# Dietary carbohydrates and insulin sensitivity: a review of the evidence and clinical implications[1,2]

*Mark E Daly, Catherine Vale, Mark Walker, K George MM Alberti, and John C Mathers*

**ABSTRACT** Insulin resistance is associated with diabetes mellitus, ischemic heart disease, and hypertension both independently and as part of syndrome X. Environmental influences on $S_I$ are incompletely understood. Exercise has a strong beneficial effect and obesity a strong adverse effect. The balance of evidence suggests that a high-fat diet is likely to reduce insulin sensitivity but the effects of dietary carbohydrates are more controversial. Extensive studies in animals showed a detrimental effect of diets very high in fructose or sucrose, particularly in association with induction of hypertriglyceridemia. The more limited studies in humans had conflicting results, partly because of heterogeneity of design. Certain groups of subjects may be more sensitive to adverse effects of high intakes of dietary sucrose or fructose. More carefully controlled studies in humans are needed to provide evidence on which to base public health policies with respect to dietary carbohydrates and $S_I$. *Am J Clin Nutr* 1997;66: 1072–85.

**KEY WORDS** Insulin sensitivity, carbohydrate, insulin resistance, hypertriglyceridemia, starch, sucrose, fructose, glucose tolerance

## INTRODUCTION

Himsworth (1), in 1935, was one of the first to explore the concept of insulin sensitivity ($S_I$). Not only did he develop the first method for its measurement but he also pursued the idea that diet might affect glucose tolerance by altering $S_I$. Over the past 25 y, there has been an explosion of interest in $S_I$ for several reasons.

First, decreased $S_I$ (insulin resistance) has been implicated as a major etiologic factor in the development of non-insulin-dependent diabetes mellitus (NIDDM) and is now identified as one of the earliest detectable abnormalities in at least some people in whom NIDDM later develops. Indeed, the attempt to elucidate the pathogenesis of NIDDM was the stimulus for much of the work reviewed in this article.

More recently, the scope has been broadened. Avogaro and Creapaldi (2) first described the association of cardiovascular risk factors such as hyperlipidemia, glucose intolerance, and obesity in NIDDM and at the time it was thought that these factors were linked to hypertension and ischemic heart disease. This concept underwent further development with the description by Reaven (3) of the metabolic syndrome, or syndrome X, a disorder in which insulin resistance, hyperinsulinemia, or both are key features. Separate from the associations in syndrome X, hypertension alone was linked to insulin resistance. High-sucrose and high-fructose diets were used in animal models both for hypertension studies (4–6) and to induce syndromes of insulin resistance to test hypoglycemic agents (7, 8). The interest in $S_I$ therefore goes beyond understanding the pathogenesis of NIDDM to encompass the major health problems of hypertension and ischemic heart disease.

There is a wide variation in $S_I$ in the healthy population because of differences in genetic make-up and environmental influences. The predisposition to NIDDM is partly inherited. Insulin resistance is one of the earliest abnormalities detected before onset of the diabetic state and was found to cluster in some NIDDM families (9), thereby providing support for the role of inherited factors. Obesity is probably the most common condition associated with insulin resistance (10) and weight loss improves $S_I$. Visceral obesity (in which the proportion of adipose tissue in the abdominal cavity is increased, measured indirectly by assessment of waist-to-hip ratio) is associated particularly with insulin resistance (11) but precise elucidation of the hormonal and metabolic causes that underlie this association remains incomplete (12). Another major environmental factor is physical exercise, which has a particularly strong influence on $S_I$ (13, 14).

The influence of diet on $S_I$ is not as well described. Since Himsworth's early work, researchers have approached the study of the effects of diet on glucose metabolism and $S_I$ from very different perspectives and this makes it difficult to compare results. The effects of dietary fat were reviewed recently and the evidence so far suggests that the pattern of consumption of fatty acids may be as important as the quantity of fat (15).

In the early 1970s, after the development of insulin assays, several workers investigated the effects of carbohydrates on glucose tolerance, insulin concentrations, and aspects of insulin-mediated metabolism in animals and humans. By the late 1970s there had been some specific work on effects on $S_I$ but

[1] From the Human Nutrition Research Centre, Department of Biological and Nutritional Sciences, Human Diabetes and Metabolism Research Centre, and the Department of Medicine, University of Newcastle upon Tyne, United Kingdom.

[2] Address reprint requests to ME Daly, Human Nutrition Research Centre, University of Newcastle upon Tyne, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, United Kingdom. E-mail: m.e.daly@newcastle.ac.uk.

Received July 19, 1996.

Accepted for publication April 24, 1997.

 

the direction of research then changed rapidly. Most of the studies in animals done since then focused on possible mechanisms responsible for diet-induced changes whereas most of the studies in humans addressed the debate regarding the best diet for people with diabetes. Evidence on which to base public health advice for the general population is scanty.

### Assessment of insulin sensitivity

$S_I$ is difficult to assess and two general problems arise when considering data from work done in this area. First, although insulin has many actions, most studies focused only on its effects on carbohydrate metabolism; little work has been done on other aspects of insulin action, such as protein or lipid metabolism. Second, it was discovered recently that the original radioimmunoassays developed for measuring insulin are not as specific as originally thought and that they are cross-reactive with proinsulin and proinsulin split products. Although these may contribute only 10% of the total measured insulin concentration in nondiabetic people, they may account for as much as 50% of the measured value in patients with NIDDM (16). The discovery of cross-reactivity thus created doubt about the conclusions of many of the earlier studies in patients with NIDDM in whom conventional immunoassays were used to measure endogenous insulin, although, of course, results from studies using exogenous insulin injection or infusion remain valid.

Measurement of fasting insulin concentrations is the most basic method of assessing $S_I$ and may be of particular value in screening studies with large numbers of subjects. A study by Laakso (17) had 132 subjects, including subjects with normal glucose tolerance, subjects with impaired glucose tolerance, and subjects with NIDDM. He found a strong correlation between fasting insulin concentrations and results obtained with a hyperinsulinemic clamp but correlations were weaker in subjects with impaired glucose tolerance. Therefore, measurement of fasting insulin concentrations is of particular value in subjects with normal glucose tolerance.

The ratio of fasting insulin concentrations to glucose has been used to assess $S_I$ but an improvement on this method is the homeostatic model assessment (18). In some of the larger population-based studies (19), this assessment was more useful than primary measurement of fasting insulin concentrations or insulin-glucose ratios. A further development is measurement of postprandial insulin and glucose concentrations throughout the day (20). This is a useful method only in people in whom insulin secretion is not impaired and is less useful in diabetic people or subjects with impaired glucose tolerance. This is also true of the oral-glucose-tolerance test for assessment of $S_I$ (21).

The frequently sampled intravenous-glucose-tolerance test (FSIGT) is a more sophisticated form of the intravenous-glucose-tolerance test developed by Bergman et al (22). This test uses physiologic models of glucose use and insulin kinetics together with computer analysis to derive a measurement of $S_I$. This computer-assisted approach is known as the minimal model method. The problem of poor insulin secretion can be overcome by using intravenous tolbutamide to boost insulin secretion in subjects with NIDDM (23) or a background insulin infusion or insulin bolus in subjects with insulin-dependent diabetes mellitus (24). $S_I$ calculated in this way correlated strongly with results obtained with use of a euglycemic clamp in some studies (25).

The more direct methods that use administration of exogenous insulin overcome the potential problems of reduced insulin secretion in some subjects. The first example of a method of this type is the glucose-insulin tolerance test developed by Himsworth et al (1) in the 1930s. This was based on a comparison of two responses to an oral-glucose load in which a bolus of insulin was given intravenously in the second experiment. Assessment of the ratios of the areas under the glucose curves allowed derivation of an index of relative $S_I$.

The insulin tolerance test is a comparatively simple technique that is based on measurement of the rate of decrease in plasma glucose concentration over 30 min in response to a bolus of insulin administered intravenously. There were problems with this method when it was first developed because of the surge in counterregulatory hormones as plasma glucose fell and the high incidence of hypoglycemia. However, when the test is modified by terminating it after 15 min, development of hypoglycemia and confounding effects of the counterregulatory hormones can be avoided. Results from this modified version of the insulin tolerance test correlate well with those obtained with euglycemic clamping, provided that arterialized blood samples are used for glucose measurement (26).

All the tests discussed so far are characterized by nonsteady state plasma insulin concentrations. The insulin suppression test developed by Shen et al (27) was the first to use steady state insulin concentrations. In the original method, glucose and insulin were infused at a predetermined rate with the combination of adrenaline to inhibit endogenous insulin secretion and propanolol to counteract the cardiovascular effects of adrenaline. Later, Yasuda et al (28) substituted somatostatin for adrenaline and propanolol. Subsequently, Heine et al (29) found that somatostatin was not necessary. $S_I$ is reflected by the steady state plasma concentrations of glucose reached after equilibration for 90–150 min, and an $M$ value that reflects the net removal of glucose from the circulation can be calculated. The main problem is that hepatic glucose output is not measured, although the simplicity and reproducibility of this test outweigh this disadvantage in most situations.

Euglycemic clamping is the most sophisticated and widely used way to assess $S_I$ (30). Insulin is infused at a fixed rate to achieve steady state insulin concentrations whereas a variable glucose-infusion rate is used to maintain euglycemia. The glucose-infusion rate provides an index of whole-body $S_I$. A combination of an isotope-labeled glucose infusion and clamping allows assessment of peripheral (predominantly skeletal muscle) and hepatic insulin sensitivities (31). Dose-response curves can be constructed by use of stepwise increases in the insulin-infusion rate. Suppression of lipolysis can be assessed by using lower doses of insulin.

