thematic review

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Nutritional determinants of insulin resistance

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Abstract Interpreting the literature relating to the nutritional determinants of insulin resistance is complicated by the wide range of methods used to determine insulin sensitivity. Excess adiposity is unquestionably the most important determinant of insulin resistance, although the effect may be tempered by a relatively high proportion of lean body mass. Weight loss is associated with improved insulin sensitivity. Thus, diet-related factors that promote excessive energy intake may be regarded as promoters of insulin resistance. In the context of energy balance, diets characterized by high intakes of saturated fat and low intakes of dietary fiber are associated with reduced insulin sensitivity. Total fat intakes greater than the usually consumed range appear to promote insulin resistance, although the relative proportions of total fat and carbohydrate within the usual range appear unimportant. Monounsaturated fatty acids with a *cis* configuration and fiber-rich carbohydrate foods appear to be appropriate substitutes for saturated fatty acids and rapidly digested glycemic carbohydrates. In animal studies, n-3 unsaturated fatty acids have been shown to enhance insulin sensitivity and fructose and sucrose to increase insulin resistance. However, human data are limited. Large prospective studies currently being conducted should confirm the most appropriate macronutrient composition of diets for preventing and treating insulin resistance as well as establishing whether a range of candidate genes explains the variation in response to dietary change.— McAuley, K., and J. Mann. **Nutritional determinants of insulin resistance. *J. Lipid Res.* 2006.** 47: **1668–1676.**

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Insulin resistance and its associated metabolic abnormalities are considered to be important determinants of coronary heart disease (1). This review summarizes the nutritional determinants of insulin resistance that may be translated into nonpharmacological interventions aimed at contributing to coronary heart disease risk reduction.

Insulin resistance was first described in the 1970s, and in 1988, Reaven (2) suggested that it was the underlying cause of a syndrome characterized by hyperinsulinemia, hypertension, increased triglyceride, reduced HDL cholesterol, hyperglycemia, and an increased risk of coronary heart disease. Several additional abnormalities have been identified, and the cluster of clinical and metabolic features is now known as the insulin resistance or metabolic syndrome (3). Despite the widespread use of the term, there are several different sets of diagnostic criteria (4–6), and some have questioned whether the cluster of abnormalities should be described as a syndrome (7, 8). It has not been established whether resistance to the action of insulin is a cause of the other abnormalities or merely another associated variable. A wide variety of methods exist for the measurement of insulin sensitivity (9, 10). Even the gold standard measures, the hyperinsulinemic, euglycemic insulin clamp and the intravenous glucose tolerance test, have been performed using different protocols in different studies. Surrogate measures of insulin sensitivity, usually based around a fasting insulin measurement, are also not standardized, and individuals with hyperinsulinemia may not have insulin resistance determined using an insulin clamp (11). Regardless of the method used, values for insulin sensitivity vary widely in healthy populations, and there is no agreed-upon cutoff for the definition of insulin-sensitive or insulin-resistant individuals. The fact that different researchers have used varying techniques to measure insulin sensitivity has greatly complicated the study of the nutritional determinants of insulin resistance. Some studies have described the effects of lifestyle-related variables on the metabolic syndrome, which has then been regarded as a surrogate measure of insulin resistance. Nevertheless, some general conclusions are possible.

EXCESS ADIPOSITY

Obese individuals are much more likely to be insulin-resistant than normal weight individuals, and increasing adiposity, however measured, is associated with reduced

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insulin sensitivity (12, 13). Conversely, weight loss is almost always associated with improved insulin sensitivity (14). However, not all overweight or obese individuals are insulin-resistant. Brochu and colleagues (15) identified a greater lean body mass as an important distinguishing characteristic of obese individuals who are not insulin-resistant compared with those who are. A higher lean body mass is associated with enhanced glucose disposal. Physical activity contributes to increased lean body mass and enhanced insulin sensitivity and favorably influences many of the other metabolic abnormalities associated with obesity and the metabolic syndrome (16, 17). Thus, physical activity may reduce the risk of insulin resistance associated with obesity directly and via enhanced lean body mass.

