

# Diet, Insulin Resistance, and Obesity: Zoning in on Data for Atkins Dieters Living in South Beach

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Insulin resistance is a central pathogenic factor for the metabolic syndrome and is associated with both generalized obesity and the accumulation of fat in the omental and intramyocellular compartments. In the context of the current obesity epidemic, it is imperative to consider diets in terms of their ability to both promote weight loss and ameliorate insulin resistance. Weight loss under any dietary formulation depends on hypocaloric intake, and only moderate weight loss (5–10%) is sufficient to augment insulin sensitivity. However, increments in insulin sensitivity may be more directly related to loss of intramyocellular or omental fat rather than loss of total body weight *per se*. The widespread acceptance of popular low-carbohydrate high-fat diets (e.g. Atkins Diet, Zone Diet, South Beach diet) further underscores the need to evaluate dietary interventions regarding their safety and metabolic effects. These high-fat diets have been shown to be safe in the short term; however, their long-term safety has not been established. With respect to insulin sensitivity, diets enriched

in saturated fats can induce insulin resistance, whereas fat substitution with monounsaturated fats can enhance insulin sensitivity. On the other hand, high-fiber, high-carbohydrate diets comprised of foods with low caloric density can similarly be used for effective weight reduction and to ameliorate insulin resistance. Although some data suggest that low-glycemic index diets are most advantageous in this regard, these effects may have more to do with increments in dietary fiber than differences in available carbohydrates.

Popular low-carbohydrate, high-fat diets are being fervently embraced as an alternative to challenging modifications in lifestyle and intentional calorie reduction. Current data do not support such unbridled enthusiasm for these diets, particularly in relationship to high-fiber, high-carbohydrate diets emphasizing intake of fresh vegetables and fruits. Long-term studies to determine the efficacy and safety of both popular and experimental diets are warranted. (*J Clin Endocrinol Metab* 89: 4197–4205, 2004)

## Insulin Resistance, Obesity, and the Insulin Resistance Syndrome

### *The insulin resistance syndrome (IRS)*

Insulin resistance is central to the pathogenesis of type 2 diabetes and helps maintain the diabetic state (1). Furthermore, insulin resistance antedates the development of diabetes and places individuals at increased risk of future diabetes. In nondiabetic individuals, insulin resistance is associated with multiple clinical and anthropometric traits, and this trait cluster is referred to as the IRS or the metabolic syndrome. Specifically, the IRS is characterized by relative hypertension, glucose intolerance, upper body fat distribution, generalized obesity, dysfibrinolysis, and dyslipidemia characterized by high triglycerides, low high-density lipoprotein cholesterol, and small, dense low-density lipoprotein (LDL) particles (2). The IRS constitutes a powerful risk factor complex, not only for future type 2 diabetes, but also for atherosclerotic diseases (3). To identify patients for more aggressive risk factor management and disease surveillance, diagnostic criteria for the IRS have recently been devised (4, 5). However, we have pointed out that these criteria exhibit poor sensitivity for identifying patients with insulin resis-

tance and dyslipidemia and do not take into account the impact of age, race, and ethnicity (6).

### *Obesity and insulin resistance*

One characteristic that can be associated with insulin resistance is obesity. This relationship is illustrated in Fig. 1A, which correlates body mass index (BMI) and maximally stimulated glucose disposal rates using the hyperinsulinemic euglycemic clamp. Glucose uptake is normalized per kilogram lean body mass, reflecting the fact that skeletal muscle accounts for the bulk of insulin-mediated glucose uptake *in vivo*. Clearly, increased obesity is associated with insulin resistance. However, there is a high degree of variation such that lean or obese individuals can be either relatively insulin sensitive or resistant. In fact, the correlation coefficient (*i.e.*  $R^2$ ) indicates that only 8% of individual differences in insulin sensitivity can be explained by differences in BMI. Thus, although obesity is an important factor (7–9), individual variation in insulin sensitivity largely exists independent of the degree of generalized obesity (10–12).

Other important factors contributing to insulin resistance include the accumulation of omental fat (*i.e.* upper body fat distribution) and fat in the intramyocellular compartment, both of which can exist independent of the degree of general adiposity. As shown in Fig. 1B, increased ratio of trunk to leg fat is more highly correlated with reduced insulin sensitivity (*i.e.* lower stimulated glucose disposal rates) than observed for BMI. Multiple authors have demonstrated that it is a relative redistribution of fat to the omental compartment that

Abbreviations: BMI, Body mass index; CLA, conjugated linoleic acid; FA, fatty acid; fsIVGTT, frequently sampled iv glucose tolerance test; GI, glycemic index; IRS, insulin resistance syndrome; LDL, low-density lipoprotein; MUFA, monounsaturated FA; PUFA, polyunsaturated FA.

