weight changes through the use of diets that provided 54%, 39%, or 26% of energy from carbohydrates plus 16% or 29% of energy from protein and 30% or 45% of energy from fat. Across all treatments, diets with reduced carbohydrates and increased protein resulted

in reduced TAG concentrations, increased LDL-particle size, and reduced ratio of TC:HDL. Comparing specific diet treatments, effects on LDL-cholesterol concentrations were the most complex. During the weight-stable period, the diet with very-low-carbohydrate (26% of energy) combined with low SFA (8%) resulted in lower LDL cholesterol concentrations than the HC (56%) control diet or either the moderately-low-carbohydrate (39%), low-SFA (8%) diet or the very-low-carbohydrate (26%), high-SFA (15%) diet. Reduced LDL cholesterol with the lowest carbohydrate intake was due to lower levels of small dense LDL, and this reduction was independent of saturated fat intake. After the period of energy restriction and weight loss, LDL cholesterol concentrations were not different across any of the treatment groups, supporting earlier reports that, in conjunction with weight loss, LDL cholesterol concentrations are more sensitive to energy intake and changes in body weight than to specific macronutrients (28).

Similar effects on lipoproteins have been reported for hypercholesterolemic subjects. Through use of diets that were isocaloric and maintained stable body weight, Wolfe and Giovannetti (29) compared lipoprotein responses in subjects randomly fed an HC/LP/LF diet (HC: 65%, 11%, 24% of energy, respectively) or a reduced-carbohydrate, moderate-protein, LF diet (LC: 53%, 23%, 24%). After 4 or 5 wk on each diet, the LC treatment resulted in 23% lower TAG, 6.5% lower TC, 6.4% lower LDL cholesterol, and 12% higher HDL cholesterol compared with the HC group.

The weight-loss studies suggest that replacement of carbohydrates with protein has beneficial effects on blood lipids. However, with reduction in total energy intake and changes in the ratios of all 3 macronutrients (carbohydrate, protein, and fat), it is difficult to untangle effects of increasing protein compared with reducing carbohydrates. McAuley et al (23) provide evidence that the primary effect on lowering TAG is associated with lowering carbohydrates. In a study that used insulin-resistant, overweight women as its subjects, they compared changes with HC, HP, and high-fat diets. After 24 wk, women in the HP and high-fat groups had greater reductions in body weight and TAG than the HC group. LDL cholesterol decreased for subjects in the HC and HP groups, and LDL cholesterol was significantly lower for the HP compared with high-fat groups. This study suggests that increasing dietary fat as an approach to lower carbohydrates may not be as efficacious as increasing protein.

The pattern of lipid changes observed with HP weight-loss diets parallels the significant body of research focused on dyslipidemia (elevated TAG and low HDL cholesterol) and insulin resistance (30, 31). It is well established that dietary carbohydrates, particularly sugars, promote atherogenic dyslipidemia (30–32). For many years investigators have recognized the associations of glucose intolerance, insulin resistance, increased TAG, low HDL cholesterol, and elevated blood pressure (33). These relationships underlie the metabolic syndrome (MetS). Both dyslipidemia and MetS are risk factors for CHD and mortality (34). Numerous studies with nondiabetic and diabetic subjects have evaluated reduced-carbohydrate diets for treatment of the dyslipidemia associated with MetS. Most of these studies reduce carbohydrates by replacement with fat as an energy substitute (35). These studies consistently find that reducing dietary carbohydrates and increasing fat reduces TAG and the ratio of TAG:HDL. These findings are consistent with similar changes through use of protein as a substitute for carbohydrates (22),

implying that the primary factor influencing TAG concentrations is dietary carbohydrates.