The importance of regional adiposity in determining insulin action has been widely assumed, but the findings have not been entirely consistent. Abdominal or truncal adiposity has been implicated as having a key role in the pathogenesis of insulin resistance (18–20). This has largely been based on cross-sectional and longitudinal epidemiological studies in which waist circumference has been used to assess abdominal obesity and surrogate measures (e.g., fasting insulin) have been used to determine insulin sensitivity (18, 21–23). An intervention study by Markovic and colleagues (24) confirmed that reduced abdominal fat was associated with increased insulin sensitivity and improved indicators of both glucose metabolism and other measures of the metabolic syndrome, changes not seen with alteration of fat stores in other sites. Interestingly, Klein et al. (25) have recently shown that reducing subcutaneous abdominal tissue alone (by liposuction) did not improve insulin sensitivity. Decreasing adipose tissue alone does not achieve the same benefit as weight loss. It has been suggested that increased visceral adiposity in particular may cause insulin resistance as a result of its high levels of metabolic activity, particularly lipolytic activity (26).

However, this hypothesis has been questioned on the basis of studies using a euglycemic insulin clamp to measure insulin action and computed tomography or MRI to measure regional adiposity. In seven of nine such studies, it appeared that visceral fat does not have a unique effect on insulin sensitivity; rather, subcutaneous abdominal fat is a better predictor of insulin resistance than visceral fat, intraperitoneal fat, or peripheral subcutaneous fat (23). Liver fat, whether associated with obesity or not, is associated with insulin resistance, which may explain why even lean individuals may be insulin-resistant (27). Fat deposition in skeletal muscle (as estimated by muscle attenuation on computed tomography) has been shown to be a better marker of insulin sensitivity than total or abdominal fat (28). State-of-the-art techniques for investigating the distribution of body fat, insulin sensitivity, and adipocyte-derived hormones are likely to clarify the importance of regional adiposity and to explain the mechanisms by which adipocytes in certain sites are especially likely to promote insulin resistance. However, in the context of the current global epidemic of obesity and the central role of excess adiposity in determining insulin resistance, it may be appropriate to consider nutritional determinants of obesity as determinants of insulin resistance, regardless of whether or not they have been linked to a reliable measure of insulin sensitivity. Conversely, dietary attributes that reduce the risk of obesity may be regarded as protective against insulin resistance. Thus, frequent consumption of large portions of energy-dense foods and sugary drinks may be regarded as promotive and high intake of fiber-rich whole-grain cereals and intact fruits and vegetables may be regarded as protective (29). The role of individual nutrients is considered below.

DIETARY FAT

Diets high in total fat are energy-dense. They may be less satiating than carbohydrates, at least in some individuals (30, 31). As a result, they tend to promote excess energy intake and are associated with an increased risk of obesity and insulin resistance (30). A meta-analysis suggests that among overweight individuals, a total fat intake of <30% total energy facilitates weight loss (32). Thus, high-fat diets may promote insulin resistance via their obesogenic potential. The contribution of fat to total energy intake, and whether the nature of dietary fat influences insulin resistance and other features of the metabolic syndrome in the context of energy balance, are less clearly established. These are important practical considerations because most overweight individuals will fairly rapidly achieve their maximum weight loss, and the appropriate dietary advice will be that which facilitates weight maintenance and ensures the greatest degree of insulin sensitivity.