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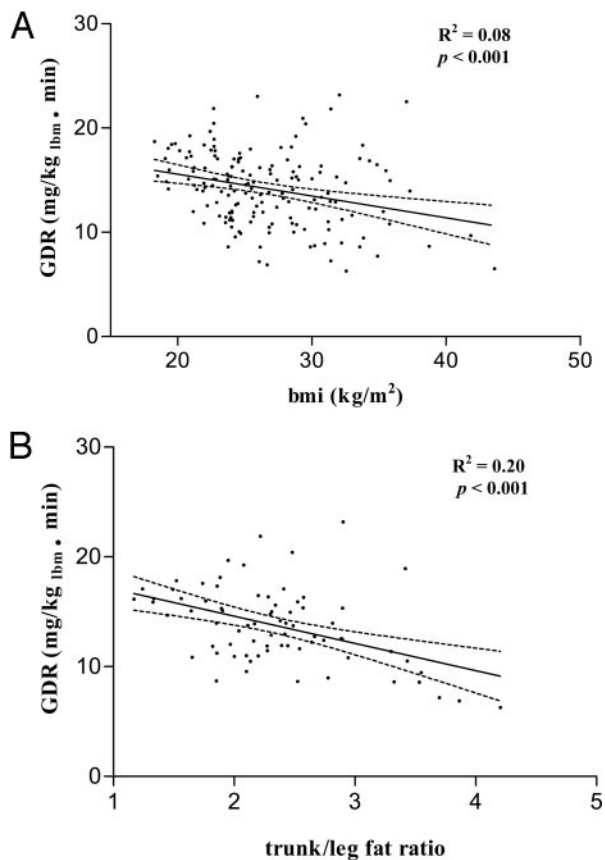


FIG. 1. A, The relationship between BMI [BMI = weight (kilograms)/height (meters)<sup>2</sup>] and insulin sensitivity as measured by maximally stimulated glucose disposal rates (GDRs) using the hyperinsulinemic euglycemic clamp. The data were obtained in nondiabetic individuals, and the glucose uptake data are normalized per kilogram lean body mass measured by dual energy x-ray absorptiometry scanning. B, The relationship between the ratio of trunk to leg fat and insulin sensitivity in the same subjects represented in panel A. Trunk and leg fat mass were assessed using dual energy x-ray absorptiometry (91).

has the greatest adverse effects, although increased sc fat also contributes to insulin resistance. This observation is central to the hypothesis that increased omental adipose tissue helps promote the IRS via the secretion of free fatty acids (FAs) and adipocyte-derived proteins such as plasminogen activator inhibitor-1, TNF $\alpha$ , leptin, adiponectin, and others. Accumulating evidence suggests that these secreted factors may constitute a mechanistic link among increased omental fat, insulin resistance, and the expression of the IRS. Whether skeletal muscle insulin resistance or omental adipose tissue is primarily responsible for IRS is not known, but clearly both are integral to the pathogenesis of the IRS.

#### Goals of review

Given the impact of obesity and omental fat, a key question is whether insulin resistance can be ameliorated via nutritional intervention in an effort to both prevent and treat obesity and type 2 diabetes. This review will consider these aspects of nutrition therapy, including effects of hypocaloric diets that produce weight loss, alterations in the macronutrient balance (fat *vs.* carbohydrate), and changes in dietary

fat or carbohydrate composition. Many nations are experiencing alarming increments in obesity and diabetes prevalence. Consequently, large numbers of individuals are experimenting with popular diets that range from the U.S. Department of Agriculture pyramid diet advocating consumption of grains, fruits, and vegetables at the expense of fat (13), to the Atkins Diet (14), which dictates low-carbohydrate/high-fat consumption, to the Zone and South Beach diets (15, 16), which lie somewhere in the middle of this continuum. Currently, the United States is engaged in a national obsession to rid itself of dietary carbohydrates in an attempt to lose weight, with low-carbohydrate meals appearing in restaurants and low-carbohydrate pasta and beer filling the grocery store shelves. Therefore, these issues have important public health implications. Any diet to counteract obesity should be evaluated for its effects on insulin resistance and the IRS given the resulting heavy burden of diabetes and cardiovascular disease. Improving insulin resistance by dietary modulation offers a potential strategy to prevent these highly prevalent diseases, which are also comorbidities of obesity. Indeed, those obese patients who experience the greater metabolic benefits of weight reduction are those who are insulin resistant before weight loss (17–19).

