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THE INSULIN RESISTANCE SYNDROME: Definition and Dietary Approaches to Treatment

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■ **Abstract** The ability of insulin to stimulate glucose disposal varies at least sixfold in apparently healthy individuals, and approximately one-third of the population that is most resistant to this action of insulin is at greatly increased risk to develop a number of adverse clinical outcomes. Type 2 diabetes occurs when insulin resistant individuals are unable to secrete enough insulin to compensate for the defect in insulin action, and this was the first clinical syndrome identified as being related to insulin resistance. Although the majority of insulin-resistant individuals are able to maintain the level of compensatory hyperinsulinemia needed to prevent the development of a significant degree of hyperglycemia, the combination of insulin resistance and hyperinsulinemia greatly increases the likelihood of developing a cluster of closely related abnormalities and the resultant clinical diagnoses that can be considered to make up the insulin resistance syndrome (IRS). Since being overweight/obese and sedentary decreases insulin sensitivity, it is not surprising that the prevalence of the manifestations of the IRS is increasing at a rapid rate. From a dietary standpoint, there are two approaches to attenuating the manifestations of the IRS: (*a*) weight loss to enhance insulin sensitivity in those overweight/obese individuals who are insulin resistant/hyperinsulinemic; and (*b*) changes in macronutrient content of diets to avoid the adverse effects of the compensatory hyperinsulinemia. This chapter will focus on defining the abnormalities and clinical syndromes that compose the IRS and evaluating the dietary changes that can ameliorate its adverse consequences.

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INTRODUCTION

The aim of this chapter is to consider the role that changes in the amount and kind of calories consumed can play in attenuating the manifestations of the insulin resistance syndrome (IRS). Prevalence of the adverse clinical consequences of the IRS is growing rapidly in parallel with worldwide increases in body weight, and successful weight loss in overweight/obese individuals can moderate the abnormalities and clinical syndromes associated with insulin resistance (9, 26, 30, 35, 37, 42, 45, 56, 58). However, weight loss is difficult to achieve, and not all overweight/obese individuals are insulin resistant (1, 35, 37, 39). Thus, a major goal of this review is to define the relationship between excess adiposity, insulin resistance, and the IRS, as well as to offer suggestions to help identify those overweight/obese individuals who will benefit the most from weight loss.

Although weight loss of 5%–10% of initial body weight can enhance insulin sensitivity in overweight/obese individuals who are insulin resistant, not all of the abnormalities in these individuals return to the levels seen in insulin-sensitive individuals (35, 37). Furthermore, normal-weight individuals are not all insulin sensitive, nor are they spared from developing manifestations of the IRS (1, 39). Fortunately, the therapeutic benefits of dietary intervention in insulin-resistant persons are not limited to decreasing total caloric intake, and evidence is reviewed showing that clinically useful changes can also occur in insulin-resistant individuals by changing the macronutrient composition of isocaloric diets. In contrast to weight loss, which both enhances insulin sensitivity and lowers plasma insulin concentrations, variations in the relative proportion of macronutrients in the diet have little, or no, effect on insulin-mediated glucose disposal. However, by modifying the level of circulating insulin required to maintain glucose homeostasis in insulin-resistant individuals, variations in diet composition have the ability to either accentuate, or attenuate, the manifestations of the IRS.

Based on the general considerations outlined above, the remainder of this chapter (*a*) describes the abnormalities and clinical syndromes associated with insulin resistance (the IRS); (*b*) defines the relationship between excess adiposity and insulin resistance, and outlines approaches to identify those overweight/obese individuals who will benefit the most from weight loss; and (*c*) explains why the usual recommended "prudent" diet based on replacing saturated fat (SF) with carbohydrate (CHO) will have adverse consequences in individuals with the IRS. Although implicit in the discussion to this point, it should be explicitly stated that

only experimental results obtained in human beings are considered in addressing the issues outlined above.