At least 11 studies (33–43) have compared the effects on insulin sensitivity of isoenergetic diets high (typically, 40–50% of total energy) and low (typically, 15–25% of total energy) in total fat intake (**Table 1**). The comparisons were made under isoenergetic conditions, with the bulk of the remaining energy provided by varying carbohydrate, protein remaining fairly constant, and insulin sensitivity assessed by means of a clamp or frequent-sampling intravenous glucose tolerance test. In 6 of the 11 studies (34, 35, 39–42), there were no appreciable differences in insulin sensitivity on the high- and low-fat diets. Four studies suggested reduced sensitivity on the high-fat diets, but in these the percentage of energy from fat was extreme, as was the intake of saturated fat (33, 36, 37, 43). In one study, insulin sensitivity appeared to be slightly enhanced on the high-fat diet compared with the high-carbohydrate diet, but that study was carried out in people with diabetes in whom the sudden substantial increase in carbohydrate may have resulted in a deterioration in glycemic control (38). Although statistically significant results have been reported, power calculations have usually not been presented, and most of the studies appear to be underpowered. In addition, the majority of studies are of short duration.

A substantial body of literature relates to the effect of dietary fat composition on insulin sensitivity in experi-

TABLE 1. Intervention studies in which the effects of altering macronutrient composition (principally the proportions of fat and carbohydrate) on insulin sensitivity have been assessed

Study	Participants (n)	Method of Insulin Sensitivity Assessment	Duration	Diet(s)	Relationship of High Fat Intake to Insulin Sensitivity
Chen, Bergman, and Porte, 1988 (33)	Healthy (18)	fsIVGTT	5 days × 2	Low (30%) CHO, 55% fat versus high (85%) CHO, 0% fat	↓ (dependent upon age)
Borkman et al., 1991 (35)	Healthy (8)	Clamp	3 weeks × 2	<40% CHO, >45% fat (mainly SAFA) versus >50% CHO, <30% fat	↔
Swinburn et al., 1991 (34)	Healthy (24)	fsIVGTT	14 days × 2	30% CHO, 50% fat, 20% protein versus 70% CHO, 15% fat, 15% protein	↔
Garg, Grundy, and Unger, 1992 (39)	T2DM (8)	Clamp	3 weeks × 2	35% CHO, 50% fat, 15% protein versus 60% CHO, 25% fat, 15% protein	↔
Parillo et al., 1992 (38)	T2DM (10)	Clamp	15 days × 2	40% CHO, 40% fat, 20% protein versus 60% CHO, 20% fat, 20% protein	↑
Sarkkinen et al., 1996 (40)	IGT (31)	fsIVGTT	8 weeks	40% fat (MUFA-enriched) versus 34% fat (PUFA-enriched)	↔
Lovejoy et al., 1998 (36)	Healthy (31)	fsIVGTT	3 weeks × 2	35% CHO, 50% fat, 15% protein versus 55% CHO, 20% fat, 15% protein	↓
Thomsen et al., 1999 (41)	Healthy (16)	fsIVGTT	4 weeks × 2	45% CHO, 40% fat, 15% protein versus 55% CHO, 30% fat, 15% protein	↔
Bisschop et al., 2001 (37)	Healthy (6)	Clamp	11 days × 3	2% CHO, 83% fat versus 44% CHO, 41% fat versus 85% CHO, 0% fat	↓
Foster et al., 2003 (42)	Obese (63) (37 completed the 52 weeks)	Quicki	52 weeks	Ad libitum caloric intake, initial CHO 20 g/day (high fat) then increased until stable weight versus caloric-restricted, low fat (25%), high CHO (60%), 15% protein	↔ at 1 year; both groups had a significant ↑ after 6 months
Samaha et al., 2003 (43)	Obese (163) (79 completed the 24 weeks)	Quicki	24 weeks	Ad libitum low CHO (≤30 g) versus caloric- and fat-restricted (≤30% fat)	↓

CHO, carbohydrate; Clamp, hyperinsulinemic euglycemic clamp; fsIVGTT, frequent-sampling intravenous glucose tolerance test; IGT, impaired glucose tolerance; Quicki, quantitative insulin sensitivity check; SAFA, saturated fatty acid; T2DM, type 2 diabetes mellitus. Arrows denote the relationship between the higher fat diet and insulin sensitivity compared with other experimental diets investigated: ↑, increased insulin sensitivity with high-fat diet; ↓, decreased insulin sensitivity with high-fat diet; ↔, no difference in insulin sensitivity on high-fat diet compared with other experimental diets. × n denotes a crossover experimental design with n diets each followed for the duration stated.