### Weight Loss

#### Hypocaloric diets

Both acute energy restriction and subsequent weight loss have been shown to benefit glucose metabolism in insulin-resistant and type 2 diabetic individuals (20–22). Sustained weight loss of as little as 5% of initial body weight can significantly decrease fasting blood glucose, insulin, hemoglobin A1c concentrations, and medication requirements in obese patients with type 2 diabetes (23). In overweight insulin-resistant individuals, both hyperinsulinemia and insulin resistance have been shown to improve with weight loss, whereas lesser improvement may be observed in insulin-sensitive overweight individuals (24). Enhanced insulin sensitivity after weight loss is partially related to the loss of total fat and highly correlated with the loss of visceral and intramyocellular fat (21, 25, 26). In these studies, it is important to emphasize that negative energy balance produces weight loss regardless of the macronutrient composition of the diet (27). Although various diet plans can emphasize factors that affect hunger and satiety (28, 29), caloric reduction is the essential component and a *sine qua non* of weight loss.

When considering the metabolic benefits of diet and weight loss, it is important to consider that lifestyle intervention resulting in a small degree of weight loss can dramatically prevent progression toward type 2 diabetes in high-risk individuals. This is best demonstrated by the Diabetes Prevention Program, a multicentered clinical trial with randomization to either control, metformin treatment, or lifestyle intervention subgroups involving 3234 adults at high risk for developing diabetes (30). The lifestyle intervention achieved and maintained a 5–7% weight loss through a low-calorie, low-fat diet, plus physical activity of approximately 150 min/wk. Results clearly indicated that this degree of weight loss was associated with a 58% reduction in diabetes incidence over a 4-yr period and that

this applied to Caucasians, African-Americans, Hispanic-Americans, and Native Americans in the study. Although the independent contributions of diet and exercise in the prevention of type 2 diabetes were not rigorously assessed, the relative degree of diabetes prevention was correlated with the degree of chronic weight loss.

#### *Paradoxical relationship between obesity and insulin resistance: a mechanistic hypothesis*

We have established that general obesity can explain only a small portion of individual variability in insulin sensitivity in cross-sectional studies (Fig. 1A). This would seem to be at odds with the observation that weight loss consistently leads to clinically significant improvements in insulin resistance. Similarly, the observation contrasts with the strong epidemiological link between obesity and the development of type 2 diabetes (31). We, therefore, suggest a hypothesis to resolve this paradox. We propose that it is not changes in general obesity *per se* that mediate benefits of weight loss or the epidemiological association with diabetes; rather, some other metabolic concomitant of the obese state is directly responsible. The fact that only moderate weight reduction, as opposed to achieving ideal body weight, yields maximal benefits of weight loss already hints at this possibility because this represents a disconnect between degree of obesity and insulin sensitivity.

There are two possible mechanistic explanations for the apparent paradox. First, changes in omental fat mass and functional adipokine secretion may directly influence insulin sensitivity in a manner that is only indirectly related to overall adiposity (32). Second, intramyocellular fat has been shown to be highly correlated with insulin resistance (33), although the mechanisms underlying this inter-relationship have not been elucidated. It remains possible that fluctuation in intramyocellular fat, which may or may not track with overall adiposity in different clinical settings, is a direct mediator of insulin resistance. To support this contention, we have shown that a short-term hypocaloric state (*i.e.* 3–5 d on a very low-calorie diet) is sufficient to cause significant improvements in insulin sensitivity, accompanied by only small changes in body weight, but dramatic 50% decrements in intramyocellular fat (26). Thus, the relationship between insulin sensitivity and obesity is complex, and determinants other than changes in general adiposity may be responsible for diet-induced improvements in insulin resistance.

#### **Alterations in Macronutrient Composition: Low-Fat vs. High-Fat Diets**

Changes in macronutrient composition have been used to promote weight loss and enhance insulin sensitivity, independent of an emphasis on overall calorie ingestion. This approach has received a great deal of attention in the popular press, where various low-carbohydrate diets in particular have been promulgated by best-selling books and have gained adherents. These diets limit the amount and composition of carbohydrates and have increased dietary fat to achieve a degree of unintentional calorie reduction through a blunting of the appetite. This can range from a proper mix or zone of complex carbohydrates that reduces postprandial

serum insulin (the Zone diet, the South Beach diet) to very high-fat diets that induce satiety by causing ketogenesis and reducing gastrointestinal motility (the Atkins diet). The purveyors of these diets portray them to be scientifically sound. Although there is some scientific rationale, two common devices used to support contentions include the overinterpretation of data and weaving together of unconnected scientific observations, and these processes often border on sophistry. Nevertheless, driven by the increased prevalence of overweight and obesity, these diets are increasingly popular despite a relative lack of rigorous scientific data. These diets present an attractive alternative to challenging lifestyle modifications (*i.e.* intentional calorie reduction and increased physical activity).