DEFINITION OF THE INSULIN RESISTANCE SYNDROME (IRS)

Differentiation from the Metabolic Syndrome

Sensitivity to insulin-mediated glucose disposal varies widely in the population at large (61). When insulin-resistant individuals cannot maintain the degree of hyperinsulinemia needed to overcome the defect in insulin action, type 2 diabetes develops (46). Although the vast majority of individuals can sustain the level of compensatory hyperinsulinemia needed to maintain normal or near-normal glucose tolerance, this philanthropic effort on the part of the pancreatic beta cell is a mixed blessing. The combination of insulin resistance and compensatory hyperinsulinemia prevents the development of frank hyperglycemia, but greatly increases the risk of having some degree of glucose intolerance, a high plasma triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C) concentration, and essential hypertension (46). In 1988, it was proposed that individuals displaying this cluster of abnormalities associated with insulin resistance/compensatory hyperinsulinemia were at significantly increased risk of cardiovascular disease (CVD) (46). Because the importance of insulin resistance and associated abnormalities as CVD risk factors was not widely appreciated at that time, the cluster of associated abnormalities was subsumed under the rubric of syndrome X.

Since the introduction of the concept of syndrome X, considerable information has evolved relevant to the role of insulin resistance in human diseases. This has resulted in two somewhat disparate approaches to thinking about the clinical implications of insulin resistance and its consequences. One view recognizes that the abnormalities related to insulin resistance have broadened considerably, and the adverse clinical outcomes extend beyond type 2 diabetes and CVD. Because CVD is recognized to be just one of the multiple clinical syndromes associated with insulin resistance, it seems appropriate to replace the term syndrome X with one that more aptly deals with this new information. In this context, the IRS seems to be a logical choice to provide a pathophysiological construct with which to view the different abnormalities and clinical syndromes that occur more commonly in insulin-resistant individuals.

During a period when the number of abnormalities and clinical syndromes related to insulin resistance was expanding rapidly, the cardiological community acknowledged the importance of this defect in insulin action as increasing CVD risk with the report of the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (12). The ATP III recognized the importance of CVD risk factors of what they referred to as a "constellation of lipid and nonlipid risk factors of metabolic origin," designated this cluster as the metabolic syndrome,

TABLE 1 ATP III[a] criteria for diagnosing the metabolic syndrome[b]

Abdominal obesity
Men: waist circumference >40 inches
Women: waist circumference >35 inches
Fasting glucose ≥110, <126 mg/dl
Blood pressure ≥130/80 mm Hg
Triglycerides ≥150 mg/dl
High-density lipoprotein cholesterol
Men <40 mg/dl
Women <50 mg/dl

[a]Adult Treatment Panel III of the National Cholesterol Education Program.

[b]The metabolic syndrome is present when three or more of the five criteria are met.

and stated, "This syndrome is closely related to insulin resistance." Table 1 lists the five criteria selected by the ATP III with which to diagnose the metabolic syndrome. Other than the inclusion of abdominal obesity, the abnormalities selected by the ATP III are those initially proposed to comprise syndrome X, and these choices reflect their view that insulin resistance is at the root of the problem. On the other hand, the stated purpose of the ATP III is to provide criteria to make a clinical diagnosis of the metabolic syndrome, not to provide a physiological construct to explain why insulin resistant/hyperinsulinemic individuals are at increased CVD risk.

Put more explicitly; in contrast to the physiological construct underlying the IRS, the metabolic syndrome is aimed at providing the means to make a clinical diagnosis. Whether or not this effort will prove to be of clinical benefit remains to be seen, but because of its broader construct, the focus of this chapter is on the IRS.

Abnormalities and Clinical Syndromes Associated with Insulin Resistance

Insulin resistance is not a disease unto itself, but a physiological abnormality that increases the likelihood that one or more of the abnormalities listed in Table 2 will be present. Furthermore, because these abnormalities occur more commonly in insulin-resistant individuals, these individuals are at increased risk to develop the clinical syndromes listed in Table 3. However, the relationship between insulin resistance and the changes listed in Tables 2 and 3 is complicated, and the abnormalities and clinical syndromes can occur in the absence of insulin resistance. It must also be emphasized that insulin-resistant individuals do not necessarily develop any of the clinical syndromes listed in Table 3.