mental animals, especially rats. There is fairly consistent evidence that saturated fats impair and n-3 unsaturated fatty acids improve insulin action in rodents. Monounsaturated and n-6 polyunsaturated fatty acids have a less marked effect on insulin sensitivity (44). Several different approaches have been used to study the effect of dietary fat composition in humans. In observational studies, both cross-sectional and longitudinal, it is difficult to disentangle the effects of diet composition from the effects of energy intake and adiposity. Furthermore, no method of measuring dietary intake is totally reliable. Nevertheless, it is of interest that in such studies there is a consistent positive association between the intake of saturated fatty acids and hyperinsulinemia (as an indicator of insulin resistance), which appears to be independent of adiposity (45–49). Some epidemiological studies have found polyunsaturated fatty acids to be inversely associated with insulin levels (48, 50), and others have reported a positive association (47). Serum or muscle fatty acid composition, a biomarker for dietary intake of some fatty acids, has also been related to insulin sensitivity measured by clamp studies (51–53). These studies have shown an association between insulin sensitivity and various fatty acids, a positive association for linoleic acid, and negative associations for palmitic, palmitoleic, and di-homo-γ-linolenic acids (52).

Definitive evidence of an association between the nature of dietary fat and insulin sensitivity can only be determined by intervention studies (**Table 2**). Several relatively underpowered studies (54–59) compared the effects of saturated and unsaturated fatty acids on insulin sensitivity in healthy individuals and those with type 2 diabetes. Perhaps not surprisingly, the results were inconclusive.

TABLE 2. Intervention studies in which the effects of altering fatty acid composition on insulin sensitivity have been assessed

Study	Participants (n)	Method of Insulin Sensitivity Assessment	Duration	Diet(s)	Relationship between High SAFA and Insulin Sensitivity
Heine et al., 1989 (54)	T2DM (14)	Insulin-glucose infusion	30 weeks × 2	SAFA versus PUFA	↔
Uusitupa et al., 1994 (55)	Healthy (10)	fsIVGTT	3 weeks × 2	20% SAFA, 15% MUFA versus 10% SAFA, 20% MUFA	↔
Schwab et al., 1995 (56)	Healthy (15)	fsIVGTT	4 weeks × 2	4% energy as palmitic acid (palm oil) versus 4% energy as lauric acid (coconut oil)	↔
Fasching et al., 1996 (57)	Healthy (8)	fsIVGTT	1 week × 3	200 g of CHO, 90 g of fat (72% SAFA) versus 200 g of CHO, 90 g of fat (60% PUFA) versus 200 g of CHO, 90 g of fat (40% MUFA)	↔
Pérez-Jiménez et al., 2001 (61)	Healthy (59)	Insulin suppression test	All participants on high SAFA for 4 weeks, then 4 weeks × 2	20% SAFA, 12% MUFA, 6% PUFA versus 10% SAFA, 12% MUFA, 6% PUFA versus 10% SAFA, 20% MUFA, 6% PUFA	↓
Vessby et al., 2001 (60)	Healthy (162)	fsIVGTT	3 months	Isoenergetic diets: high SAFA (17% SAFA, 14% MUFA, 6% PUFA) versus high MUFA (8% SAFA, 23% MUFA, 6% PUFA); within each group there was a second random assignment to fish oil (n-3 FA) capsules or placebo	↓ during high-SAFA diet, ↔ during high-MUFA diet; the difference between the two diets was of borderline significance
Summers et al., 2002 (58)	T2DM (6), healthy (6), obese (5)	Clamp	5 weeks × 2	High SAFA versus high PUFA	↑