Low-carbohydrate diets, the preferred term for those who market these diets, can also be termed high-fat diets because it is impractical to make up the carbohydrate caloric deficit with dietary protein. Low-carbohydrate, high-fat diets were first described by Banting in 1863 (34). Studies examining the effects of modulating total dietary fat and carbohydrate can be difficult to compare because investigators have employed variable duration, diet composition, end points, methodologies (in particular those used to assess insulin sensitivity), and nonrandomized design. Nevertheless, investigators have shown that high-fat diets can be used to achieve short-term weight loss. Furthermore, these studies have produced variable results with no consistent detrimental effects of high-fat diets on insulin sensitivity over a broad range of dietary fat content, including several randomized studies using the hyperinsulinemic glucose clamp technique or frequently sampled iv glucose tolerance test (fsIVGTT) to quantify insulin sensitivity (35–38). However, as discussed in the next section, the composition of fat in high-fat diets is a critical, but often neglected, variable that could determine effects of these diets on insulin sensitivity. One study by Lovejoy *et al.* (39) used the clamp technique to show that a 3-wk high-fat diet (50% fat, 35% carbohydrate, and 15% protein) did induce relative insulin resistance compared with an isocaloric low-fat diet (20% fat, 55% carbohydrate, and 15% protein); however, this could be explained by a higher proportion of saturated FAs in the high-fat diet (see below). Table 1 describes aspects of key studies assessing high-fat diets and their effects on insulin sensitivity.

Recently, two randomized controlled trials that compared the longer term effects (6 months to 1 yr) of traditional low-fat diets *vs.* *ad libitum* high-fat diets have received a great deal of attention (40, 41). Foster *et al.* (40) compared the efficacy of the low-carbohydrate (initially restricted to 20 g carbohydrate/d), high-fat Atkins diet with a conventional low-fat (25% of calories), low-calorie diet (1200–1500 kcal/d in females and 1500–1800 kcal/d in males) in otherwise-healthy obese subjects (mean BMI, 34 kg/m<sup>2</sup>). The high-fat diet produced a greater weight loss than the low-fat diet after 6 months (6.7 *vs.* 2.7 kg), but at 1 yr, the amount of weight loss was not significantly different between the two groups (4.3 *vs.* 2.5 kg). About 40% of the 63 randomized subjects did not finish the study. Insulin sensitivity was assessed using the quantitative insulin sensitivity check index, which is an index based on fasting glucose and insulin concentrations. This is a suboptimal measure of insulin sensitivity because

**TABLE 1.** Intervention studies assessing effects of dietary fat and carbohydrate macronutrient composition on insulin sensitivity

Study	Participants	No. (gender)	Diet	Follow-up	Design	Method	IS
Borkman <i>et al.</i> 1991 (35)	Healthy	8 (M)	Isocaloric 45% fat, 40% cho <i>vs.</i> 30% fat, 50% cho	3 wk	Randomized crossover	Clamp	—
Swinburn <i>et al.</i> 1991 (37)	Healthy	24 (M/F)	Isocaloric 50% fat, 30% cho <sup>a</sup> <i>vs.</i> 15% fat, 70% cho	2 wk	Randomized crossover	fsIVGTT	↓
Garg <i>et al.</i> 1992 (38)	T2DM	8 (M)	Isocaloric 50% fat, 35% cho <i>vs.</i> 25% fat, 60% cho	3 wk	Randomized crossover	Clamp	—
Parillo <i>et al.</i> 1992 (92)	T2DM	10 (M/F)	Isocaloric 40% fat, 40% cho <sup>a</sup> <i>vs.</i> 20% fat, 60% cho	2 wk	Randomized crossover	Clamp	↑
Hughes <i>et al.</i> 1995 (93)	IGT	20 (M/F)	Isocaloric 30% fat, 50% cho <i>vs.</i> 20% fat, 60% cho	12 wk	Randomized controlled	Clamp	—
Lovejoy <i>et al.</i> 1998 (39)	Healthy	31 (F)	Isocaloric 50% fat, 35% cho <sup>a</sup> <i>vs.</i> 20% fat, 55% cho	3 wk	Randomized crossover	fsIVGTT	↓
Bisschop <i>et al.</i> 2001 (94)	Healthy	6 (M)	Isocaloric 83% fat, 2% cho <sup>a</sup> <i>vs.</i> 41% fat, 44% cho	11 d	Balanced assignment	Clamp	↑
Samaha <i>et al.</i> 2003 (41)	Obese (T2DM, IRS)	79 (M/F)	<i>Ad libitum</i> caloric intake low-cho (<30 g cho) <sup>a</sup> <i>vs.</i> caloric restricted, <30% fat	24 wk	Randomized controlled	Quicki	↑
Foster <i>et al.</i> 2003 (40)	Obese	63 (M/F)	<i>Ad libitum</i> caloric intake low-cho (<20 g cho) <i>vs.</i> caloric restricted, <25% fat	48 wk	Randomized controlled	Quicki	—