TABLE 2 Abnormalities associated with insulin resistance/ compensatory hyperinsulinemia

- Some degree of glucose intolerance
  - Impaired fasting glucose
  - Impaired glucose tolerance
- Dyslipidemia
  - ↑ Triglycerides
  - ↓ HDL-C
  - ↓ LDL-particle diameter (small, dense LDL particles)
  - ↑ Postprandial accumulation of triglyceride-rich lipoproteins
- Endothelial dysfunction
  - ↑ Mononuclear cell adhesion
  - ↑ Plasma concentration of cellular adhesion molecules
  - ↑ Plasma concentration of asymmetric dimethylarginine
  - ↓ Endothelial-dependent vasodilatation
- Procoagulant factors
  - ↑ Plasminogen activator inhibitor-1
  - ↑ Fibrinogen
- Hemodynamic changes
  - ↑ Sympathetic nervous system activity
  - ↑ Renal sodium retention
- Markers of inflammation
  - ↑ C-reactive protein, white blood cell count, etc.
- Abnormal uric acid metabolism
  - ↑ Plasma uric acid concentration
  - ↓ Renal uric acid clearance
- Increased testosterone secretion (ovary)
- Sleep-disordered breathing

HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein.

TABLE 3 Clinical syndromes associated with insulin resistance

- Type 2 diabetes
- Cardiovascular disease
- Essential hypertension
- Polycystic ovary syndrome
- Nonalcoholic fatty liver disease
- Certain forms of cancer
- Sleep apnea

The focus of this chapter does not permit an extensive discussion of the complex relationship between insulin resistance, compensatory hyperinsulinemia, and the abnormalities and clinical syndromes that make up the IRS, but an extensive review of these issues has recently been published (51). However, it is important to briefly address the question of differential tissue insulin sensitivity, for if this phenomenon did not exist, there would be no IRS. The ability of insulin to stimulate muscle glucose uptake and inhibit free fatty acid (FFA) release from the adipose tissue is highly correlated (3), and the similar degree of insulin resistance in these two tissues initiates the series of events that leads to the abnormalities and clinical syndromes listed in Tables 2 and 3. There are many instances of this phenomenon, but the following three should suffice to make the point. Perhaps the most important example is the relationship between muscle, adipose tissue, and liver. Daylong increases in plasma insulin (muscle insulin resistance) and FFA (adipose tissue insulin resistance) concentrations act upon a liver that is insulin sensitive to stimulate hepatic TG synthesis (44, 53). One consequence of these events will be an increase in hepatic very-low-density lipoprotein (VLDL)-TG synthesis and secretion, leading to hypertriglyceridemia, while at the same time there will be a tendency for the fat content of the liver to increase, and nonalcoholic fatty liver disease to develop. The kidney is another example of an organ that retains normal insulin sensitivity in the presence of muscle and adipose tissue insulin resistance (48), and the compensatory hyperinsulinemia increases renal sodium retention and decreases uric acid clearance, thus contributing to the increased prevalence of essential hypertension and higher plasma uric acid concentrations in individuals with the IRS. The third example is polycystic ovary syndrome, in which the hyperinsulinemia in insulin-resistant women acts on an ovary, which may even be hypersensitive to the ability of insulin to increase testosterone secretion (11). Indeed, the compensatory hyperinsulinemia that prevents the development of type 2 diabetes in insulin-resistant individuals is responsible for most, if not all, of the abnormalities and clinical syndromes that constitute the IRS.

IMPROVING INSULIN SENSITIVITY WITH WEIGHT LOSS

Consideration of dietary approaches to attenuate the abnormalities and clinical syndromes related to the IRS should differentiate between efforts to enhance insulin sensitivity and changes aimed at minimizing its adverse consequences. In this context, there is substantial evidence that insulin sensitivity can be enhanced, and manifestations of the IRS improve when insulin-resistant individuals lose weight (9, 26, 30, 35, 37, 42, 45, 49, 50, 56, 58). In contrast, variations in macronutrient content of isocaloric diets have little, if any, impact on insulin sensitivity (5, 17, 20), and their benefits are limited primarily, if not entirely, to decreasing the adverse metabolic consequences of insulin resistance/hyperinsulinemia (49, 50). Thus, in this section, attention is focused on the ability of weight loss to improve insulin sensitivity, and thereby to attenuate the abnormalities associated with the IRS.