CHO, carbohydrate; Clamp, hyperinsulinemic euglycemic clamp; fsIVGTT, frequent-sampling intravenous glucose tolerance test; SAFA, saturated fatty acid; T2DM, type 2 diabetes mellitus. Arrows denote the relationship between the higher saturated fat diet and insulin sensitivity compared with other experimental diets investigated: ↑, increased insulin sensitivity with high saturated fat diet; ↓, decreased insulin sensitivity with high saturated fat diet; ↔, no difference in insulin sensitivity on high saturated fat diet compared with other experimental diets. × n denotes a crossover experimental design with n diets each followed for the duration stated.

However, a relatively recent study known as KANWU (signifying the collaborating centers in five countries) was sufficiently powered to obtain a convincing outcome (60). A large group (162) of healthy individuals was randomized to receive high-saturated-fat or high-monounsaturated-fat diets. A randomly selected subsample within each group was given fish oil supplements or placebo. Insulin sensitivity, measured by the intravenous glucose tolerance test, was reduced by 10% on the diet high in saturated fatty acids. Interestingly, when the subjects were divided into those consuming above and below the median total fat intake for the group as a whole (37% of total energy as fat), a difference between saturated and monounsaturated fatty acids was apparent only in those with a total fat intake below the median. Indeed, among them, the difference in insulin sensitivity was twice that (20.3%) seen in the group as a whole. All of those with the higher fat intake showed a reduction in insulin sensitivity. This finding suggests that total fat may indeed adversely affect insulin sensitivity when intakes are particularly high and that this may not have been apparent in all of the studies mentioned above because intakes on the high-fat diet were not high enough. A study by Pérez-Jiménez et al. (61) examining the effects of a high-MUFA Mediterranean diet also suggests an improvement in insulin sensitivity compared with a diet richer in saturated fatty acids. Changing from a saturated to a monounsaturated fat diet may be a particularly important means of improving insulin sensitivity in the context of more moderate intakes of total fat.

In the KANWU study, supplementation with n-3 fatty acids did not influence insulin sensitivity when considering the group as a whole or when considering participants on the saturated or monounsaturated fat diets. Failure to show a beneficial effect of n-3 fatty acids in human studies has been a fairly consistent finding, even in studies of sufficient duration to permit a change in the composition of cell membrane phospholipids (62–67).

The mechanism by which the nature of dietary fat might influence insulin sensitivity is not clearly understood. It is possible that a change in the fatty acid composition of cell

membranes, which can be achieved by dietary modification, influences insulin receptor binding or activity as well as ion permeability and cell signaling (53).

Overwhelmingly, the most important messages with regard to fat modification in the treatment of insulin resistance are the avoidance of excessive intakes and reduction of saturated fatty acids and replacement by monounsaturated fatty acids and some polyunsaturated fatty acids with a *cis* configuration. Two recent reviews describing the effects of dietary conjugated linoleic acid on the regulation of adiposity and insulin sensitivity suggest that more subtle effects of fatty acids may also be relevant (68, 69). It appears that specific isomers of conjugated linoleic acid may reduce adiposity, especially abdominal fat, but insulin sensitivity is also reduced. Thus, the last word on the effects of the nature of dietary fat on insulin has yet to be written.

CARBOHYDRATE, FIBER, AND GLYCEMIC INDEX

Diets rich in low-energy-dense foods, including whole-grain cereals and cereal products and other foods rich in dietary fiber, promote satiety and may, as a consequence, facilitate appropriate energy intake (29). Thus, by reducing the risk of obesity, such foods may be regarded as reducing the risk of insulin resistance. In the context of energy balance and weight maintenance, there is evidence that the type of carbohydrate may influence insulin sensitivity and associated metabolic features. The findings in some studies that increasing the proportions of carbohydrate in relation to fat in the range of usually consumed quantities will influence insulin resistance and other metabolic abnormalities may be explained more by the type of carbohydrate than the amount.

