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A new look at dietary protein in diabetes[1,2]

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The optimal diet for patients with diabetes continues to be evaluated. Currently, at least 3 nutritional issues are important to consider in patients with type 2 diabetes. Because overweight and obesity exist in most patients with type 2 diabetes, the first—but not always the highest—dietary priority relates to energy balance. Typically what is needed is a hypocaloric diet, in which energy expenditure is greater than energy intake. The second and third nutrition-related issues in patients with diabetes are glycemic control and macrovascular or microvascular complications, both of which relate more to the macronutrient composition of the diet than body weight. The near-consensus opinion about diet and macrovascular complications of diabetes is to restrict the consumption of saturated and *trans* fats and cholesterol (1). Concerning microvascular complications, there is some—albeit insufficient—evidence to recommend restrictions in dietary protein for patients with nephropathy, as defined by gross proteinuria, diminished renal function, or both (2–4).

Glycemia is the most immediate and lasting effect of diet therapy in patients with diabetes. Historically, the emphasis has been placed on dietary carbohydrate restriction, with the related and necessary increases in dietary fat and protein to achieve reductions in fasting and postprandial plasma glucose concentrations (5). The increase in protein was an "innocent bystander" because most fat-containing foods are higher in protein. After insulin became available for the treatment of diabetes and after the potential relation between high fat intake, hypercholesterolemia, and atherosclerosis was appreciated, the pendulum swung toward recommended increases in dietary carbohydrate and relative restrictions in dietary fat—particularly saturated fat and its associated protein. Although the restriction of saturated fat remains the recommendation, the carbohydrate-fat ratio continues to get attention (6). The effect of dietary protein on glycemic control has been more carefully examined in the past 15 y; however, the science has suffered from flaws in experimental design, small sample size, and insufficient short-term and long-term data.

The typical design of published glycemia studies involves the examination of the effect of a single meal of added protein compared with that of other macronutrients on postingestion plasma glucose and insulin concentrations. In general, these studies showed no or only modest increases in postprandial insulin concentrations; most often, however, no changes in glucose were shown (7–10). The study by Gulliford et al (8) points out the limitations of interpretation that accompany many of these published studies. In the study by Gulliford et al (8), the consumption of 25 g protein as tuna fish in combination with 25 g carbohydrate as either mashed potatoes or spaghetti failed to modify postprandial insulin concentrations in subjects with type 2 diabetes, but a lower glycemic response was seen with mashed potatoes than with spaghetti. The further co-ingestion of 25 g fat as margarine reduced the differences in the glycemic effect of the 2 carbohydrates. Thus, as expected, the glycemic index of a single dietary protein was modified by the co-ingestion of a single 25-g load of carbohydrate with different physical properties and then again by the co-ingestion of one form of fat. The possible macronutrient combinations to examine are infinite, and applied conclusions remain extremely limited from this type of experimental design.

The study design is the strength of the study by Gannon et al (11) in this issue of the Journal, although sample size was small and the duration of the study was limited. Gannon et al tested the hypothesis that a 5-wk period of increased dietary protein through a variety of foods would produce a lower plasma glucose response to feeding in subjects with type 2 diabetes. The subjects typically had mild, untreated type 2 diabetes and had a mean age of 61 y and a mean body mass index (in kg/m^2) of 31. Subjects were randomly assigned to consume a high-protein (30% of energy) or a lower-protein (15% of energy; control) diet—with differences in carbohydrate intake (40% compared with 55% of energy) but not fat (30% of energy in both diets) between the 2 diets—for 5 wk with a washout period before crossover to the alternative diet. In addition, dietary fat was fixed at 30% of caloric intake by using a balance of polyunsaturated, monounsaturated, and saturated fats (10% of energy from each). Importantly, all meals were provided to the subjects, weight was maintained, and 24-h assessments of plasma glucose and insulin and other metabolites were made under close observation. Subjects were considered to have been compliant if they had a 2-fold increase in the ratio of urinary urea to creatinine with the high-protein diet. Impressively, the high-protein diet resulted in a 40% reduction in the 24-h integrated plasma glucose area and a significant decrease in glycated hemoglobin after just a 5-wk interval. Although the plasma insulin, C-peptide, and free fatty acid area responses were not significantly different and the plasma glucagon concentrations were higher with the high-protein diet than with the low-protein diet, the triacylglycerol area response was also reduced.

Despite these impressive results, additional questions remain. Are these results reproducible, and, if so, how long will the benefit of high-protein feeding last? What would the effect of such a diet be in patients with diabetes taking oral hypoglycemics or insulin? Does the type of oral hypoglycemic drug taken—ie, sulfonylurea compared with metformin compared with thiazolidinedione—matter? If the caloric content were not controlled,

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would patients lose weight, and, if so, would the glycemic effect be exaggerated? Of interest, a trend for weight reduction was seen in the high-protein group. What effects would result if the study lasted for months, years, or even a lifetime? Will high-protein diets remain palatable and not overly restrictive over the long term? Moreover, in this setting, will patients with diabetic nephropathy experience the same benefit without progression of renal disease? A similar question could be posed about patients with autonomic neuropathy, ie, gastroparesis. Because some concerns exist about the effect of higher protein intakes on urinary calcium excretion, would skeletal mass be adversely affected long term (12)?

Many myths about dietary protein and diabetes control need to be recognized, as recently summarized (13). Although nonessential amino acids may promote glucose production, plasma glucose does not increase after protein ingestion. Moreover, increases in dietary protein do not promote sustained elevations in glucose, slow the absorption of dietary carbohydrate, or accelerate the increase in plasma glucose in response to insulin-induced hypoglycemia. The variable ability of dietary protein to increase insulin secretion or to decrease insulin clearance may be related to the experimental design, the type of protein ingested, or both. Additional work is clearly needed here. With the studies of Gannon et al (11) now in hand, the substitution of dietary protein for carbohydrate may improve glycemic control without increasing the risk of atherosclerosis. The recommended percentage of energy in the diet from saturated fat, however, should not exceed 7% (1, 14). The stage is set for long-term studies that use different food sources of dietary protein and to determine the relevance of increasing dietary protein in patients with more complicated diabetes.

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