Weight Loss Can Improve Insulin Sensitivity

The results of the Third National Health and Nutrition Examination Survey (28) indicated that more than 50% of those surveyed between 1988 and 1994 were overweight/obese, and the magnitude of this problem continues to increase. Although the gravity of the obesity epidemic is well appreciated, efforts to deal with it effectively are compromised by widespread pessimism concerning the ability to achieve sustained weight loss in overweight/obese individuals. The problem is further confounded by continuing controversies concerning the relative superiority of weight-loss diets that vary widely in their macronutrient content. In the absence of compelling evidence that compliance is greater with any specific macronutrient combination, other than the necessity that the individuals are willing and able to follow a diet containing less energy than they use, it does not seem possible to propose the "best" diet to help overweight/obese individuals with the IRS lose weight.

On the other hand, it is possible to address the fact that not all overweight/obese individuals are insulin resistant and at increased risk of developing the adverse consequences associated with the defect in insulin action. Prospective studies from our research group have indicated that the upper one-third of an apparently healthy population is sufficiently insulin resistant to develop the adverse clinical syndromes of the IRS, whereas those in the lower one-third of the population are at much less risk (13, 62). Although approximately 75% of individuals in the most insulin-resistant tertile are overweight/obese, 30% of those in the most insulin-sensitive tertile are also overweight/obese, and at low risk of the IRS (39). Thus, it seems sensible that the most intensive efforts at weight loss be initiated in those overweight/obese individuals who will benefit the most if the intervention is successful. Obviously, the first step in accomplishing that goal would be the ability to identify such individuals, and it appears that there is a relatively simple way to accomplish that task (36).

How to Identify Overweight/Obese Individuals Who Will Benefit the Most from Weight Loss

Because there is no simple clinical way to quantify insulin resistance, the alternative is to either initiate similar effort at weight loss in all overweight/obese persons, or to use surrogate estimates of insulin resistance to identify those who will benefit the most from weight loss. Health care professionals electing the second course usually rely on measurements of fasting plasma insulin (FPI) concentrations, or various formulae involving the use of both fasting plasma glucose (FPG) and insulin concentrations (HOMA-IR, QUICKI, FPG $\times$ FPI, etc.) to identify insulin-resistant persons. FPI concentrations are reasonably predictive of direct measures of insulin resistance in nondiabetic individuals, but the relationship (r-value $\sim$0.6) only accounts for $\sim$36% of the variability in insulin action, and the use of the more complicated surrogate estimates of insulin action does not substantially increase the magnitude of the relationship (25, 61). More importantly, plasma

insulin measurements are not standardized, and it is not possible to interpret the clinical significance of values from one laboratory to another. We have shown in overweight/obese individuals that the plasma TG/HDL-C concentration ratio is as good a surrogate marker of insulin resistance as is FPI concentration; in addition, it can be used to identify individuals who have the atherogenic profile that characterizes the IRS and thereby are at increased risk of CVD (36). Based upon the results of these studies, we have suggested that an overweight/obese person with a TG/HDL-C concentration ratio (mg/dl) $\geq$3.0 is highly likely to be both insulin resistant and at increased CVD risk; the higher the value, the less sensitive and the more specific the ratio, whereas values $<$3.0 increase sensitivity and lose specificity. This approach is certainly not perfect, but it does provide a way to decrease the number of overweight/obese individuals who meet the criteria for intensive weight loss efforts and to identify those who will benefit the most if weight loss can be accomplished.

Insulin-Resistant Individuals Can Lose Weight

Although there appears to be a perception that insulin-resistant/hyperinsulinemic individuals cannot lose weight, several studies, performed in different ethnic groups, have indicated that insulin-resistant individuals, using either insulin concentrations as a surrogate measure of insulin resistance or direct measures of insulin-mediated glucose disposal, either gain the same weight, or less weight, over time (18, 23, 55, 57, 59, 63). Furthermore, the ability to lose weight in response to calorie-restricted diets does not vary as a function of differences in either insulin resistance or insulin secretion (35, 37, 38). Consequently, although it is very difficult to carry out successful weight loss programs, the impediment is not because the individual may be insulin resistant /hyperinsulinemic.