Other tests use a continuous infusion of glucose with model assessment (32) and a low-dose infusion of insulin without glucose replacement (33).

### Effects of diet on insulin sensitivity: strength of the evidence

The studies reviewed in this article can be categorized into two groups: intervention studies, in which intakes of one or more components of the diet were deliberately changed and responses in individual $S_I$ compared (most studies in humans and animals are in this category); and natural experiments or epidemiologic studies, in which individuals with freely chosen

diets were studied. Problems exist in both groups. One inherent problem of interventional studies in both humans and animals is that when the proportion of energy from one macronutrient, eg, carbohydrate, is changed, the contribution by one or more other components is inevitably affected. Thus, when a person switches from a diet supplying 40% of energy as carbohydrate, 40% as fat, and 20% as protein to a diet supplying 60% as carbohydrate, 20% as fat, and 20% as protein, fat content is reduced by 50%. If an increase in $S_I$ is detected in this context, it cannot be concluded that this is due to the change in carbohydrate alone. However, if intake of a subcomponent, eg, a simple sugar, can be changed without changing the total intake of carbohydrate, conclusions about the effects on $S_I$ that are not confounded by changes in fat or protein content can be drawn. If the quantity and source of protein content are fixed, conclusions can be made about high-fat, low-carbohydrate diets compared with high-carbohydrate diets. In this review we focus on studies that allowed conclusions with respect to type of dietary carbohydrate.

In studies in animals, extreme diets are often chosen [eg, a diet in which fructose or glucose accounted for $\leq$ 70% of total dietary energy (34)] whereas, in studies in humans, the highest contribution made by fructose is $\approx$15%. This difference between studies in animals and those in humans makes it more difficult to compare results. Another potential problem of studies in animals is variation in the nature of the control diet. This can be a particular problem with nonpurified diets but most studies in animals discussed in this review used synthetic diets. Furthermore, results were consistent between studies using nonpurified diets for controls and those that used synthetic diets.

In studies in humans, dietary variation before the experimental period can be a confounding factor, although proper randomization and the use of crossover designs should help prevent this problem. Epidemiologic studies are often characterized by use of poor dietary assessment methods (35). Quantitative evidence of dietary intake can be obtained by use of 7-d weighed-food assessments combined with determinations of appropriate biomarkers (there are not yet any known reliable biomarkers for intakes of specific carbohydrates) but such studies are the most difficult to conduct. Many authors rely too heavily on inadequate dietary data. In summary, the problems in assessing the literature in this area have three main sources: the differing perspectives from which the problem was approached, which lead to incomplete and incompatible data; the problems in assessing $S_I$ quantitatively; and the problems inherent in assessing both habitual intake and dietary intervention.

## Studies in animals

The studies in animals reviewed here provide strong evidence for links between the amount and type of carbohydrate in the diet and $S_I$. Additionally, some also explored possible sites and mechanisms of diet-induced insulin resistance and the effect of other variables, such as age, exercise, or use of lipid-lowering drugs. There has been an extensive amount of work in this area and some selectivity is necessary. The focus is on studies that provide quantitative information on the effect of the source of dietary carbohydrate. Examples of studies that used less specific changes in macronutrient composition are mentioned only briefly.

Boyd et al (36) found that a high-fat, high-sucrose diet compared with a conventional nonpurified diet (61% of total dietary energy from starch and 10% from fat) decreased $S_I$ (assessed by in vitro maximal stimulated glucose uptake by the diaphragm muscle) to only 55% of that with the control diet. However, so many dietary variables were changed that it is not possible to attribute the effects of the diet to any specific component. Similarly, Barnard et al (37) examined the effects of a high-fat, high-sucrose diet compared with a low-fat, high-complex-carbohydrate diet in young and old rats and found that diet but not aging had an adverse effect on $S_I$, with decreased in vitro glucose transport in skeletal muscle.

To distinguish between the effects of fat and sucrose, Maegawa et al (38) compared a high-sucrose diet (73% by weight) with a high-fat diet (60% by weight) and found that insulin concentrations were highest in the high-sucrose group but were also raised, although to a lesser extent, in the high-fat group compared with the control group (a standard nonpurified diet). Insulin-stimulated 2-deoxyglucose uptake into soleus muscle was impaired during both experimental diets but more so during the high-fat diet. In contrast, glucose uptake was increased markedly in adipocytes from animals in the sucrose group but decreased in adipocytes from animals consuming the high-fat diet.

Conclusions from these two types of studies regarding the effects of carbohydrates on $S_I$ are limited because more than one dietary variable changed between the control and experimental groups; however, in both examples, a high-fat, high-sucrose diet increased insulin resistance. When high-fat and high-sucrose diets were considered separately, each seemed capable of inducing hyperinsulinemia and decreasing insulin-stimulated glucose uptake into muscle.

A second approach is to supplement a standard nonpurified diet with a sugar-containing drink that replaces water in the diet. Three of the studies reviewed here used this approach. Although their main aim was to assess the effect of adding sugar to the diet, if the rest of the diet remains constant, the percentage of total energy contributed by components other than the added sugar decreases proportionately and there may be an increase in total energy intake.

An example of this occurred in the study by Vallerand et al (39), which used a 2 $\times$ 2 factorial design to investigate the effects of adding sucrose to tap water in combination with the effects of exercise. The carbohydrate contribution to energy intake in the control group was 60%; it rose to 87–89% in the sucrose-supplemented group. The results were complex. Rats fed sucrose had higher fasting and postprandial insulin concentrations but the area under the glucose curve was lower in both sucrose groups, particularly the exercise groups. The authors concluded that sucrose and exercise had a synergistic effect on glucose tolerance in that the sucrose-rich diet increased insulin concentrations but did not alter $S_I$ whereas exercise increased $S_I$. However, the lower fat intakes in the sucrose groups (3.2% and 3.7% of total energy compared with 12%) may have improved $S_I$ and thus offset any detrimental effect of sucrose on $S_I$.

Rawana et al (40) investigated the effects of replacing water with either a fructose or a glucose solution in rat dams and their offspring during gestation and lactation. In dams, fructose increased glucose, insulin, and triacylglycerol concentrations and insulin-glucose ratios whereas glucose produced values

intermediate between those in the fructose group and those in controls given water. However, note that energy intakes were much higher in the sugar-supplemented groups and this may have contributed to differences between the experimental and control groups. Dai and McNeil (41) attempted to determine the most suitable amount of fructose for inducing hypertension by using different concentrations of fructose in drinking water. They found that a 10% solution, which was equal to 48–57% of energy as fructose in their study, was most effective in increasing fasting insulin concentrations.

The final investigative strategy is to keep the macronutrient proportions constant and either to vary the supply of polysaccharides compared with sugars or to compare one sugar with another, eg, fructose with glucose. These studies provide the most unambiguous information and therefore merit a more detailed examination of their experimental design and results.

There are several important features of the experimental design of these studies. In most cases, diet composition was expressed as the proportion of total dietary energy contributed by each component, and the other dietary components that contribute energy (ie, fat and protein) were the same in the experimental and control diets. If diet composition was calculated by weight, this was indicated. Feeding pattern may influence the response to diet; animals given ad libitum access to food may consume different amounts of energy, which may confound attempts at interpreting $S_I$ results. Pair feeding is the method of choice for ensuring comparable intakes between treatment groups. Although this method ensures similar energy intakes, patterns of intake within a day may vary and this has well-recognized metabolic consequences. In instances in which the information was available, however, feeding pattern had no apparent effect on results. Because changes in body mass and, particularly, body composition may affect $S_I$, results for these variables are also included if available.

Results of studies of the most basic reflection of $S_I$, ie, fasting insulin concentrations, are summarized in **Table 1**. Most of these studies found increased fasting insulin concentrations when sucrose replaced starch in the diet (42–47). When the monosaccharide components of sucrose were considered separately, fructose had the greater effect in two studies (4, 49) and produced no difference in fasting insulin concentrations in others (50–53). Only one study using sucrose as the experimental carbohydrate (48) did not show an effect of a sucrose diet on fasting insulin concentrations. However, this was a complex study that also looked at effects of aging and exercise. Perhaps more important, it was the study that used the lowest dietary amount of sucrose.

Several methods for assessing $S_I$ in vivo and some ingenious in vitro techniques were used in these studies (**Table 2**). In general, $S_I$ was decreased in animals with a high percentage of sucrose in their diets compared with those in a starch-consumption control group (42, 44–46, 54). These findings were supported by observations of decreased maximal tyrosine kinase activity (48) and reduced diaphragmatic glucose uptake (57). The effect of fructose was similar to that of sucrose. Compared with starch, fructose decreased $S_I$ (55, 56). This was not, however, due simply to the effect of hexose compared with complex carbohydrate causing insulin resistance because when glucose and fructose were compared directly (4, 34, 53), fructose appeared to be the culpable moiety.

This is best illustrated by two studies of almost identical design, one of which investigated sucrose compared with starch (42) and the other fructose compared with glucose (50) (**Figure 1**). Glucose-infusion rates during euglycemic clamping indicated reduced $S_I$ in both the fructose and sucrose groups compared with the glucose and starch groups (the greater the glucose-infusion rate the higher the $S_I$). These studies were performed by the same investigators, who used identical designs (pair feeding for 4 wk) that resulted in no significant weight differences between groups.