Clamp, Hyperinsulinemic euglycemic glucose clamp; T2DM, type 2 diabetes mellitus; IGT, impaired glucose tolerance; cho, carbohydrate; IS, insulin sensitivity; M, male; F, female; Quicki, quantitative insulin-sensitivity check; ↓, decrease; ↑, increase; —, unchanged.

<sup>a</sup> Dietary subgroup experiencing the change in insulin sensitivity.

the index is affected by insulin secretion, which can vary independently from insulin sensitivity among individuals (42). Despite this limitation, the index was interpreted to show an increase in insulin sensitivity at 6 months but no change from baseline at 1 yr in both dietary subgroups, with no significant differences between the subgroups. In the second study, Samaha *et al.* (41) compared the effects of a low-carbohydrate ( $\leq 30$  g/d), high-fat diet *vs.* a low-fat ( $\leq 30$  g/d) National Heart Lung and Blood Institute diet (43) designed to create a caloric deficit of 500 kcal/d. Their subjects were severely obese (mean BMI, 43 kg/m<sup>2</sup>), and most were African-Americans, hypertensive, and characterized by either type 2 diabetes or the IRS. In this 6-month study, subjects on the high-fat diet lost more weight than those on the low-fat diet; however, the amount of weight loss was low (5.8 *vs.* 1.9 kg), and the dropout rate was again very high, particularly in the high-fat diet group (47 *vs.* 33% in the low-fat diet group), indicative of pervasive noncompliance. The authors also emphasized that the high-fat diet led to greater improvements in insulin sensitivity than the low-fat diet group, but these effects were minimal, and the authors again used a suboptimal index based on fasting glucose and insulin levels as a measure of insulin sensitivity.

An alternative approach to an *ad libitum* high-fat diet is an *ad libitum* high-carbohydrate diet consisting of high-fiber foods with low caloric density (44, 45). This approach can also be used effectively to promote weight loss. An example is the EatRight program employed at the University of Alabama at Birmingham (46). This program emphasizes the ingestion of large quantities of high-bulk, low-energy density

foods (primarily vegetables, fruits, high-fiber grains, and cereals) and moderation in high-energy density foods (meats, cheeses, sugars, and fats). This approach produces equal satiety at reduced energy intake compared with a high-fat diet comprised of energy-dense foods. EatRight participants lose an average of 6.3–8.2 kg by the end of the 12-wk program, and, overall, 53% of participants maintain their reduced weight or continue to lose weight 2 yr later, whereas only 23% regain all their lost weight (47, 48).

On balance, the studies published to date indicate that high-fat diets can be used safely to effect short-term weight loss, without adversely affecting cardiovascular risk factors such as blood pressure and circulating lipids (40, 41, 49). The few studies that have compared high- *vs.* low-fat diets cannot be construed as indicating that high-fat diets are more effective in achieving weight loss than low-fat, high-fiber diets. For example, in addition to high rates of dropout and noncompliance, the studies by Foster *et al.* (40) and Samaha *et al.* (41) did not control for the types or composition of fat or carbohydrates in the diets, which could have affected study end points. As discussed below, variations in the types of fats in the high-fat diets [*e.g.* amount of saturated *vs.* monounsaturated FAs (MUFAs)] or types of carbohydrate in the low-fat diets (*e.g.* ratio of available carbohydrate to fiber) may have influenced study parameters and contributed to inconsistent results with respect to weight loss, insulin sensitivity, and lipid levels. Regardless, the extent of weight loss is directly related to reduced caloric ingestion. Previous metabolic studies have shown that when the energy content of an

energy-deficient diet is stable, macronutrient composition does not influence weight loss (50, 51). Additional research is needed to explore differential effects of low- and high-fat diets on weight loss, appetite behavior, satiety, insulin sensitivity, and cardiovascular disease risk factors in both the short and long term. Very little is known regarding long-term safety of high-fat diets and their long-term effects on metabolism and cardiovascular disease risk.