Along with changes in TAG and LDL cholesterol concentrations, there are also significant changes in the LDL particle size with reduction in the number of small, dense LDL particles (phenotype pattern B) to large, buoyant particles (pattern A) (22, 36). It is well established that there is an inverse relation between LDL particle size and plasma TAG concentration (37, 38) and TAG/HDL (39). As TAG concentration increases, the size of the LDL particle is reduced. Further, as subjects with atherogenic dyslipidemia (pattern B) modify their diet to reduce carbohydrates, their LDL particle size shifts to the less atherogenic pattern A. These studies suggest that diets that reduce carbohydrate intake by replacement with either protein or fat produce similar changes in blood lipids particularly associated with atherogenic dyslipidemia (22, 27, 36, 40). These lipoprotein changes can occur in conjunction with changes in glucose homeostasis and insulin action (35). Use of protein as a substitute for dietary carbohydrate may have independent effects on glycemic regulation (41, 42), a possibility that makes the use of protein a more attractive dietary change than increases in fat intake.

Perhaps the strongest protective influence of increased protein intake per se is for lowering blood pressure (BP). Elevated BP is a major risk factor for CHD. Inverse relations between protein intake and BP have been reported in many (43, 44) but not all (45) studies. The NHANES III study found no relation of protein with reducing BP but did show an attenuation of the age-related increase in blood pressure with protein intake (45). Reaven (33) has also argued that BP is one of the fundamental components of MetS and that decreases in dietary carbohydrates reduce BP in people with essential hypertension and insulin resistance. So, whereas evidence is consistent that diets with increased protein and reduced carbohydrates lower BP, no definitive mechanisms are available to explain either direct or indirect effects of protein or carbohydrates on BP.

Individual amino acids have also been proposed as mediators of metabolic effects that may alter risks for CHD. Amino acids such as arginine may be important through their influence on nitric oxide synthesis or methionine as a precursor to homocysteine. Current studies have not found any significant relations of protein intake and plasma homocysteine (25). These are obvious areas for further research.

PROTEIN INTAKE, GLUCOSE HOMEOSTASIS, AND TYPE 2 DIABETES

Central questions in evaluating the significance of dietary protein on glycemic regulations are similar to questions discussed previously for CHD and include:

- Does an HP diet have a metabolic advantage over LP/HC diets for improvement of glucose homeostasis or insulin action?
- Are the benefits of an HP diet due to the increase in protein or, rather, reduction in carbohydrates or fats?

Diets with increased protein and reduced carbohydrates have been shown to improve glycemic regulations in normal subjects (42, 54) and people with T2D (13, 46–48) or obesity (20, 49, 50). Improvements in glycemic regulations include reduced postprandial (PP) glucose response (ie, area under the curve) (20, 46, 47), modification of insulin response (20, 46, 47), and reduced glycated hemoglobin percentage (HbA1c) (46–48).

Interactions of protein and amino acids with carbohydrate metabolism have been recognized for years. Amino acids directly contribute to de novo synthesis of glucose via gluconeogenesis and participate in recycling of glucose carbon via the glucose-alanine cycle. Dietary protein and, specifically, the amino acids glycine (51) and leucine (41) stimulate insulin release from the pancreas, and leucine serves to modulate the intracellular insulin signal in skeletal muscle and adipose tissue (41). Whereas these interactions of amino acids with glucose metabolism are well established, the net impact of amino acids on glucose homeostasis remains unclear. The research literature (9, 42) contains reports of both positive and negative impacts of amino acids on glycemic regulations.

Studies by Sweeney (52) and Himsworth (6) reported that normal subjects fed increasing levels of carbohydrates increased their capacity for disposal of an oral glucose challenge. These studies are often cited as early evidence that HC diets increase insulin sensitivity, and the converse, LC diets are argued to be diabetogenic (53). Later studies reported that amino acids decrease glucose disposal, induce hyperinsulinemia and hyperglycemia, and potentially lead to insulin resistance (9, 54). These studies used intravenous infusion of amino acids with euglycemic clamp techniques to measure glucose uptake and insulin resistance. Acute increases in plasma amino acids were found to increase plasma glucose concentrations, decrease glucose uptake, and increase plasma insulin levels (9, 54).