Eiffert et al (48) investigated the combined effects of aging, exercise, and sucrose-rich diets on numbers of insulin receptors and tyrosine kinase activity in 12-mo-old compared with 24-mo-old Sprague-Dawley rats. They found greater effects from sucrose (decreased sensitivity) or exercise (improved sensitivity) than from aging. Storlien et al (56) reported that when insulin resistance was induced by a high-fructose or high-fat diet, it could be completely ameliorated by administration of

**TABLE 1**
Changes in fasting insulin concentrations in animals given different amounts of sucrose and fructose

| Carbohydrate | | Duration of dietary period | Energy intake | Effect on fasting insulin concentration | Weight changes | Reference |
|---|---|---|---|---|---|---|
| Control | Experimental | | | | | |
| | | | *% of total* | | | |
| Starch | Sucrose | 4 wk | 69 | Increased | Comparable | 42 |
| Starch | Sucrose | 8 wk | 68 | Increased | Comparable | 43 |
| Starch, sucrose | Sucrose | 13 wk | 66 | Increased | Comparable | 44 |
| Starch | Sucrose | 6 wk | 65 | Increased | Comparable | 45 |
| Starch | Sucrose | 90–120 d | 63[1] | Increased | Comparable | 46 |
| Starch | Sucrose | 12 wk | 54 | Increased | Higher gain[2] | 47 |
| Starch | Sucrose | 17–20 wk | 33 | Not studied | Comparable | 48 |
| Glucose and starch | Fructose | 1 wk | 66 | Increased | Lower gain in fructose group | 49 |
| Glucose | Glucose | 30 d | 34 | Not studied | Comparable | 50 |
| Glucose | Glucose | 20–28 d | 60 | Increased | Comparable | 4 |
| Starch | Glucose | 27 wk | 69.5 | Not studied | Comparable | 51 |
| Starch, glucose | Glucose | 6 wk | 62 | Not studied | Higher gain in glucose group | 52 |
| Glucose | Glucose | 4 wk | 60 | Not studied | Not applicable | 53 |

[1] Percentage by weight.
[2] Higher weight gain in sucrose group fed ad libitum.

**TABLE 2**
Summary of effects of specific carbohydrates on insulin sensitivity in animals

| Dietary intervention[1] | Duration of experimental period | Results and comments | Reference |
|---|---|---|---|
| Starch compared with sucrose (68%) | 8 wk | Sucrose decreased sensitivity as assessed by clamp | 43 |
| Starch compared with sucrose (69%) | 4 wk | Sucrose decreased sensitivity as assessed by clamp | 42 |
| Starch compared with sucrose (62–63%)[2] | 90–120 d | Sucrose decreased sensitivity as assessed by clamp | 46 |
| Starch (66%) compared with sucrose (33%) | 17–20 wk | Decreased insulin receptor numbers in old, sucrose-fed rats | 48 |
| | | Decreased maximal tyrosine kinase activity in young, sucrose-fed rats | 48 |
| Starch compared with sucrose (64%)[2] | 3 wk | Decreased insulin sensitivity in sucrose group as assessed by IST[3] | 54 |
| Starch (69%) compared with fructose (34%) | 30 d | Decreased insulin sensitivity in fructose group as assessed by clamp | 50 |
| Starch (60%) compared with fructose (66% or 33%) | 7 d | Decreased insulin sensitivity in both fructose groups as assessed by IST | 55 |
| Starch compared with sucrose (54%) | 12 wk | Insulin sensitivity of in vitro fat cells decreased in sucrose group (more weight gain in ad libitum–fed rats on sucrose diet) | 47 |
| Fructose compared with glucose (70%) | 4 wk | Less diaphragm glucose oxidation in fructose-fed rats | 34 |
| Starch (70%) compared with fructose (35%) | 4 wk | Fructose decreased insulin sensitivity as assessed by clamp (less weight gain with fructose) | 56 |
| Starch (67%) compared with sucrose (67, 40, 33%) | ≤ 100 d | Reduction of glucose uptake by the diaphragm in sucrose groups, developing earlier with higher concentrations | 57 |
| Sucrose (66%) compared with starch, sucrose (47/19%) | 13 wk | Decreased sensitivity as assessed by clamp in sucrose group | 44 |
| Fructose compared with glucose (60%) | 20–28 d | Fructose decreased insulin sensitivity as assessed by clamp | 4 |
| Fructose compared with glucose (60%) | 4 wk | Fructose decreased insulin sensitivity as assessed by hyperinsulinemic, euglycemic clamp | 53 |

[1] Percentage of energy in parentheses.
[2] Insulin sensitivity test.
[3] Composition by weight.

benfluorex (a hypolipidemic agent) in the high-fructose group but only partly ameliorated in the high-fat group. Interestingly, this corresponded with a return to normal triacylglycerol concentrations in the fructose group.

Raised triacylglycerol concentrations are often observed in studies showing a striking association with dietary fructose or sucrose concentrations (**Table 3**). However, the hypolipidemic agent was also associated with a lower body mass in both the high-fat and high-sucrose groups that was in turn related to a reduced food intake during the first week of the study. Also note that benfluorex was used to improve $S_I$ in patients with NIDDM, although the precise mechanisms of this action are not understood.

In one study, triacylglycerol concentrations correlated directly with insulin resistance (50). It remains uncertain whether elevated triacylglycerol concentrations are involved in the development of insulin resistance or whether hypertriglyceridemia is a result of decreased $S_I$. Holness (58) fed a 52%-fructose diet to rats for 10 d and found that although this diet induced hypertriglyceridemia, in vitro insulin-stimulated glucose uptake into skeletal muscle was not impaired. Holness therefore concluded that if hypertriglyceridemia is involved in mediation of the reduced $S_I$ associated with such diets, it is not an acute effect of raised circulating triacylglycerol concentrations. More consideration of the relation between hypertriglyceridemia and insulin resistance is given later.

*Studies in animals: conclusions*

Three main conclusions may be drawn from the studies in animals. First, increasing the content of sucrose in the diet to > 60% (or of fructose to > 34%) decreases $S_I$. Evidence for effects at lower proportions is unclear. One study (48) found that a 33%-sucrose diet had no effects on fasting insulin concentrations but observed decreased numbers of insulin receptors in old sucrose-fed rats and decreased maximal tyrosine kinase activity in young sucrose-fed rats. Second, the decreased $S_I$ caused by sucrose diets is probably due to the fructose component of sucrose. Third, hypertriglyceridemia in animals is associated with sucrose- or fructose-induced insulin resistance.

A potential confounding factor is the effect of fructose on copper metabolism. Both fructose and sucrose decrease bioavailability of copper. One group of investigators observed repeatedly the ability of fructose or sucrose to cause or exacerbate copper deficiency in rats (59–62). A review by O'Dell (63) concluded that high-fructose diets (60% of energy) reduce copper availability or exacerbate copper deficiency in rats but not in humans (at 20% of energy). Rizkalla et al (64) examined the effects of fructose diets with adequate (12 μg Cu/g food) or high (24 μg Cu/g food) amounts of copper (6 μg Cu/g is normally considered sufficient). Fasting plasma insulin was higher in the group consuming 12 μg Cu/g food but not in the group consuming the high-copper diet. No further measurement of $S_I$ was done in this study. Fields et al (65) reported an interaction between copper deficiency and fructose that caused impaired glucose tolerance but concluded that the impaired tolerance was not a result of copper deficiency. Although fructose can exacerbate copper deficiency, there is no firm evidence that copper deficiency per se causes insulin resistance. It seems unlikely that induced copper deficiency is a

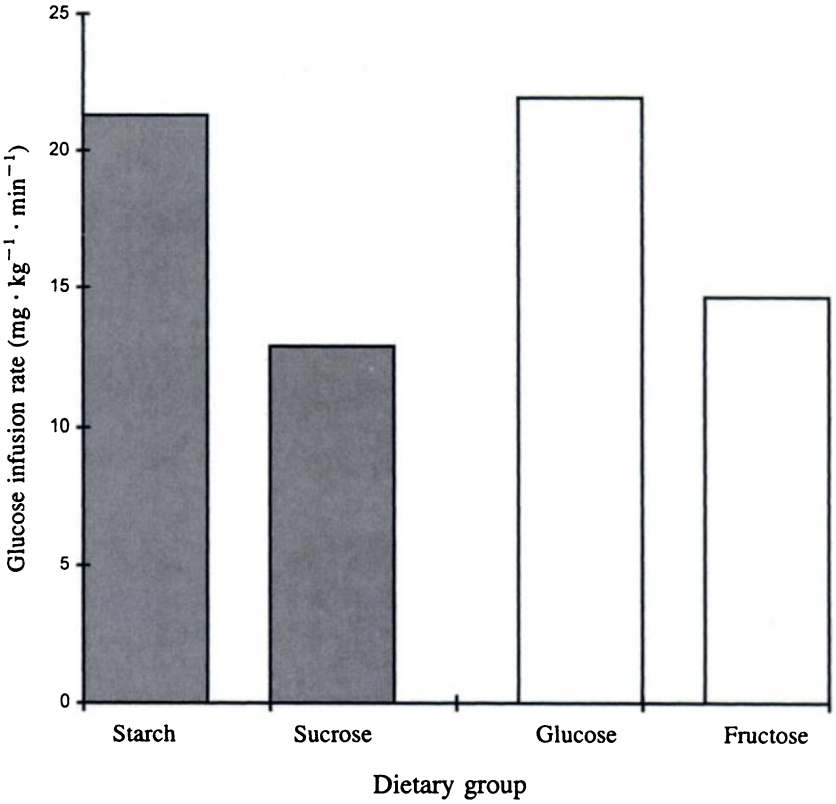


**FIGURE 1.** Effects on insulin sensitivity of starch compared with sucrose in a study by Storlien et al (42) (■) and of glucose compared with fructose in a study by Thorburn et al (50) (□).

major mechanism by which fructose or sucrose mediates its effects on $S_I$.