Insulin resistance and its associated dyslipidemia (high triglyceride, low HDL) have been shown to be more marked on a high-carbohydrate diet compared with a diet rich in monounsaturated fatty acids (38, 39, 70–77). In individuals with diabetes, glycemic control may also be adversely influenced and plasminogen activator inhibitor type 1 levels are increased, suggesting an increased thrombogenic tendency (77). However, studies that have examined this issue have generally failed to consider the importance of the nature of the carbohydrate. Several dietary intervention studies have shown that many, if not all, of these untoward effects can be avoided if the carbohydrate is rich in dietary fiber, especially the soluble forms, and if most of the carbohydrate-containing foods have a low glycemic index (i.e., are associated with a relatively low postprandial glucose excursion as a result of slow digestion and absorption) (78–80). Whether the beneficial effects are attributable to the fiber content, the fact that the plant cell walls remain intact and encapsulate the carbohydrate, or simply that the foods have a low glycemic index for whatever reason has not been fully resolved. Most carbohydrate-containing, fiber-rich foods also have a low glycemic index. A single carefully conducted intervention study in people with type 2 diabetes (81) showed that insulin and plasminogen activator inhibitor type 1 levels were reduced when the overall glycemic index of the diet was reduced, even though dietary fiber content remained consistent. Glycemic index was modified by altering food structure (e.g., fiber-rich cooked dried beans were eaten either whole or finely ground).

Two large cross-sectional studies using validated food frequency questionnaires to assess nutrient intakes and either the frequent-sampling intravenous glucose tolerance test or homeostasis model assessment for insulin resistance found that intake of dietary fiber was inversely associated with the probability of having insulin resistance (82, 83). In the Insulin Resistance Atherosclerosis Study (83), it was possible to demonstrate that fiber increased insulin sensitivity even after adjustment for body mass index. However, neither study found any relationship between insulin sensitivity and glycemic index or glycemic load. Although cross-sectional studies do have limitations, these findings, considered in conjunction with the favorable effects of dietary fiber on other metabolic derangements associated with insulin resistance, provide a relatively strong case for including a recommendation regarding dietary fiber in nutritional guidelines aimed at increasing insulin sensitivity. It is less certain that particular foods should be recommended on the basis of their glycemic index.

There has been considerable interest in the potential role of sugars as determinants of insulin resistance. Free sugars (principally comprising sucrose or high fructose corn syrup added to foods or drinks by manufacturer, cook, or consumer, plus concentrated sugars in honey, syrups, and fruit juices) may contribute to excessive weight gain and so to a reduction in insulin sensitivity (29, 84). Such foods are energy-dense, and sugary drinks, although not energy-dense, appear not to be satiating. Analysis of a subgroup of individuals in the CARMEN study who were diagnosed with the metabolic syndrome showed that the reduction in body weight and improved metabolic indices seen when simple carbohydrates (sugars) were replaced with complex ones were more striking in people with this disorder than in the general population (85). The fact that fructose, compared with glucose, is preferentially metabolized to lipid in the liver and that fructose consumption induces insulin resistance, impaired glucose tolerance, hyperinsulinemia, hypertriglyceridemia, and hypertension in animal models have led to the suggestion that fructose, sucrose, or high fructose corn syrup may have uniquely untoward effects compared with other carbohydrates in humans in the context of energy balance. However, the existing evidence is limited and conflicting, and no conclusions can be drawn (86, 87).