### Alterations in Composition of Dietary Fat

#### Composition of dietary fat: saturated vs. polyunsaturated

Investigators have examined whether the composition of dietary FAs, as opposed to total fat consumption, can modulate insulin sensitivity and cardiovascular risk factors (52, 53). With respect to saturated fat, epidemiological studies show that high intake of total and saturated fat is associated with insulin resistance, and this relationship may be dependent on increased body adiposity (54). However, multiple cross-sectional studies have found that intake of both saturated and trans FAs is associated with hyperinsulinemia and with risk of type 2 diabetes, independent of general obesity (55–57). High intake of polyunsaturated FAs (PUFAs) does not appear to have the same adverse effects and may even result in an increase in insulin sensitivity (58). For example, Summers *et al.* (59) recently studied the effect of substituting dietary saturated fat with polyunsaturated fat on insulin sensitivity in healthy, obese, and type 2 diabetic subjects. Their findings demonstrated that an isocaloric diet enriched in polyunsaturated fat resulted in both an increase in insulin sensitivity assessed by glucose clamp and a lowering of LDL

cholesterol when compared with a diet rich in saturated FAs. However, it was not possible in this study to conclude whether it was the increase in dietary PUFA or the decrease in saturated fat that produced the relative benefits in the PUFA diet subgroup. In addition, diets enriched in polyunsaturated fat have not consistently been shown to improve insulin sensitivity (60), and long-term intervention trials have not been conducted. Discrepancies in the short-term studies are often attributable to the failure to control for dietary FA and carbohydrate composition (*e.g.*, amount of MUFA), total calories, physical activity, and population characteristics such as age, gender, and adiposity.

#### MUFAs

Beneficial effects of a high-MUFA diet on glycemic control in type 2 diabetes have been demonstrated in a metaanalysis of randomized trials using isoenergetic high-MUFA diets (61). More recently, short-term intervention studies in healthy volunteers have shown that the isocaloric substitution of MUFA for saturated fat (62), or even substituting MUFA for carbohydrates, can have positive effects on insulin sensitivity (63). Similar results were obtained in a 3-month trial that evaluated insulin sensitivity in healthy volunteers receiving diets varying in FA composition ( $\omega$ -3 PUFA vs. MUFA vs. saturated fat). It was the MUFA-enriched diet that led to significant increases in insulin sensitivity, and this effect was greater when the total amount of fat was modest (<37% of calories) (64). Table 2 summarizes randomized design studies assessing effects of diets with variable fat composition on insulin sensitivity.

**TABLE 2.** Intervention studies assessing effects of dietary FAs (degree of saturation) on insulin sensitivity

Study	Participants	No. (gender)	Diet	Follow-up	Design	Method	IS
Garg <i>et al.</i> 1992 (38)	T2DM	8 (M)	Isocaloric 50% fat (32% MUFA, 11% sat) 35% cho vs. 25% fat (12% MUFA, 8% sat) 60% cho	3 wk	Randomized crossover	Clamp	—
Parillo <i>et al.</i> 1992 (92)	T2DM	10 (M/F)	Isocaloric 40% fat (MUFA 29%, 7% sat) 40% cho <sup>a</sup> vs. 20% fat (MUFA 13%, sat 5%) 60% cho	2 wk	Randomized crossover	Clamp	↑
Thomsen <i>et al.</i> 1999 (63)	First-degree relatives of T2DM	16 (M/F)	Isocaloric 40% fat (MUFA 25%) 45% cho vs. 30% fat (10% MUFA) 55% cho	4 wk	Randomized crossover	fsIVGTT	—
Perez-Jimenez <i>et al.</i> 2001 (62)	Healthy	59 (M/F)	Isocaloric 38% fat (12% MUFA, 20% sat) 47% cho vs. 38% fat (22% MUFA) 47% cho <sup>a</sup> vs. 28% fat (12% MUFA) 57% cho <sup>a</sup>	4 wk	Randomized crossover	ITT	↑
Lovejoy <i>et al.</i> 2002 (95)	Healthy	25 (M/F)	Isocaloric All with 28% fat, 57% cho; 9% MUFA vs. 9% sat vs. 9% trans fatty acid	4 wk	Randomized, double-blind crossover	fsIVGTT	—
Summers <i>et al.</i> 2002 (59)	Healthy, obese, T2DM	18 (M/F)	Isocaloric High PUFA <sup>a</sup> vs. high sat fat	5 wk	Randomized crossover	Clamp	↑
Vessby <i>et al.</i> 2001 (71)	Healthy, obese	162 (M/F)	Isocaloric All with 37% fat; high sat fat (17% sat, 14% MUFA) vs. high MUFA (8% sat, 23% MUFA) <sup>a</sup>	12 wk	Randomized controlled	fsIVGTT	↑

Clamp, Hyperinsulinemic euglycemic glucose clamp; ITT, modified insulin tolerance test; T2DM, type 2 diabetes mellitus; IS, insulin sensitivity; cho, carbohydrate; sat, saturated; M, male; F, female; ↑, increase; —, unchanged.