## Studies in humans

Evaluating the studies in humans is more difficult because there is a much wider range of investigations to be considered. Much of this work is related to either the pathogenesis of NIDDM or development of an "ideal" diet for diabetic patients. One particular point is the argument over the safety of fructose in the diet fueled by the increasing consumption of this sugar, particularly in the United States.

There are three main groups of studies. The first group includes observational population-based studies that investigated associations between diet, impaired glucose tolerance, incidence of NIDDM, and other variables. The second group includes experimental work that examined the effect of healthy or idealized diets, eg, a high-starch, low-fat, high-fiber diet. These studies provide only limited evidence as far as this review is concerned because more than one dietary variable was changed between the control and experimental groups. The final area of research consists of studies in which there was a deliberate alteration in the carbohydrate component of the diet under controlled conditions. These provide some of the most robust evidence.

### *Population-based studies*

Population-based studies fall into two groups: prospective studies with large cohorts conducted over long periods and cross-sectional studies. Although an extensive amount of work has been done on the relation between incidence of diabetes mellitus and diet, few studies measured variables that reflect

**TABLE 3**
Plasma triacylglycerol concentrations in rats fed high-sucrose or high-fructose diets

| Dietary group | Control group | Energy intake | Effect on plasma triacylglycerol | Reference |
|---|---|---|---|---|
| | | *% of total* | | |
| Sucrose | Starch | 68 | Increased | 43 |
| Sucrose | Starch | 65 | Increased | 45 |
| Fructose | Starch | 34 | Increased, inverse correlation with change in insulin sensitivity | 50 |
| Fructose | Glucose | 70 | Increased | 34 |
| Fructose | Starch | 35 | Increased | 56 |
| Fructose | Starch | 69.5 | No difference after 23 wk, elevated 2 wk | 51 |
| Fructose | Starch and glucose | 62 | Increased[1] | 52 |

[1] Increased weight gain during glucose diet.

$S_I$—let alone measuring sensitivity directly—and this approach will not be considered further here.

Two cross-sectional studies deserve consideration: the investigation of the relation between diet and hyperinsulinemia in South Asian and white men in an area of London (66) and the study by Lovejoy and DiGirolamo (67) that looked specifically at $S_I$ by using FSIGT tests in lean and obese individuals for whom dietary intakes were estimated. The study of South Asian and white men sought to identify dietary factors that might explain the different incidences of NIDDM and cardiovascular disease in the indigenous white population and the population of South Asian origin. Dietary assessments using the 7-d weighed-food method were carried out in 173 subjects in whom insulin concentrations were measured during fasting and 2 h after a glucose load. Regression analyses controlling for age and ethnicity showed that insulin concentrations 2 h after a glucose load correlated positively with carbohydrate intake, with a stronger correlation for sucrose than for starch. The same pattern was observed for fasting insulin concentrations although the correlations were weaker. However, no dietary factor explained the differences between the ethnic groups in incidence of NIDDM and cardiovascular disease.

Lovejoy and DiGirolamo (67) investigated habitual dietary intake and $S_I$ in 22 lean and 23 obese adults. Dietary assessment consisted of retrospective administration of a food-frequency questionnaire; $S_I$ was measured by FSIGT tests. The index of $S_I$ correlated inversely with fat intake but positively with dietary fiber intake. When body mass index (BMI) was controlled for, the effects were no longer significant but the regression coefficients from before and after control for BMI remained within 1 SD; the authors concluded that the effect was not mediated entirely by BMI. Food-frequency questionnaires, however, have limited precision in estimating nutrient intakes of individuals and are more appropriately used with larger numbers of subjects (35). The study in South Asian and white men used the 7-d weighed-food assessment in a larger number of subjects, which is a more robust method for a study of this size. In summary, the strongest evidence that a high sucrose intake correlates with any variables likely to reflect insulin resistance was provided by the correlation with postprandial and fasting insulin concentrations in the study of South Asian and white men in London.

### *Experimental studies: multicomponent dietary interventions*

Many studies examined the effects of low-fat, high-carbohydrate diets in healthy and diabetic individuals (**Table 4**). Two studies (68, 69) showed a clear improvement in subjects consuming a high-carbohydrate diet whereas other studies were inconclusive (70–73). The type of design used in these studies, however, does not permit independent conclusions to be drawn regarding the effect of type of dietary carbohydrate. The positive effects on $S_I$ in two of the studies may have resulted from the lowered dietary fat intake.

### *Controlled studies of altered dietary carbohydrate intake*

Studies that examined the effects of varying the intake of different carbohydrates while keeping other dietary variables constant merit a more detailed assessment. The designs and results of these studies are summarized in **Table 5** (74–85). The first three studies (74–76), which were conducted by the same group, focused on subjects with hypertriglyceridemia and hyperinsulinemia, used larger numbers of subjects than did any of the other studies ($\leq$ 24), and generally tested the diets for longer periods.

Reiser et al (74) investigated effects of diets in which 30% of total dietary energy was provided by sucrose or starch and 43% by carbohydrate. When subjects consumed the high-sucrose diet, fasting insulin concentrations and insulin-glucose ratios in response to a sucrose load were higher than when they consumed the starch-rich diet. The effect was greater in subjects who were hypertriglyceridemic. The second study by Reiser et al (75) used different sucrose intakes in a group of subjects who were all hyperinsulinemic and found similar results: a rise in fasting insulin concentrations corresponding with an increase in sucrose intake. The next step was to see whether fructose

**TABLE 4**
Human studies—generalized dietary intervention

| Dietary intervention | Duration of dietary period | Subject group | Methods used | Results | Reference |
|---|---|---|---|---|---|
| High carbohydrate, high fiber (68% carbohydrate compared with control (free choice—43% carbohydrate) | 21–28 d | Healthy ($n$ = 6 young and 6 old) | Euglycemic clamp | Sensitivity increased with high-carbohydrate diet | 68 |
| 85% carbohydrate compared with 30% carbohydrate | 3–5 d | Healthy ($n$ = 8 young and 10 old) | FSIGT with minimal model analysis | Sensitivity increased with high-carbohydrate diet | 69 |
| Substitution of complex carbohydrate for saturated fat | 5–7 wk | Obese with NIDDM and obese healthy with comparisons between whites and Pima Indians ($n$ = $\leq$12 per group) | Modified IVGTT with IV tolbutamide. Glycemic clamp with arginine | No difference detected | 70 |
| High carbohydrate compared with high fat | 3 wk | Healthy ($n$ = 8) | Euglycemic clamp | No difference detected | 71 |
| 60% carbohydrate compared with 30% carbohydrate | 21 d | NIDDM, diet-controlled only ($n$ = 8) | Euglycemic clamp | No difference detected | 72 |
| 60% carbohydrate with or without exercise | 12 wk | Impaired glucose tolerance ($n$ = 10 per group) | Euglycemic clamp | Minor improvement in sensitivity in both groups | 73 |

NIDDM, non-insulin-dependent diabetes mellitus; FSIGT, frequently sampled intravenous-glucose-tolerance test; IVGTT, intravenous-glucose-tolerance test.

**TABLE 5**
Human studies—effects of sugars compared with starch on insulin sensitivity

| Dietary intervention | Design and reference | Time period | Subject group | Change in basal insulin concentrations | Insulin sensitivity |
|---|---|---|---|---|---|
| Isoenergetic exchange of sucrose for starch at 30% of energy | Crossover (74) | 6 wk | Healthy, with subgroup with hypertriglyceridemia ($n$ = 19) | Greater in sucrose group | — |
| Sucrose at 5%, 18%, and 33% of energy | Crossover (75) | 6 wk | Hyperinsulinemia ($n$ = 24) | Increased as sucrose content rose | — |
| Fructose at 0%, 7%, and 15% of energy | Crossover (76) | 5 wk | Healthy with subgroup with hyperinsulinemia ($n$ = 23) | NS, but increased postprandial insulin | — |
| Addition of 250 g fructose or glucose | Case control (77) | 1 wk | Healthy ($n$ = 7) | No change from basal | 25% fall in fructose group as assessed by IVITT[1] |
| Fructose substituted for 24% of the carbohydrate, ie, 13.2% | Single factor (78) | 2 wk | NIDDM ($n$ = 7) | NS | — |
| Fructose substituted for 20% of carbohydrate during 45%- or 85%-carbohydrate diet | Crossover (79) | >2 wk | Hypertriglyceridemia with or without NIDDM ($n$ = 6) | NS | — |
| Fructose substituted for 20% starch | Crossover (80) | 4 wk | NIDDM ($n$ = 10) | | Increased sensitivity in fructose group as assessed by euglycemic clamp |
| Fructose at 13% | Single factor (81) | 3 mo | NIDDM ($n$ = 6) | NS | No change during euglycemic clamp |
| Sucrose (32%) for starch at 70% of energy | Crossover (82) | 4 wk | Healthy ($n$ = 9) | NS | — |
| Replacement of 45 g starch with sucrose | Crossover (83) | 6 wk | NIDDM or IDDM ($n$ = 12 of each) | NS | — |
| Exchange of starch and sucrose at 23% of energy | Crossover (84) | 14 d | Healthy ($n$ = 9) | NS | — |
| Low glycemic compared with high glycemic (25% sucrose compared with 1% sucrose) | Crossover (85) | 28 d | Healthy men ($n$ = 7) | NS | Decreased insulin sensitivity with low-glycemic diet |

[1] IVITT, intravenous-insulin-tolerance test.

might be responsible for these effects. Hallfrisch et al (76) found increased insulin and glucose responses to a sucrose load in subjects consuming 15% of dietary energy as fructose (comparable with a 30%-sucrose diet in terms of its fructose content) compared with a starch-rich control diet, but there was no change in fasting insulin concentrations. None of these studies used specific assessments of $S_I$.