Benefits of Weight Loss in Insulin-Resistant Overweight/Obese Individuals

Studies published 30 years ago demonstrated that insulin sensitivity improved when nondiabetic overweight/obese individuals lost weight, which was associated with a decrease in the plasma insulin response to oral glucose and lower plasma TG concentrations (45). Similar improvements in insulin sensitivity have been demonstrated in several subsequent studies, and we have also shown that following moderate weight loss the slightly elevated daylong plasma glucose and FFA concentrations seen in nondiabetic, insulin-resistant, overweight individuals return to the values of equally overweight, insulin-sensitive person (35, 37, 38). However, although the daylong hyperinsulinemia that characterizes nondiabetic, overweight, insulin-resistant individuals also declines with weight loss, it does not fall to the level seen in insulin-sensitive, equally obese individuals (35, 37, 38). Similarly, C-reactive protein concentrations are higher in insulin-resistant than in insulin-sensitive individuals matched for adiposity, and although concentrations fall in association with weight loss in the insulin-resistant persons, they

do not reach the level seen in the insulin-sensitive subjects (37). Thus, a moderate amount of weight loss in insulin-resistant, overweight/obese individuals improves insulin sensitivity, resulting in changes in carbohydrate and lipid metabolism and a marker of vascular inflammation that would decrease the risk of type 2 diabetes, CVD, and other clinical syndromes associated with the IRS.

EFFECT OF VARIATIONS IN MACRONUTRIENT CONTENT ON THE MANIFESTATIONS OF THE INSULIN-RESISTANCE SYNDROME

In contrast to the lack of compelling evidence showing that variations in macronutrient content affect the ability to lose weight, data concerning the metabolic effects of such manipulations in weight-maintenance diets are more consistent. In this section, the ability of changes in relative amounts and kinds of dietary CHO and fat to modify the abnormalities and clinical syndromes associated with the IRS is discussed.

Variations in Amount of Fat and Carbohydrate

Until relatively recently, the prudent diet recommended for all Americans contained (as percentages of total calories) approximately 15% protein, 25%–30% fat, and 55%–60% CHO; this approach was aimed at decreasing SF intake. The rationale for this recommendation was that it would help decrease CVD risk by maintaining the lowest possible plasma low-density lipoprotein cholesterol (LDL-C) concentration (15, 41).

Replacing SF with CHO in isocaloric diets requires that more insulin be secreted to maintain glucose homeostasis, and the more insulin resistant the individual, the greater will be the requisite degree of compensatory hyperinsulinemia. The additional CHO does not require a substantial increase in insulin secretion in order for insulin-sensitive persons to maintain glucose homeostasis, and low-fat/high-CHO diets will help maintain low LDL-C concentration in these individuals without adverse metabolic consequences. Although the beneficial effects of low-fat/high-CHO diets on LDL-C concentrations are not lost in insulin-resistant individuals, this dietary modification will have one of two effects in these persons, neither of which is desirable. If they are unable to respond to the need to secrete even more insulin, their ability to maintain normal glucose tolerance will be compromised. Alternatively, if they are capable of further increasing their degree of compensatory hyperinsulinemia, the abnormalities associated with the IRS (Table 1) will be accentuated, and the likelihood of developing one of the clinical syndromes listed in Table 2 will increase.

It is not possible within the context of this review to discuss all of the adverse consequences of low-fat/high-CHO diets in insulin-resistant/hyperinsulinemic individuals. However, the relationship between CVD risk and the dyslipidemic

changes of the IRS are well established, and there is considerable evidence of the metabolic effects of low-fat/high-CHO diets on lipoprotein metabolism in insulin-resistant individuals. Thus, a brief summary of these issues will hopefully serve the useful purpose of pointing out the dangers of replacing SF with CHO in the approximately one-third (13, 62) of the U.S. population that is sufficiently insulin resistant to be at increased risk of all of the adverse manifestations of the IRS.

TRIGLYCERIDE-RICH LIPOPROTEINS The fact that low-fat/high-CHO diets increase fasting plasma TG concentrations has been repeatedly confirmed since the pioneering studies by Ahrens and associates (4). Fasting hypertriglyceridemia is perhaps the most characteristic metabolic abnormality in insulin-resistant/hyperinsulinemic individuals, and the ingestion of low-fat/high-CHO diets increases hepatic VLDL-TG synthesis and secretion, resulting in higher fasting TG concentrations in both nondiabetic individuals and in patients with type 2 diabetes (2, 14, 16, 40, 47, 53).