<sup>a</sup> Dietary subgroup experiencing the change in insulin sensitivity.

### *$\omega$ -3 and $\omega$ -6 FAs and conjugated linoleic acids (CLAs)*

$\omega$ -6-FAs and  $\omega$ -3-FAs are the two main types of dietary PUFAs. Although evidence suggests that  $\omega$ -3-FA from fish or fish oil may help prevent heart disease (65), the effects of  $\omega$ -3 and  $\omega$ -6 FA on glucose homeostasis are inconsistent (58, 66, 67). Human studies have shown that enhanced insulin sensitivity is associated with an enrichment in tissue levels of long-chain  $\omega$ -3 FAs in skeletal muscle (68) and that a high ratio of phospholipid  $\omega$ -6/ $\omega$ -3 in muscle membrane lipids is associated with increased fasting insulin levels and relative body weight (69). However, these associations do not necessarily imply causality with respect to dietary ingestion, which can be confirmed only by intervention studies. Short-term diet intervention studies in subjects with and without type 2 diabetes have shown that there is no effect of  $\omega$ -3 FAs on insulin sensitivity. Interventions in these studies involved dietary fish oil supplementation (3–6 g/d), with a duration that ranged from 2–12 wk (53). Longer term intervention studies are few in number but have also failed to show significant improvements in insulin sensitivity in healthy and diabetic patients (70, 71). For example, a 6-month randomized controlled trial in diabetic patients evaluated the effects of a moderate supplementation of fish oil (2.7 g/d for the first 2 months and 1.7 g/d for the remaining 4 months) on glucose control and lipid metabolism. Fish oil had a significant hypotriglyceridemic effect, without any change in glucose control and no change in peripheral glucose use measured by hyperinsulinemic clamp (71).

More recently, investigators have hypothesized that CLAs can modulate human adiposity and insulin sensitivity. This is based on studies in human adipocytes showing that trans 10, *cis*-12 CLA attenuates triglyceride content and differentiation, whereas *cis*-9, trans-11 CLA isomers increase triglyceride accumulation and expression of adipocyte-specific genes (72, 73). Also, in rodents, there is evidence that mixed CLA isomers may reverse insulin resistance and exert beneficial effects on glucose metabolism in diabetes (74). However, *in vivo* metabolic studies have provided conflicting results in humans. Obese subjects receiving 3.4 g/d of the trans-10, *cis*-12 CLA isomer lost weight and waist circumference after 12 wk but surprisingly became more insulin resistant. In contrast, subjects receiving 3.4 g/d of a mixture of CLA isomers, *cis*-9, trans-11 and trans-10, *cis*-12, during the same period experienced no effects on body weight or insulin sensitivity from baseline (75). Additional trials are needed to assess whether specific CLAs affect human adiposity and insulin action.

In conclusion, with respect to dietary fat composition, diets enriched in saturated and trans FAs may increase insulin resistance, whereas monounsaturated fat appears to improve insulin sensitivity. On the other hand, metabolic studies using diets high in PUFAs have provided conflicting conclusions on the effect of these compounds in glucose metabolism.

### **Alterations in Composition of Dietary Carbohydrate**

As observed for fat, the composition of dietary carbohydrates, as opposed to the total amount, may potentially influence body weight and insulin sensitivity. The glycemic

index (GI) has been established to physiologically classify carbohydrates based on postmeal glycemic responses because this is not always predictable based on simple *vs.* complex chemical structure (76). The South Beach and Zone diets advocate low carbohydrates or the right kind of carbohydrates in an attempt to minimize dietary GI, whereas the Atkins diet minimizes ingestion of all carbohydrates. The originators of these diets purport that high-GI responses are central to mechanisms promoting weight accretion and should be avoided for effective dieting. The scientific basis for these claims falls far short of the enthusiasm with which the lay public has embraced the low-carbohydrate phenomenon. Nevertheless, there exist some supportive data, although any benefits may relate more to dietary fiber than to available carbohydrate.

