Could lowering fat intake reduce diabetes risk even if it doesn’t lead to weight loss?

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“...both patient characteristics and energy balance status may be important variables to consider when making decisions on diet recommendations for at-risk patients.”

Diabetes affects 8.3% of the US population, and has an annual economic burden of $174 billion (data from 2007) [1]. By some estimates, over 300 million people worldwide will have diabetes by the year 2030 [2]. The majority of these cases will be Type 2 diabetes (T2D), a disease closely tied to obesity and lifestyle. Although weight loss is often recommended for treatment/prevention of T2D, weight loss is difficult to achieve for many individuals. Effective, easily implementable, non-pharmacologic means that do not depend on weight loss are needed for prevention of T2D.

Diet modification is an obvious choice for a lifestyle change that can be implemented at the individual level, and that may have significant positive benefits for prevention of T2D, but the optimal diet to recommend is not clear. Traditionally, high-fat diets have been considered the villain with regards to metabolic health. Indeed the American Diabetes Association currently recommends minimizing fat intake for the prevention of T2D [3]. However, it recently has been proposed that excessive intake of highly processed carbohydrate (CHO)-containing foods may also contribute to the development of T2D [4]. Should clinical care providers suggest that their patients cut back on fat or CHOs?

The answer to this question is not simple and may depend on patient characteristics. For example, is the patient also looking to lose weight? Has he or she already progressed to impaired glucose tolerance or impaired fasting glucose (IFG)? Do they have a unique genetic background that may predispose them to T2D? Individuals of certain racial/ethnic backgrounds, such as African-Americans (AAs), native Americans, and Asian Indians, are at disproportionately greater risk for T2D than those of European ancestry.

We recently completed a study designed to address some of these issues [5,6]. Specifically we looked at the effects of a lower fat (higher CHO) versus a higher fat (lower CHO) diet on fasting glucose, glucose tolerance, insulin sensitivity and β-cell function, all of which are processes that reflect metabolic health as it relates to risk for T2D. Our subject population comprised individuals considered at-risk for T2D: all were overweight or obese, half were AA and a third had IFG. We fed the participants a tightly controlled,
weight-maintenance diet for 8 weeks, providing them with all of their food. The lower-fat (higher-CHO) diet had a macronutrient composition of 55% energy from CHO, 18% energy from protein and 27% energy from fat. This diet also contained foods with a relatively high glycemic index, such as mashed potatoes, white rice and white bread. The higher-fat diet (43% CHO:18% protein:39% fat) had a lower glycemic load and higher fiber intake. Sources of fat in both diets were predominantly poultry, nut butters, eggs and dairy products.

Results indicated that the lower-fat diet (which was higher-CHO) was associated with a number of beneficial metabolic effects. Among all subjects combined, the lower-fat diet resulted in improved ‘static’ β-cell function, which is the amount of insulin secreted for a given amount of glucose across the entire test. This change in β-cell response was associated with improved glucose tolerance, and was particularly strong among AAs. We also noted that the lower-fat diet resulted in lower fasting glucose and improved ‘dynamic’ β-cell responsiveness among the subgroup with IFG. The dynamic response is similar to the acute-phase or first-phase response, and is the phase that declines among individuals who are beginning to progress towards T2D (e.g., those with impaired glucose tolerance or IFG). In addition, the lower-fat diet improved insulin sensitivity among subjects who were normal glucose tolerant. By contrast, the higher-fat diet (which was lower-CHO) was associated with no metabolic benefits. Although the molecular mechanism responsible for the adverse effects of high dietary fat is not known, recent data obtained with mouse models implicated impaired glucose transport in the β-cell [7].

These results would seem to verify that current recommendations regarding diet composition remain valid. Despite the fairly unfavorable types of CHO foods provided with the lower-fat diet, this diet nonetheless was more beneficial than the lower-CHO, higher-fat diet. Do these observations imply that lower-CHO diets have no place in diabetes prevention? Not necessarily. One important point must be made about our results: we conducted the study under weight maintenance conditions. It is entirely possible that results may have differed if the subjects were in negative energy balance. Indeed, in the context of weight loss, favorable effects of lower-CHO diets on metabolic outcomes have been observed [4]. Furthermore, lower-CHO diets may enhance weight loss [4,8], particularly loss of metabolically unfavorable abdominal fat [9]. Thus, it may be important to consider energy balance status when formulating diet recommendations. This concept has not been widely appreciated and bears further study. The idea that lower-CHO diets might be best for promoting weight loss, but that lower-fat is preferable for metabolic health during weight maintenance is an interesting hypothesis, but one not yet adequately tested.