Thus, international guidelines for the nutritional management and prevention of type 2 diabetes mellitus (88), which may be regarded as also being appropriate for reducing insulin resistance, emphasize that carbohydrate intake may range between 45% and 60% of total energy (**Table 3**). Although vegetables, legumes, intact fruits, and whole-grain cereals are always the preferred source of carbohydrates, it is particularly important to emphasize foods that are rich in dietary fiber when carbohydrate

TABLE 3. Optimal range of dietary macronutrients for weight loss and maintenance in insulin-resistant states

Macronutrient	Percentage of Total Energy
Carbohydrates[a]	45–60%
Sugars	<10%
Protein	15–25%
Total fat[b]	25–30%
Saturated fat	<8%
Monounsaturated fat	10–20%
Polyunsaturated fat	5%
Cholesterol	<200 mg
Dietary fiber	30–40 g/day (half should be soluble fiber)

[a] Preferred sources of carbohydrate include vegetables, legumes, intact fruit, and whole-grain cereals that are high in dietary fiber.
[b] *Trans* fatty acids should be avoided.

intake is at the upper end of the recommended range. Similarly, when carbohydrate intake is at the lower end of this range, or perhaps even as low as 40% in the context of a relatively high-protein diet, it is essential to ensure that the nature of dietary fat is appropriate (i.e., predominantly monounsaturated fatty acids with modest intakes of n-6 polyunsaturated fatty acids, with the diet also providing at least some n-3 fatty acids). Restriction of free sugars to 10% or less of total energy is justified on the grounds of reducing the obesogenic potential of the diet.

DIETARY PATTERNS

Recently, much interest has centered on the potential of the Mediterranean diet to protect against insulin resistance, type 2 diabetes, and coronary heart disease. An Italian study reported on a randomized trial in which patients with the metabolic syndrome received advice either regarding a Mediterranean dietary pattern or a "prudent" diet relatively low in fat and high in fiber-rich carbohydrate (89). Those randomized to the Mediterranean diet were advised to increase their daily consumption of whole grains, fruits, vegetables, nuts, and olive oil, whereas those given advice regarding the prudent diet received information about healthy food choices. The Mediterranean diet was associated with lower levels of high-sensitivity C-reactive protein and interleukins 6, 7, and 18, reduced insulin resistance, and improved endothelial function score compared with the control prudent diet group, among whom these measures showed little change. After 2 years, 40 of the 90 subjects in the intervention group still had features of the metabolic syndrome compared with 78 of the 90 patients in the control group. These findings do indeed suggest that the Mediterranean-style dietary pattern reduces insulin resistance and associated abnormalities. However, because the Mediterranean diet was more vigorously implemented and weight loss was greater, the findings do not provide evidence for superiority over the so-called prudent diet. McAuley et al. (90) examined the effects on insulin sensitivity of a high-carbohydrate/high-fiber/low-fat diet by comparing the effects of two different levels of lifestyle intervention in a randomized controlled trial. They reported an appreciable (20%) improvement in insulin sensitivity (measured by means of the hyperinsulinemic euglycemic clamp), but only when the diet was implemented by substantially increasing appropriate fiber-rich carbohydrate. Participants consumed whole-grain cereals, vegetables, and fruits, and substantially reduced saturated fatty acids and dietary advice were combined with an increase in physical activity, so that weight loss was achieved. Such dietary advice is similar to that intended in the prudent diet, and these data suggest that several different dietary patterns can achieve improvements in insulin sensitivity provided that they are implemented vigorously and result in weight loss.

Although the prudent diet is comparable to that recommended for high-risk individuals and populations by authorities in many countries, and indeed is similar to traditional dietary patterns in many parts of the world, a new range of dietary patterns has now emerged and several are being widely recommended and adapted for weight loss and cardiovascular risk reduction. Among the best known of these are the high-fat/low-carbohydrate diets (e.g., Atkins) and the high-protein dietary approach (e.g., Zone, South Beach diet).