Beck-Nielsen et al (77), using an insulin tolerance test, found a 25% decrease in $S_I$ in a fructose-supplemented group compared with a glucose-supplemented group. They also found that insulin binding to monocytes was decreased in the fructose group, thereby offering a possible mechanism for the change. However, both diets in the study were hyperenergetic because 4.2 MJ sugar was consumed in addition to the subjects' normal diets. Additionally, the groups were quite small ($n$ = 7) for a study that did not have a crossover design. Although it could be argued that the small size of the study was a weakness, smaller studies generally show no effect and the observation of a significant difference in such a small study was likely to be valid. The only problem would be if there was a bias in assignment of subjects to the two experimental groups; however, nothing in the experimental design indicated that this occurred.

Two studies done at the Beltsville Human Nutrition Research Center (74, 75) that produced results consistent with those of studies in animals provided the most convincing evidence that high intakes of sucrose compared with starch impair $S_I$. This concept is supported by a third study (76) that showed an increased insulin response to a sucrose load after a 15%-fructose diet.

In contrast with these studies, Koivisto and Yki-Jarvinen (80), in a study of patients with NIDDM, found that increasing fructose intake produced a 34% improvement in $S_I$ measured by euglycemic clamping. This study used a randomized, double-blind, placebo-controlled crossover design with subjects consuming each diet for 4 wk and a 4-wk washout period. During both dietary periods, the patients lived in a hospital environment. We have two comments about this study. The amount of fructose used was relatively low (≈10% of total energy replacing 20% of dietary starch) and the experimental group consisted of patients with NIDDM, 7 of 10 of whom had their condition controlled with oral hypoglycemic agents.

The recent study by Kiens and Richter (85) compared low-glycemic and high-glycemic diets that provided a 25%- and 1%-sucrose diet, respectively, in young healthy males. Using two-step euglycemic clamping, the researchers found a decreased glucose uptake in subjects consuming the diet with a low glycemic index but only during the stage of clamping in which high-dose insulin was infused.

The main aim of many of these studies was not to examine the effect of fructose on $S_I$ but to determine whether diabetic patients may consume small amounts of fructose safely. This leads to certain problems in interpreting the data and extrapolating results to the general population. In diabetic patients treated with oral hypoglycemic agents, certain agents may have stimulated insulin secretion and this might have offset any adverse effect induced by the experimental diet. NIDDM is thought to be a heterogeneous disease and, especially in view of the potential susceptibility to dietary intervention of subjects with hypertriglyceridemia (which applies to many patients with NIDDM), results in different populations of patients with NIDDM may be quite different.

All the remaining studies in this section found no effect of diet. Among the studies of sucrose, an early study by Dunnigan et al (82) that compared a 32%-sucrose diet with a sucrose-free diet found no change in fasting insulin concentrations despite 4 wk of consumption of each diet. There was no washout period between the diets and, although the diets were consumed in random order, effects from the diet consumed first may have affected results with the second diet. A reasonable degree of compliance was ensured because all patients remained in the hospital throughout the study. Similarly, Mann and Truswell (84) found no changes in fasting insulin concentrations during consumption of a 23%-sucrose diet for 2 wk. Although none of the subjects had diabetes, they were inpatients with chronic neurologic problems and therefore may not have been entirely representative of the population at large.

The remaining three studies examined changes in fructose intake in diabetic patients. Crapo et al (78) found no change in fasting insulin concentrations in seven patients with NIDDM (not taking oral hypoglycemic agents) who used fructose as a sweetener in an amount fixed at 13.2% of total energy (replacing 24% of total carbohydrate) but there was a 13% increase in blood triacylglycerol concentrations in those who were initially hypertriglyceridemic. Turner et al (79) measured triacylglycerol turnover and glucoregulatory hormones in subjects with hypertriglyceridemia and found no changes during consumption of either a 45%-carbohydrate diet (9% fructose) or a fat-free, 85%-carbohydrate diet (17% fructose) over 2 wk compared with a 45%- or 85%-starch diet. Finally, the second of the three studies to use a euglycemic clamp in this group found no effects on $S_I$ of a 13%-fructose diet consumed for 3 mo in which fructose replaced sucrose (81). However, one subject was withdrawn from the study after becoming severely hypertriglyceridemic, leaving only five subjects. None were taking oral hypoglycemic agents.

### Studies in humans: summary

In summary, one study (80) found a positive effect of high fructose consumption on $S_I$ assessed by euglycemic clamping and one (85) found a positive effect of a diet with a high glycemic index (25% sucrose) in healthy young men. Most of the other studies, which found no effect, had fairly low numbers of subjects and most studied patients with NIDDM. The strongest evidence indicating an adverse effect of fructose-rich or sucrose-rich diets (reflected by raised fasting or postprandial insulin concentrations) was provided by the work at the Beltsville Human Nutrition Research Center (74–76). The only study that found an adverse effect of fructose by using further assessments of $S_I$, ie, an intravenous-insulin-tolerance test, used a hyperenergetic diet (77).

These conflicting results have several possible explanations. First, the proportions of sugars used were much smaller than those in the studies in animals, most of which found an effect when sucrose contributed $\geq 50\%$ of dietary energy. Second, laboratory rats are much more uniform genetically than are humans, in whom it is more difficult to detect an effect because of heterogeneity of responses. Third, dietary compliance cannot be assumed in studies in humans, except possibly in investigations in which patients are hospitalized throughout the study. Several studies relied simply on providing some meals under supervision and monitoring body weight over the trial period. Fourth, different subject groups may respond in different ways to dietary intervention. This is exemplified by the contrasting results of the study at the Copenhagen Muscle Research Center (85), which enrolled young active men, and the Beltsville studies (74–76), which enrolled hyperinsulinemic subjects.

## DISCUSSION

The substantial differences in experimental design between the studies in humans and those in animals preclude simple pooling of results. Instead, we examined two conclusions from the experiments in animals and ascertained the extent to which they were supported by data from studies in humans. The first conclusion was that sucrose-rich diets decrease $S_I$. The studies in animals provide strong support for this statement from several well-designed studies that used euglycemic clamps to assess $S_I$. The studies in humans that used euglycemic clamps (and in which other dietary variables were constant) either showed no effect or, on two occasions, showed improved $S_I$ but with much lower dietary concentrations of sucrose or fructose. Using the insulin tolerance test, one study found a 25% decrease in $S_I$. However, this study used hyperenergetic diets in which 4.2 MJ fructose was added to the subjects' normal diets. The only other positive evidence in favor of this conclusion were the raised fasting insulin or postsucrose-load insulin concentrations (74–76).

The studies in animals provide unambiguous evidence for the second conclusion, ie, that fructose is responsible for the adverse effect of sucrose on $S_I$ (Figure 1). There is limited supporting evidence for this conclusion from the Beltsville studies in humans, which found that fasting or postprandial-load insulin concentrations were increased during both sucrose-rich and fructose-rich diets.

### Importance of hypertriglyceridemia

An interesting result from the Beltsville studies (74–76) was the particular sensitivity to type of dietary carbohydrate in subjects with hypertriglyceridemia and hyperinsulinemia. Two other papers from this center (86, 87) reported effects on blood lipid concentrations of varying the proportions of dietary energy provided by sucrose (5%, 18%, and 33%) and fructose (0%, 7%, and 15%). Raised triacylglycerol concentrations accompanied elevated insulin concentrations during the diet with the highest proportion of sucrose. In the study of the fructose-rich diets, raised blood triacylglycerol concentrations were

found only in subjects with initially raised fasting insulin concentrations.

Some of the strongest evidence from studies in humans was provided by Liu et al (88), who found that as the sucrose content of the diet increased, plasma triacylglycerol concentrations [predominantly very-low-density-lipoprotein triacylglycerol (VLDL-TG)] increased in parallel and that these changes were associated with increased fasting insulin concentrations. A study by Turner et al (79) that found no effects of diet on insulin concentrations observed a 13% increase in triacylglycerol concentrations in subjects who were already hypertriglyceridemic. Thorburn et al (81) had to exclude one of their six subjects part way through the study because his fasting insulin concentration increased from an initial value of 50 to 294 pmol/L; this subject's initial triacylglycerol concentrations were twice those in any other subject. One might tentatively conclude that for carbohydrate-sensitive individuals (those with hypertriglyceridemia and hyperinsulinemia), diets that provide $\geq$ 30% of dietary energy as sucrose and fructose-rich diets ($\geq$ 15%) may decrease $S_I$ and exacerbate hypertriglyceridemia.

Hypertriglyceridemia has long been known to be associated with insulin resistance in syndrome X or type IV hyperlipidemia (89). It is not clear, however, whether hypertriglyceridemia is caused by increased insulin resistance or insulin resistance is caused by hypertriglyceridemia. Mechanisms exist to explain both possibilities. Hypertriglyceridemia has the potential to cause insulin resistance by means of the glucose-fatty acid cycle by increasing fatty acid flux to the muscle and liver (90). The main mechanism by which insulin resistance could induce hypertriglyceridemia has been proposed to be hepatic insulin resistance to the inhibitory effect of insulin on VLDL-TG secretion. Furthermore, the inhibitory effect of insulin on fatty acid mobilization is reduced with insulin resistance, leading to increased flux of nonesterified fatty acids to both muscle and liver. Increased flux of fatty acids to the liver is likely to lead to a further increase in secretion of VLDL (91, 92). Studies in three areas have examined the causal relation between insulin resistance and hypertriglyceridemia.