The original suggestion by Zilversmit (64) that atherogenesis is a postprandial phenomenon continues to gain support (31), and there is evidence that degree of postprandial lipemia is accentuated in insulin resistant/hyperinsulinemic individuals (22, 24, 32, 33). Not surprisingly, there is also evidence that increasing dietary intake of CHO accentuates the postprandial accumulation of TG-rich lipoproteins (2, 7, 8, 24). Thus, the predictable effect of low fat-high CHO diets in insulin resistant and hyperinsulinemic individuals will be to both increase fasting plasma TG concentration, and accentuate the daylong accumulation of TG-rich remnant lipoproteins.

HIGH-DENSITY LIPOPROTEIN CHOLESTEROL CONCENTRATION In light of evidence that there is an independent relationship between insulin resistance/hyperinsulinemia and HDL-C concentration (29), the conclusion from two meta-analyses (15, 41) that low-fat/high-CHO diets result in lower HDL-C concentrations is not unexpected. More controversial is whether the kind of fat affects HDL-C concentration. Thus, Mattson & Grundy (34) suggested some time ago that there was an accentuated decline in HDL-C concentrations when SF was replaced with polyunsaturated fat (PUF), as compared with substitution of SF with monounsaturated fat (MUF), whereas Howard and associates (19) were unable to confirm this observation. If the data from the meta-analyses (15, 41) are considered, it appears that the effect on HDL-C concentration is reasonably similar when either MUF or PUF replaces SF.

LOW-DENSITY LIPOPROTEIN CHOLESTEROL PARTICLE DIAMETER A study in 100 healthy volunteers (52) demonstrated that a highly significant inverse relationship exists between degree of insulin resistance and LDL particle diameter. The study also demonstrated that individuals with small, dense LDL (pattern B) are relatively insulin resistant, glucose intolerant, hyperinsulinemic, with higher TG and lower HDL-C concentrations, and elevated levels of blood pressure as compared

with individuals with a preponderance of larger LDL particles (pattern A). Given evidence that the appearance of small, dense LDL particles is one of the abnormalities that occurs more commonly in patients with the IRS, it is not surprising that the prevalence of pattern A is more common in patients on diets relatively high in fat, whereas conversion to pattern B is seen when the switch is made to a diet relatively high in CHO (10, 27, 60).

LOW-DENSITY LIPOPROTEIN CHOLESTEROL CONCENTRATION There is abundant evidence that LDL-C concentrations will fall when SF is replaced with PUF or MUF (15, 41), and because differences in insulin resistance and/or hyperinsulinemia do not modulate LDL-C concentration, this effect will be similar in insulin-resistant individuals. Furthermore, it has been shown (43) that the effect on LDL-C concentrations of diets containing ∼20% versus ∼40% of total fat was similar, as long as the ratios of polyunsaturated to saturated fat (P:S) were identical (1.0), as well as the n-3:n-6 ratio and the ratio of MUF to total fat. In other words, it appears that there may be little or no increase in LDL-C levels in response to the ingestion of more fat, as long as the fat is unsaturated. These data are congruent with the results of two large meta-analyses (15, 41), and seem to apply equally well to patients with type 2 diabetes (16, 17).

Variations in the Kind of Carbohydrate

Replacement of SF with MUF and/or PUF, rather than CHO, will lower LDL-C concentrations and will not lead to a significant increase in ambient plasma insulin concentrations and the manifestations of the IRS, thus providing a simple and useful dietary approach for patients with pure hypercholesterolemia, the IRS, or combined dyslipidemia. On the other hand, other dietary modifications have been suggested in order to limit the untoward metabolic consequences of the conventional low-fat/high-CHO diets.