Why would energy balance status alter the effect of diet composition? Data from animal models suggest that the interactive effects of glucose and fatty acids may explain this conundrum. According to the theory of ‘gluco-lipotoxicity,’ fat is bad when glucose is high [10,11]. The combination of high glucose and high fat overwhelms the metabolic machinery of the β-cell. ‘Fuel overload’ results in impaired mitochondrial function and concomitant excessive production of reactive oxygen species. β-cells have fewer antioxidant defenses than other tissues [11], making them particularly vulnerable to oxidative stress-induced damage. Fasting glucose concentration increases with obesity, and decreases with negative energy balance (and active weight loss). This lowering of glucose may minimize the adverse effects of a higher-fat (lower-CHO) diet on β-cell function and metabolic processes. Thus, from a clinical care perspective, it may be critical to consider the energy balance status of the patient when devising diet composition.

The adverse interactive effect of fat and glucose may explain why our lower-fat diet was particularly effective among subjects with IFG. The IFG subgroup was not only overweight, but had elevated fasting glucose. Furthermore, this group had greater fasting glucose. Furthermore, this group had greater fasting glucose, which is associated with elevated circulating free fatty acids [12]. When on the lower-fat (higher-CHO) diet, these individuals showed both a decline in fasting glucose and an increase in the dynamic β-cell response. These events are likely to be linked, as several cross-sectional studies have shown that elevated fasting glucose is associated with depressed β-cell response (reviewed in [13]). Experimental studies have indicated that elevation in fasting glucose results in decreased β-cell responsiveness. Thus, it is possible that a lower-fat diet may be particularly beneficial for individuals with impaired fasting glucose.
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Another subgroup that appeared to derive relatively greater benefit from the lower-fat diet was AAs, who showed a stronger improvement in β-cell responsiveness than did the European–American (EA) subgroup. Why would ethnicity matter? AAs may be particularly susceptible to the adverse metabolic effects of fat owing to their inherent energetic efficiency. In *vitro* [14] and *in vivo* [5,16] studies have shown that bioenergetic ‘economy’ is significantly higher among AAs than EAs. This economy would render AAs less able to accommodate excess fuel, and in the presence of excess fuel, would lead to greater production of reactive oxygen species and oxidative damage at the molecular level [17]. Because β-cells have fewer antioxidant defenses than other tissues [11], β cells may be particularly vulnerable to a higher-fat diet. Although our higher-fat diet did not have more energy on an absolute level than the lower-fat diet, it was more energy dense, which may have been metabolically relevant on an acute basis. We also have observed that β-cell function compromises body fat [18] and circulating free fatty acids (Unpublished observation) to a greater extent in AAs than in EAs. Taken together, these observations suggest that the β cells of AAs may be particularly sensitive to the insult of a higher-fat diet. It is noteworthy that the Dietary Approaches to Stop Hypertension (DASH) diet, which is similar in composition to our lower-fat diet, appeared more effective in reducing both blood pressure and estimated coronary heart disease risk in black compared with white individuals [19].

In summary, the relative merits of ‘low-CHO’ and ‘low-fat’ diets undoubtedly will be debated for years to come. Both reduction in simple (processed) CHO and saturated fat are likely to be beneficial for metabolic health, regardless of overall dietary macronutrient composition. Beyond that, our recent data suggest that in a weight-maintenance situation, reduction in dietary fat to <27% may reduce risk for T2D in overweight/obese individuals, particularly those with IFG and who are AA. Unique metabolic properties of these subgroups may render them particularly sensitive to the adverse effects of dietary fat. Thus, both patient characteristics and energy-balance status may be important variables to consider when making decisions on diet recommendations for at-risk patients.

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**Bibliography**