First, there are situations in which isolated hypertriglyceridemia exists. Mice transgenic for the human apolipoprotein C-III gene were profoundly hypertriglyceridemic yet had no changes in whole-body glucose disposal (93). This suggests clearly that hypertriglyceridemia is not the primary defect. However, this model of hyperlipidemia is the result of impaired VLDL clearance rather than enhanced secretion. A 1982 study in rats of the mechanisms of fructose-induced insulin resistance found increased VLDL secretion (94). This relatively early study concluded that fructose-induced hypertriglyceridemia was produced by a combination of two factors: a direct effect of fructose in increases in hepatic VLDL secretion and a secondary effect of resistance to the insulin-inhibitory effect on hepatic VLDL secretion. In contrast with results of studies in transgenic mice, a study of lean hypertriglyceridemic humans found that they were insulin resistant (89).

A second line of evidence is the effect of hypolipidemic agents on $S_I$. Storlien et al (56) examined syndromes of insulin resistance induced in rats by either high-fat or high-sucrose diets and found raised muscle triacylglycerol concentrations in rats that consumed a high-fat diet and raised circulating triacylglycerol concentrations in the fructose group. When each group was treated with benfluorex, a hypolipidemic agent, insulin resistance was overcome completely in the fructose group (and was associated with a return to normal triacylglycerol concentrations) but was only partly ameliorated in the high-fat group. Some researchers noted a potential for improvement of $S_I$ in hypertriglyceridemic patients (95, 96) but others found no effect on $S_I$ despite an improvement in lipid profiles in patients with NIDDM (97) and people with mild hypertriglyceridemia (98).

A third approach is the artificial induction of hypertriglyceridemia. Laville et al (99) used a combination of three-step euglycemic clamping, *di*-deuterated glucose, and [$^{13}$C]palmitate infusions together with indirect calorimetry and breath sampling for $^{13}$C enrichment to investigate the effects of infusion of an emulsion of triacylglycerols. Infusion resulted in a fivefold increase in plasma triacylglycerols, impairment of $S_I$ both peripherally and for hepatic glucose production, and an increase in lipid oxidation.

On balance, there is conflicting evidence with regard to the causal relation between insulin resistance and hypertriglyceridemia. Indeed, the coexistence of the two mechanisms may explain some of the observed discrepancies in the literature. With regard to the more specific situation of hypertriglyceridemia associated with fructose- or sucrose-induced insulin resistance, however, evidence that hypertriglyceridemia is a cause of insulin resistance is provided by the study of Storlien et al (56). In that study, fructose-induced insulin resistance was completely ameliorated by administration of benfluorex, a hypolipidemic agent, and this change was associated with normalization of triacylglycerol concentrations.

### Clinical implications in the healthy population

If dietary sucrose has an adverse effect on $S_I$, this effect may occur only at high intakes, ie, $\geq$ 30% of total energy intake. It might be argued that because the average consumption of sucrose is much lower than this in most populations, the phenomenon has little practical importance. A small proportion of the population, however, consumes well above the average amount. The 1990 UK national dietary and nutritional survey (100) provided information on daily intakes of nonmilk extrinsic sugars (predominantly sucrose) (**Figure 2**). A considerable proportion of people had high intakes; some consumed > 30% of total energy in the form of nonmilk extrinsic sugars. Additionally, a substantial number of apparently healthy people are hyperinsulinemic or have an exaggerated insulin response to glucose and appear to be more sensitive to dietary change. If it is established that impaired $S_I$ occurs in these individuals if they have high sucrose intakes, they may benefit specifically from advice to reduce sucrose intakes.

This review has pointed to fructose as the culpable moiety of sucrose in potentially decreasing $S_I$. Fructose is marketed as a healthy fruit sugar and is consumed by people trying to lose weight and patients with diabetes. In the United States consumption of fructose, particularly in the form of high-fructose corn sweeteners, has risen steadily since the late 1960s (101). There is a need for continued monitoring of intakes of sucrose and fructose and further investigation of the health of those with high intakes of either sugar.

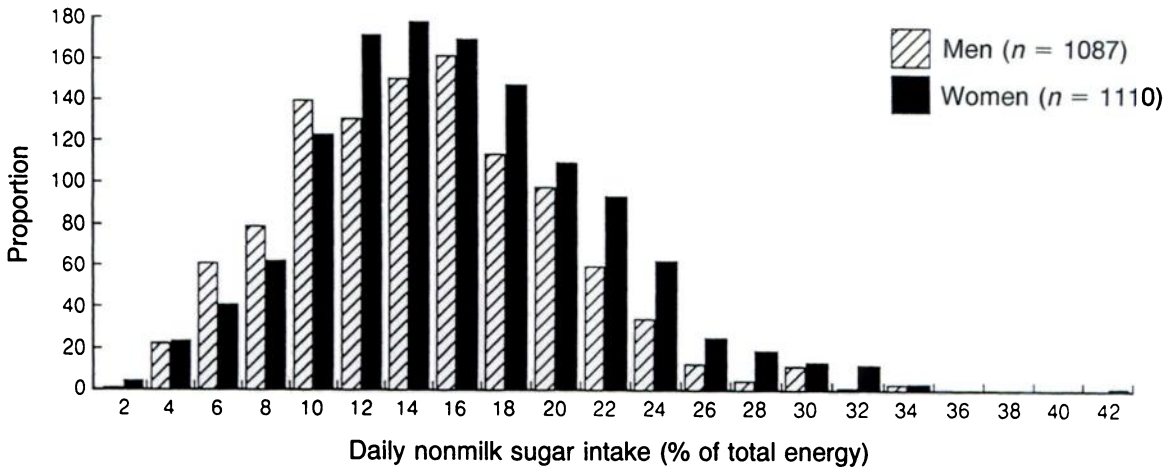


**FIGURE 2.** Daily intake of nonmilk sugars as a percentage of total daily energy intake in the United Kingdom. Crown copyright is reproduced with the permission of the Controller of Her Majesty's Stationery Office (100).

### Clinical implications in specific clinical groups

Individuals with hypertriglyceridemia, hyperinsulinemia, or both may be more sensitive than others to any harmful effect of high intakes of fructose or sucrose. For such people there is a particular need for sound evidence on which to base advice on consumption of these sugars. Existing evidence comes largely from studies at one center (74–76) but the strength of evidence from well-designed studies suggests that this is a real problem and should promote further investigations of this important area.

Arguments over the effects of sucrose and fructose in diets of people with diabetes, which were perhaps strongest in the middle-to-late 1980s, have continued. Indeed, it was this controversy that inspired many studies discussed in this review. The arguments against including sucrose in diets of diabetic patients were summarized in 1986 by Hollenbeck et al (102) in a strongly worded article. The Beltsville Human Nutrition Research Center showed a particular sensitivity to alterations in dietary intakes of carbohydrates by subjects with hyperinsulinemia. Given that people with syndrome X invariably have fasting hyperinsulinemia, it will be necessary to establish whether they are more sensitive to the deleterious effects of fructose or sucrose on $S_I$.

### Research implications

Many questions remain to be answered. It is now widely accepted that the risk of cardiovascular disease and some cancers in Western societies may be reduced by decreasing intakes of dietary fat (103, 104). If energy intakes are not to fall, the energy from carbohydrates must be increased proportionally. From the perspective of $S_I$, it remains to be proved whether there are specific advantages in supplying this extra energy as starch rather than sugars. The dietary amounts at which fructose or sucrose affect $S_I$ in healthy subjects and well-defined clinical groups need to be established by using reliable techniques, such as euglycemic or hyperinsulinemic clamping or the modified insulin tolerance test.

The long-term effects of these dietary interventions are unknown. It is essential to ascertain whether individuals adapt to high intakes of these sugars with an increase or loss of detrimental effects. The influence of quantitatively smaller carbohydrate dietary components, eg, indigestible oligosaccharides (105) and nonstarch polysaccharides, on $S_I$ has been little studied. Given that potential health benefits (particularly with respect to large bowel disease) appear to be associated with consumption of these carbohydrates and that intakes may rise, there is a need to investigate both their beneficial and adverse effects on $S_I$. Finally, because studies in animals and some studies in humans found changes in VLDL-TGs, establishment of a model of carbohydrate-induced insulin resistance with associated hypertriglyceridemia may provide clues to the underlying abnormalities in diabetes mellitus and syndrome X.

## REFERENCES

1. Himsworth HP. The dietetic factor determining the glucose tolerance and sensitivity to insulin of normal men. Clin Sci 1935;2:68–94.
2. Avogaro P, Creapaldi G. Essential lipemia, obesity and diabetes. Diabetologia 1965;1:137 (abstr).
3. Reaven GM. The role of insulin resistance in human disease. Diabetes 1988;37:1595–607.
4. Martinez F, Rizza RA, Romero C. High-fructose feeding elicits insulin resistance, hyperinsulinism, and hypertension in normal dogs. Hypertension 1994;23:456–63.
5. Reaven GM, Ho H. Sugar-induced hypertension in Sprague-Dawley rats. Am J Hypertens 1991;4:610–4.
6. Iimura O, Shimamoto K, Matsuda K, et al. Effects of angiotensin receptor antagonist and angiotensin converting enzyme inhibitor on insulin sensitivity in fructose-fed hypertensive rats and essential hypertensives. Am J Hypertens 1995;8:353–7.
7. Lee M, Miles PD, Khoursheed M, Gao KM, Moossa AR, Olefsky J. Metabolic effects of troglitazone on fructose-induced insulin resistance in the rat. Diabetes 1994;43:1435–9.
8. Bhanot S, McNeil JH, Bryer-Ash M. Vanadyl sulfate prevents fructose-induced hyperinsulinemia and hypertension in rats. Hypertension 1994;23:308–12.
9. Martin B, Warram G, Rosner B, Rich S, Soeldner S, Krolaski A. Family clustering of insulin sensitivity I. Diabetes 1992;41:850–4.
10. Bonadonna R, Groop L, Kraemer N, Ferrannini E, Del Prato S, DeFronzo R. Effect of insulin on oxidative and non-oxidative pathways of free fatty acid metabolism in human obesity. Am J Physiol 1992;263:E79–84.