For example, one suggestion aimed at avoiding the untoward effects of low-fat/high-CHO diets in patients with type 2 diabetes has been to vary the glycemic index of the CHO ingested, rather than to simply replace SF with unsaturated fat (UF) and reduce the CHO intake (21, 54). Alternatively, it has been suggested that the untoward effects of low-fat/high-CHO diets in patients with type 2 diabetes can be avoided by doubling the recommended fiber intake to 50 g/d (6). Even if it is assumed that patients would be willing to consume diets made up almost entirely of oranges (300 g/d), green peas (110 g/d), zucchini (195 g/d), papaya (250 g/d), peaches (300 g/d), fruit cocktail (200 g/d), and cherries (100 g/d), it did not appear that the improvement in daylong plasma glucose and insulin concentrations and fasting plasma lipid concentrations in this study (6) was as great as when a low-fat/high-CHO diet was compared with a diet in which MUF was increased and CHO decreased (16). Similarly, in a study in which the glycemic index was varied in low-fat/high-CHO diets (21), the improvements in daylong plasma glucose and insulin concentrations were also of lesser magnitude than the study in which the

CHO intake was reduced and the MUF intake increased (16). It is worth noting that the results of these two studies, in which either the fiber intake (6) or the glycemic index (21) was varied, indicated that estimates of insulin sensitivity and several aspects of lipoprotein metabolism improved on *both* the control and experimental diets, without any significant differences between them for many of the experimental variables measured. A more recent study (54) compared the metabolic effects of two diets that seemed to be approximately equal in fat and CHO intake, but differed in glycemic index. It was concluded that four weeks of the lower glycemic index diet led to a variety of benefits, including lower postprandial glucose and insulin concentrations and enhanced insulin sensitivity. Unfortunately, these values were also significantly lower at baseline when the lower glycemic diet was used, and measurements of diet-associated changes in insulin secretion and sensitivity did not show any consistent diet effect.

It is not clear from the available data whether the clinical utility of increasing the fiber content or decreasing the glycemic index of low-fat/high-CHO diets is preferable to simply replacing SF with UF and decreasing CHO intake. In order to resolve this question it is necessary to initiate studies in which these alternatives can be directly compared. In the absence of such information, it is argued that it is simpler, and at least as beneficial, to simply replace SF with UF, not CHO, and thereby avoid the adverse effects of low-fat/high-CHO intake.

SUMMARY

The most dramatic improvements in manifestations of IRS occur in overweight, insulin-resistant/hyperinsulinemic individuals when they lose weight. However, as long as the energy content is kept constant, there appears to be little, or no, evidence that low fat-/high CHO diets will directly improve insulin sensitivity. On the other hand, there is considerable evidence that isocaloric diets, low in fat and enriched in CHO, will accentuate the manifestations of the IRS. The more insulin resistant an individual, the greater is the amount of insulin that must be secreted in response to a CHO-enriched diet in order to maintain glucose homeostasis. Thus, the inevitable, and consistently replicated, effect of replacing SF with CHO in insulin-resistant individuals is to increase daylong concentration of glucose or insulin, or both. In addition, this dietary approach has consistently been shown to stimulate hepatic VLDL-TG synthesis and secretion, leading to an increase in concentration of TG-rich lipoproteins, both in the fasting and postprandial states. The increase in the ambient TG-rich lipoproteins seen following low-fat/high-CHO diets has previously been shown to be associated with a decrease in HDL-C concentration, and it appears that such diets will change the LDL subclass pattern to B in 36 of 87 individuals (41%) who had either pattern A or an intermediate pattern at the outset (27).

Given the evidence that low-fat/high-CHO diets do not modify the basic defect in the IRS (insulin resistance) and accentuate all of its metabolic manifestations,

there seems to be little rationale for substituting SF with CHO. This is particularly true in light of the multiple observations that replacing SF with MUF or PUF, or both, will lead to the same fall in LDL-C concentrations, without any of the adverse metabolic effects seen with low-fat/high-CHO diets (15, 41).

Finally, the prevalence of the manifestations of the IRS is increasing rapidly as the world becomes heavier and less fit. There is considerable evidence that dietary manipulations can play a powerful role in modulating the manifestations of the IRS, as well as reasonably good understanding of interventions that either can be helpful or actually make the situation worse. Thus, inability of nutritional means to prevent and/or treat the manifestations of the IRS will result from a failure of implementation, not from a lack of clinically relevant information.

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