There is no doubt that such alternative dietary approaches can facilitate weight loss, decrease insulin levels, and improve many of the metabolic derangements associated with insulin resistance in the short term (42, 43, 91–95). However, long-term data are limited. Two 12 month randomized trials suggest that any initial benefit achieved by the high-fat Atkins approach compared with the high-carbohydrate/high-fiber/low-fat approach (the prudent diet) is lost after 1 year (42, 96). A study by McAuley et al. (97, 98) comparing, in the same study, the high-fat, high-protein, and high-carbohydrate/high-fiber approaches in insulin-resistant women provided some useful additional information. In that study, the early benefits of the high-fat diet compared with the high-carbohydrate diet in terms of weight loss, fasting insulin, and triglyceride were not significant after 1 year. The high-protein approach, on the other hand, appeared to be associated during the first 6 months with an impressive improvement in metabolic and clinical measurements, which were sustained over a 1 year follow-up period. The more modest changes seen on the high-carbohydrate/high-fiber prudent diet were also sustained. The improvements in the metabolic variables appear to be proportional to the reduction in fat mass. The greater improvement in the high-protein compared with the high-carbohydrate diet may be attributable to the lesser degree of compliance with the high-carbohydrate diet in terms of consumption of the appropriate fiber-rich cereals, vegetables, and fruit as well as in the quantity of carbohydrate. The high-fat approach appears not to be sustainable in the long term, and even in the short term it may be associated with both atherogenic and thrombogenic effects, despite the potentially beneficial effects on insulin sensitivity and associated metabolic variables. These observations suggest that weight loss (reduction in fat mass) rather than nutrient distribution may be responsible for improvement in insulin sensitivity and that a range of dietary

patterns, although not a very-high-fat diet, may be equally acceptable approaches to enhance insulin sensitivity and to treat the abnormalities of the metabolic syndrome.

SUMMARY

Despite the difficulty of interpreting the literature relating to the nutritional determinants of insulin resistance, there are several nutritional interventions that can significantly improve insulin sensitivity. Excess adiposity, especially when centrally distributed, is clearly the most important nutrition-related factor determining insulin resistance. Although it is generally assumed that visceral abdominal obesity is especially relevant, further research involving more direct measurements of both insulin sensitivity and the localization of excessive adipose tissue are required to confirm the importance of regional adiposity. Reducing adiposity by dietary modification and increased physical activity improves insulin sensitivity and the range of abnormalities associated with insulin resistance. High-carbohydrate/high-fiber/low-glycemic index/low-fat diets are the tried and tested means of treating overweight and obesity and reversing the associated clinical and metabolic abnormalities, including insulin resistance. On the other hand, more moderate intakes of carbohydrate (~40% of total energy) with higher intakes of protein and appropriate fat appear to be more acceptable to some people. This alternative dietary approach has been shown to achieve comparable or greater weight reduction and improvement in insulin sensitivity and clinical and biochemical variables associated with insulin resistance. Importantly, these benefits appear to be sustained. For successful weight maintenance, a wide range of carbohydrate intakes is acceptable, the generally accepted range being between 45% and 60% of total energy. Vegetables, legumes, intact fruits, and whole-grain cereals are the preferred sources of carbohydrate, and when carbohydrate intake is at the upper end of the recommended range, it is particularly important to emphasize foods rich in dietary fiber and with a low glycemic index. Ideally, dietary fiber intake should be at least 40 g/day (or 20 g/1,000 kcal/day), approximately half of which should be soluble, but beneficial effects are also obtained with lower, and for some, more acceptable amounts. As diets high in fructose, sucrose, and possibly other free sugars, such as high fructose corn syrup, may promote obesity and thus insulin resistance and other metabolic abnormalities, total free sugars should not exceed 10% of total energy. In diets of more moderate carbohydrate intakes, it is imperative that *cis* unsaturated fatty acids, especially monounsaturated fatty acids, should predominate. In both moderate- and high-carbohydrate diets, saturated fatty acids should be substantially restricted, *trans* unsaturated fatty acids should be eliminated as much as possible, and n-6 and n-3 unsaturated fatty acids should be consumed in moderation. Although n-3 fatty acids are essential fatty acids, there are no proven beneficial effects on insulin sensitivity in humans. Prospective studies under way at present should confirm the distribution of macronutrients most likely to achieve maximum insulin sensitivity as well as determine whether a range of candidate genes explain variation in response to diet.

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