11. Bjorntrop P. Abdominal obesity and the development of NIDDM. Diabetes Metab Rev 1989;4:615–22.
12. Bjorntrop P. Metabolic implications of body fat distribution. Diabetes Care 1991;14:1323–43.
13. Mikines K, Sonne B, Farrell P, Tronier B, Galbo H. Effect of physical exercise on sensitivity and responsiveness to insulin in humans. Am J Physiol 1988;254:E248–59.
14. Richter E, Mikines K, Galbo H, Kiens B. Effect of exercise on insulin action in skeletal muscle. J Appl Physiol 1989;66:876–85.
15. Storlien LH, Baur LA, Kriketos AD, et al. Dietary fats and insulin action. Diabetologia 1996;39:621–31.
16. Temple R, Clark P, Nagi D, Schneider A, Yudkin J, Hales C. Radioimmunoassay may overestimate insulin in non-insulin dependent diabetics. Clin Endocrinol (Oxf) 1990;32:689–93.
17. Laakso M. How good a marker is insulin level for insulin resistance? Am J Epidemiol 1993;137:959–65.
18. Turner R, Holman R, Matthews D, Hockaday T, Peto J. Insulin deficiency and insulin resistance interaction in diabetes: estimation of their relative contribution by feedback analysis from basal plasma insulin and glucose concentrations. Metabolism 1979;28:1086–96.
19. Dowse G, Qin H, Collins V, et al. Determinants of estimated insulin resistance and B-cell function in Indian, Creole and Chinese Mauritians. Diabetes Res Clin Pract 1990;10:265–79.
20. Fraze E, Donner C, Swislocki A, Chiou Y-AM, Chen Y-DI, Reaven G. Ambient free fatty acid concentrations in non-insulin dependent diabetes mellitus: evidence for insulin resistance. J Clin Endocrinol Metab 1985;39:1157–75.
21. Olefsky J, Reaven GM. Insulin and glucose responses to identical oral glucose tolerance tests performed forty-eight hours apart. Diabetes 1974;23:449–53.
22. Bergman R, Phillips L, Cobelli C. Physiological evaluation of factors controlling glucose tolerance in man. Measurement of insulin sensitivity and beta-cell sensitivity from the response to intravenous glucose. J Clin Invest 1981;68:1456–67.
23. Beard J, Bergman R, Ward W, Porte D. The insulin sensitivity index in nondiabetic man. Correlation between clamp-derived and IVGTT-derived values. Diabetes 1986;35:362–9.
24. Prigeon RL, Roder ME, Porte D Jr, Kahn SE. The effect of insulin dose on the measurement of insulin sensitivity by the minimal model technique. Evidence for saturable insulin kinetics in humans. J Clin Invest 1996;97:501–7.
25. Bergman RN, Prager R, Volund A, Olefsky JM. Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. J Clin Invest 1989;79:790–800.
26. Akinmokun A, Selby PL, Ramaiya K, Alberti KG. The short insulin tolerance test for determination of insulin sensitivity: a comparison with the euglycaemic clamp. Diabet Med 1992;9:432–7.
27. Shen S, Reaven GM, Farquhar J. Comparison of impedance to insulin-mediated glucose uptake in normal subjects and in subjects with latent diabetes. J Clin Invest 1970;49:2151–60.
28. Yasuda H, Harano Y, Ohgaku S, et al. Insulin sensitivity in pancreatitis, liver diseases, steroid treatment and hyperthyroidism assessed by glucose, insulin and somatostatin infusion. Horm Metab Res 1984;16:3–6.
29. Heine RJ, Home PD, Poncher M, et al. A comparison of 3 methods for assessing insulin sensitivity in subjects with normal and abnormal glucose tolerance. Diabetes Res 1985;2:113–20.
30. DeFronzo R, Tobin J, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 1979;237:E314–23.
31. Steele R. Influences of glucose loading and injected insulin on hepatic glucose output. Ann N Y Acad Sci 1959;82:420–30.
32. Turner RC, Rudenski AS, Hosker JP, Matthews DR, Levy JC, O'Rahilly SP. CIGMA as a tool in the study of NIDDM. Prog Clin Biol Res 1988;265:13–26.
33. Robertson DA, Singh BM, Nattrass M. Impaired glucose tolerance in obesity is associated with insensitivity to insulin in multiple aspects of metabolism as assessed by a low dose incremental insulin infusion technique. Diabet Med 1991;8:718–25.
34. Vrana A, Poledne R, Fabry P, Kazdova L. Palmitate and glucose oxidation by diaphragm of rats with fructose-induced hypertriglyceridemia. Metabolism 1978;27:885–8.
35. Nelson M, Bingham S. Assessment of food consumption and nutrient intake. In: Margetts BM, Nelson M, eds. Design concepts in nutritional epidemiology. New York: Oxford University Press, 1991:153–91.
36. Boyd JJ, Contreras I, Kern M, et al. Effect of a high fat sucrose diet on in vivo insulin receptor kinase activation. Am J Physiol 1990;259:E111–6.
37. Barnard RJ, Youngren JF, Martin DA. Diet, not aging causes skeletal muscle insulin resistance. Gerontology 1995;41:205–11.
38. Maegawa H, Kobayashi M, Ishibashi O, Takata Y, Shigeta Y. Effect of diet change on insulin action—difference between muscle cells and adipocytes. Am J Physiol 1986;251:E616–23.
39. Vallerand AL, Lupien J, Bukowiecki LJ. Synergistic improvement of glucose tolerance by sucrose feeding and exercise training. Am J Physiol 1986;250:E607–14.
40. Rawana S, Clark K, Zhong S, Buison A, Chackunkal S, Jen C. Low dose fructose ingestion during gestation and lactation affects carbohydrate metabolism in rat dams and their offspring. J Nutr 1993;123:2158–65.
41. Dai S, McNeill JH. Fructose-induced hypertension is concentration- and duration-dependent. J Pharmacol Toxicol Methods 1995;33:101–7.
42. Storlien LH, Kraegen EW, Jenkins AB, Chisholm DJ. Effects of sucrose vs starch diets on in vivo insulin action, thermogenesis, and obesity in rats. Am J Clin Nutr 1988;47:420–7.
43. Pagliosotti MJ, Shahrokhi KA, Moscarello M. Involvement of liver and skeletal muscle in sucrose-induced insulin resistance: dose response studies. Am J Physiol 1994;266:R1637–44.
44. Hulman S, Falkner B. The effect of excess dietary sucrose on growth, blood pressure, and metabolism in developing Sprague-Dawley rats. Pediatr Res 1994;36:95–101.
45. Pugazhenthi S, Angel JF, Khandelwal RL. Effects of vanadate administration on the high sucrose diet-induced aberrations in normal rats. Mol Cell Biochem 1993;122:69–75.
46. Gutman RA, Basilico MZ, Bernal CA, Chicco A, Lombardo YB. Long-term hypertriglyceridemia and glucose intolerance in rats fed chronically an isocaloric sucrose-rich diet. Metabolism 1987;36:1013–20.
47. Reiser S, Hallfrisch J. Insulin sensitivity and adipose tissue weight of rats fed starch or sucrose diets and libitum or in meals. J Nutr 1977;107:147–55.
48. Eiffert KC, McDonald RB, Stern JS. High sucrose diet and exercise: effects on insulin-receptor function of 12- and 24-month old Sprague-Dawley rats. J Nutr 1991;121:1081–9.
49. Sleder J, Chen YD, Cully MD, Reaven GM. Hyperinsulinemia in fructose-induced hypertriglyceridemia in the rat. Metabolism 1980;29:303–5.
50. Thorburn AW, Storlien LH, Jenkins AB, Khouri S, Kraegen EW. Fructose-induced in vivo insulin resistance and elevated plasma triglyceride levels in rats. Am J Clin Nutr 1989;49:1155–63.
51. van der Schaaf MR, Joles JA, van Tol A, Koomans HA. Long-term fructose versus corn starch feeding in the spontaneously hypertensive rat. Clin Sci 1995;88:719–25.
52. Luo J, Rizkalla SW, Lerer-Metzger M, et al. A fructose-rich diet decreases insulin-stimulated glucose incorporation into lipids but not glucose transport in adipocytes of normal and diabetic rats. J Nutr 1995;125:164–71.
53. Pamies-Andreu E, Fiksen-Olsen M, Rizza RA, Romero JC. High-fructose feeding elicits insulin resistance without hypertension in normal mongrel dogs. Am J Hypertens 1995;8:732–8.
54. Wright DW, Hansen RI, Mondon CE, Reaven GM. Sucrose-induced