Contrary to these reports, studies examining metabolic responses in normal subjects consuming meals in which protein was substituted for carbohydrates found that HP/LC diets reduced PP insulin response and decreased 24-h area under the curve for both glucose and insulin (42, 49, 55, 56). Floyd et al (55, 56) compared intravenous infusion of amino acids with oral consumption of whole protein and found acute hyperinsulinemia after the intravenous infusion but minimal PP insulin response after oral consumption. These findings highlight the importance of the gastrointestinal tract and liver in modulating amino acid metabolism and glycemic regulations (41, 57).

Other variables that influence the impact of dietary protein on glycemic regulations include energy intake (ie, weight status) and baseline glucose homeostasis (ie, diabetes). Weight loss or just a reduction in food energy has repeatedly been shown to reduce fasting glucose concentrations and improve blood glucose control in people with (13, 58, 59) or without (20, 49) T2D. As discussed in the preceding section on protein and CHD, increases in dietary protein can facilitate weight loss (60), in part because of effects on satiety.

Krezowski et al (42) reported similar effects on glycemic regulations for normal, weight-stable subjects. Through the use of isoenergetic meals, they found that substituting dietary protein for carbohydrates reduced meal responses for both plasma glucose and insulin (42). Comparing subjects after consumption of a test meal containing 50 g of protein (lean beef) compared with 50 g of glucose, they found that consumption of protein alone had essentially no impact on PP plasma glucose concentrations, and the insulin response to the protein was <30% of the response with a comparable energy intake from glucose (42).

Treatment of T2D with restriction of dietary carbohydrates has produced similar improvements for glycemic regulations (7, 46–48, 61–63). HP/LC diets decreased fasting plasma glucose and reduced HbA1c when compared with responses with HC/LP diets (46–48, 63). Through the use of controlled feeding studies

in a metabolic ward, Gannon et al (46, 47) and Gannon and Nuttall (62) conducted direct comparisons of HP/LC compared with HC/LP diets in subjects with T2D. They found that HP/LC diets reduced fasting plasma glucose, 24-h glucose area under the curve, and HbA1c; the reduction in HbA1c was proportional to the reduction in carbohydrates (62). An important difference in people with T2D is that dietary protein appears to stimulate insulin release at levels similar to dietary carbohydrates (64). Therefore, whereas replacement of dietary carbohydrates with protein results in reduced PP glucose response, protein maintains an equivalent insulin response that is significantly higher than replacement with dietary fat (65). This difference may be important for long-term maintenance of muscle mass and bone health, but the long-term outcomes of diets with increased protein on health outcomes in people with T2D remains to be determined.

Studies with free-living subjects report similar findings for HP/LC diets; however, differences between diets are less consistent (13, 48, 63). Use of HP/LC diets for weight loss also improves glycemic control (13, 46). In studies in which subjects from both diet treatments had similar weight losses, effects on glycemic regulations were similar between groups. Differences in glycemic control between diet treatments are more readily observed in studies with highly controlled feeding protocols (7, 14, 46, 62) compared with studies with free-living subjects with presumably lower diet compliance and/or less-regular meal patterns (26, 63, 66).

In summary, these studies demonstrate that either HP/LC or HC/LP diets can be effective for management of T2D, particularly if body weight and total food intake are carefully controlled. In a recent review of the research by a joint committee of the American Diabetes Association, North American Society for the Study of Obesity, and the American Society for Clinical Nutrition (10), the panel concluded that weight loss should be a primary goal for management of T2D and that weight loss and "glycemic control was better with low-carbohydrate than with low-fat diet therapy in subjects with T2D." However, the panel also advised that "it is unlikely that one diet is optimal for all overweight or obese persons" and that "dietary guidance should be individualized to allow for specific food preferences and individual approaches to reducing energy intake." Thus, at least for certain individuals, a diet with increased protein and reduced carbohydrates, which is effective for weight management and also improves lipid and lipoprotein profiles and glycemic regulations, may be an optimal choice.

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