In terms of weight management, the data are equivocal as to whether high-GI diets promote weight gain. A recent evidence-based report from the World Health Organization found that the only convincing dietary factor protecting against weight gain and obesity was a high dietary fiber intake (77). In addition, popular low-carbohydrate diets attempt to lower dietary GI to prevent high insulin secretory responses because insulin is considered the culprit acting as a direct appetite stimulant. This is despite any rigorous supportive evidence and convincing data to the contrary that central administration of insulin acts to suppress appetite and reduce energy intake in primates and rodents (78). For the most part, studies on the effects of low- *vs.* high-GI foods have assessed short-term effects of foods or liquid meals on hunger, satiation, satiety, and short-term energy intake. Overall, results from these investigations indicate that consumption of high-GI carbohydrates has less of an effect to suppress appetite and a diminished ability to induce satiation and satiety than foods with lower GI (79, 80). The implication is that long-term consumption of high-GI diets may lead to energy overconsumption and, therefore, promote weight gain and/or the maintenance of excess body weight. However, long-term controlled clinical trials demonstrating beneficial effects of low- *vs.* high-GI diets on body weight are lacking. Furthermore, because the method of food preparation and multiple dietary and physiological factors all affect GI, its validity as a meaningful way to characterize food has been questioned, and its implementation in nutritional recommendations is problematic (81).

With respect to effects on insulin sensitivity, observational studies suggest that diets enriched in simple carbohydrates and/or fructose can be associated with lower plasma high-density lipoprotein cholesterol and insulin resistance (82, 83), whereas diets supplying higher amounts of complex carbohydrates and fiber are associated with increased insulin sensitivity (84, 85). Consistent with this idea, studies in rodents demonstrate that high-sucrose and high-fructose diets induce insulin resistance. However, controlled intervention studies in humans indicate that high-sucrose or high-fructose diets do not have these same consequences and do not worsen insulin sensitivity when assessed by hyperinsulinemic clamps (reviewed in Ref. 86).

Available data suggest that dietary fiber, rather than available carbohydrates or dietary GI *per se*, may be directly responsible for effects of carbohydrates on insulin sensitivity

in humans. In a randomized crossover study comparing isocaloric high- vs. low-GI diets, there was no observed benefit of the low-GI diet on insulin sensitivity (87). However, a low-GI diet with a greater amount of fiber and whole-grain products seemed to improve glycemic and insulin responses and lowered the risk of type 2 diabetes (52), indicating that the fiber content in low-GI foods may play a role in their metabolic effects. In support of this contention, studies on the effects of dietary intake of fiber, particularly whole-grain foods, have been fairly consistent in demonstrating an effect to enhance insulin sensitivity (88–90). In the Insulin Resistance Atherosclerosis study, which included 978 adults with normal or impaired glucose tolerance, whole-grain intake was significantly associated with insulin sensitivity, as assessed by the fsIVGTT. The analyses indicated that the fiber and magnesium content of whole-grain foods accounted for a large part of their effect on insulin sensitivity (88). In the Framingham Offspring Cohort, whole-grain intake was inversely associated with BMI, LDL cholesterol, and fasting insulin, and this was again largely attributable to dietary fiber and magnesium (89). Finally, a randomized controlled experiment employing hyperinsulinemic euglycemic clamps showed that a whole-grain diet improved insulin sensitivity over baseline, whereas a refined-grain diet had no effects over a 6-wk period (90).

### Conclusions

Weight loss under any dietary formulation depends on hypocaloric intake, and moderate weight loss will result in augmented insulin sensitivity. However, increments in insulin sensitivity may be more directly related to loss of intramyocellular or omental fat rather than loss of total body weight *per se*. Alterations in dietary composition can also facilitate weight loss and/or increase insulin sensitivity. Popular low-carbohydrate diets are in essence high-fat diets because the caloric deficit from carbohydrate restriction is not easily compensated by an increase in protein calories. These high-fat diets have been shown to be safe in the short term; however, their long-term safety has not been established. With respect to insulin sensitivity, diets enriched in saturated fats can induce insulin resistance, whereas fat substitution with monounsaturated fats can enhance insulin sensitivity. Therefore, in assessing the safety of high-fat diets, it is important to control for the composition of ingested fat. High-fiber, high-carbohydrate diets comprised of foods with low caloric density can similarly be used for effective weight reduction and to ameliorate insulin resistance. Although some data suggest that low-GI diets are most advantageous in this regard, these effects may have more to do with increments in dietary fiber than differences in available carbohydrates.

Popular low-carbohydrate, high-fat diets are being widely embraced as an alternative to challenging modifications in lifestyle and intentional calorie reduction. Current data do not support such unbridled enthusiasm for these diets, particularly as a substitute for high-fiber, high-carbohydrate diets emphasizing intake of fresh vegetables and fruits. Long-term studies to determine the efficacy and safety of

both popular and experimental diets are warranted in the current context of the obesity epidemic.

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