insulin resistance in the rat: modulation by exercise and diet. Am J Clin Nutr 1983;38:879–83.
55. Zavoroni I, Sander S, Scott S, Reaven GM. Effect of fructose feeding on insulin secretion and insulin action in the rat. Metabolism 1980;29:970–3.
56. Storlien LH, Oakes ND, Pan DA, Kusonoki M, Jenkins AB. Syndromes of insulin resistance in the rat: inducement by diet and amelioration with benfluorex. Diabetes 1993;42:457–62.
57. Cohen AM, Teitelbaum A. Effect of dietary sucrose and starch on oral glucose tolerance and insulin-like activity. Am J Physiol 1964;206:105–8.
58. Holness MJ. Hypertriglyceridaemia precedes impaired muscle glucose utilization during fructose feeding. Biochem Soc Trans 1994;22:105S.
59. Fields M, Ferretti RJ, Smith JC, Reiser S. Effect of copper deficiency on metabolism and mortality in rats fed sucrose or starch diets. J Nutr 1983;113:1335–45.
60. Reiser S, Ferretti RJ, Fields M, Smith JC Jr. Role of dietary fructose in the enhancement of mortality and biochemical changes associated with copper deficiency in rats. Am J Clin Nutr 1983;38:214–22.
61. Fields M, Ferretti RJ, Reiser S, Smith JC Jr. The severity of copper deficiency in rats is determined by the type of dietary carbohydrate. Proc Soc Exp Biol Med 1984;175:530–7.
62. Lewis CG, Fields M, Beal T. The effects of various levels of fructose in a copper-deficient diet on Cu deficiency in male rats. Br J Nutr 1990;63:387–95.
63. O'Dell BL. Fructose and mineral metabolism. Am J Clin Nutr 1993;58(suppl):771S–8S.
64. Rizkalla SW, Boillot J, Tricottet V, et al. Effects of chronic dietary fructose with and without copper supplementation on glycaemic control, adiposity, insulin binding to adipocytes and glomerular basement membrane thickness in normal rats. Br J Nutr 1993;70:199–209.
65. Fields M, Ferretti RJ, Smith JC Jr, Reiser S. Impairment of glucose tolerance in copper-deficient rats: dependency on the type of dietary carbohydrate. J Nutr 1984;114:393–7.
66. Sevak L, McKeigue P, Marmot MG. Relationship of hyperinsulinemia to dietary intake in south Asian and European men. Am J Clin Nutr 1994;59:1069–74.
67. Lovejoy J, DiGirolamo M. Habitual dietary intake and insulin sensitivity in lean and obese adults. Am J Clin Nutr 1992;55:1174–9.
68. Fukagawa NK, Anderson JW, Hageman G, Young VR, Minaker KL. High-carbohydrate, high-fiber diets increase peripheral insulin sensitivity in healthy young and old adults. Am J Clin Nutr 1990;52:524–8.
69. Chen M, Bergman R, Porte D. Insulin resistance and beta-cell dysfunction in aging: the importance of dietary carbohydrate. J Clin Endocrinol Metab 1988;67:951–7.
70. Howard BV, Abbott WGH, Swinburn BA. Evaluation of metabolic effects of substitution of complex carbohydrates for saturated fat in individuals with obesity and NIDDM. Diabetes Care 1991;14:786–95.
71. Borkman M, Campbell LV, Chisholm DJ, Storlien LH. Comparison of the effects on insulin sensitivity of high carbohydrate and high fat diets in normal subjects. J Clin Endocrinol Metab 1991;72:432–7.
72. Garg A, Grundy SM, Unger RH. Comparison of effects of high and low carbohydrate diets on plasma lipoproteins and insulin sensitivity in patients with mild NIDDM. Diabetes 1992;41:1278–85.
73. Hughes VA, Fiatarone MA, Fielding RA, Ferrara CM, Elahi D, Evans WJ. Long-term effects of a high-carbohydrate diet and exercise on insulin action in older subjects with impaired glucose tolerance. Am J Clin Nutr 1995;62:426–33.
74. Reiser S, Handler HB, Gardner LB, Hallfrisch JG, Michaelis OE IV, Prather ES. Isocaloric exchange of dietary starch and sucrose in humans. II. Effect on fasting blood insulin, glucose, and glucagon and on insulin and glucose response to a sucrose load. Am J Clin Nutr 1979;32:2206–16.
75. Reiser S, Bohn E, Hallfrisch JG, Michaelis OE IV, Keeney M, Prather ES. Serum insulin and glucose in hyperinsulinemic subjects fed three different levels of sucrose. Am J Clin Nutr 1981;34:2348–58.
76. Hallfrisch J, Ellwood KC, Michaelis OE IV, Reiser S, O'Dorisio TM, Prather ES. Effects of dietary fructose on plasma glucose and hormone responses in normal and hyperinsulinemic men. J Nutr 1983;113:1819–26.
77. Beck-Nielsen H, Pedersen O, Lindskov HO. Impaired cellular insulin binding and insulin sensitivity induced by high-fructose feeding in normal subjects. Am J Clin Nutr 1980;33:273–8.
78. Crapo PA, Kolterman OG, Henry RR. Metabolic consequences of two-week fructose feeding in diabetic subjects. Diabetes Care 1986;9:111–9.
79. Turner JL, Bierman EL, Brunzell JD, Chait A. Effect of dietary fructose on triglyceride transport and glucoregulatory hormones in hypertriglyceridemic men. Am J Clin Nutr 1979;32:1043–50.
80. Koivisto VA, Yki-Jarvinen H. Fructose and insulin sensitivity in patients with type 2 diabetes. J Intern Med 1993;233:145–53.
81. Thorburn AW, Crapo PA, Griver K, Wallace P, Henry RR. Long-term effects of dietary fructose on carbohydrate metabolism in NIDDM. Metabolism 1990;39:58–63.
82. Dunnigan MG, Fyfe T, McKiddie MT, Crosbie S. The effects of isocaloric exchange of dietary starch and sucrose on glucose tolerance, plasma insulin and serum lipids in man. Clin Sci 1970;38:1–9.
83. Peterson DB, Lambert J, Gerring S, et al. Sucrose in the diet of diabetic patients—just another carbohydrate? Diabetologia 1986;29:216–20.
84. Mann JI, Truswell AS. Effects of isocaloric exchange of dietary sucrose and starch on fasting serum lipids, postprandial insulin secretion and alimentary lipaemia in human subjects. Br J Nutr 1972;27:395–405.
85. Kiens B, Richter EA. Types of carbohydrate in an ordinary diet affect insulin action and muscle substrates in humans. Am J Clin Nutr 1996;63:47–53.
86. Reiser S, Bickard MC, Hallfrisch J, Michaelis OE IV, Prather ES. Blood lipids and their distribution in lipoproteins in hyperinsulinemic subjects fed three different levels of sucrose. J Nutr 1981:111:1045–57.
87. Hallfrisch J, Reiser S, Prather ES. Blood lipid distribution of hyperinsulinemic men consuming three levels of fructose. Am J Clin Nutr 1983;37:740–8.
88. Liu G, Coulston A, Hollenbeck C, Reaven G. The effect of sucrose content in high and low carbohydrate diets on plasma glucose, insulin, and lipid responses in hypertriglyceridemic humans. J Clin Endocrinol Metab 1984;59:636–42.
89. Steiner G, Soichiro M, Vranic M. Resistance to insulin but not glucagon in lean human hypertriglyceridemics. Diabetes 1980;29:899–905.
90. Randle PJ, Garland PB, Newsholme EA, Hales CN. The glucose-fatty acid cycle in obesity and maturity onset diabetes mellitus. Ann N Y Acad Sci 1965;131:324–33.
91. Frayn K. Insulin resistance and lipid metabolism. Curr Opin Lipidol 1993;4:197–204.
92. Bjorntorp P. Fatty acids, hyperinsulinemia and insulin resistance: which comes first? Curr Opin Lipidol 1994;5:166–74.
93. Reaven GM, Mondon CE, Chen YD, Breslow JL. Hypertriglyceridemic mice transgenic for the human apolipoprotein C-III gene are neither insulin resistant nor hyperinsulinemic. J Lipid Res 1994;35:820–4.
94. Zavaroni I, Chen YD, Reaven GM. Studies of the mechanism of fructose-induced hypertriglyceridemia in the rat. Metabolism 1982;31:1077–83.
95. Steiner G. Altering triglyceride concentrations changes insulin-glucose relationships in hypertriglyceridemic patients. Double-blind study with gemfibrozil with implications for atherosclerosis. Diabetes Care 1991;14:1077–81.
96. Fulcher G, Walker M, Catalano C, Agius L, Alberti K. Metabolic

effects of suppression of non-esterified fatty acid levels with acipimox in obese diabetic subjects. Diabetes 1992;41:1400–8.
97. Stewart MW, Dyer RG, Alberti KG, Laker MF. The effects of lipid lowering drugs on metabolic control and lipoprotein composition in type 2 diabetic patients with mild hyperlipidemia. Diabet Med 1995;12:250–7.
98. Sane T, Knudsen P, Vuorinen-Markkola H, Yki-Jarvinen H, Taskinen MR. Decreasing triglyceride by gemfibrozil therapy does not affect the glucoregulatory of antilipolytic effect of insulin in non-diabetic subjects with mild hypertriglyceridemia. Metabolism 1995;44: 589–96.
99. Laville M, Rigalleau V, Riou J, Beylot M. Respective role of plasma non-esterified fatty acid oxidation and total lipid oxidation in lipid-induced insulin resistance. 1995;44:639–44.
100. Gregory J, Foster K, Tyler H, Wiseman M. The dietary and nutritional survey of British adults—further analysis. Ministry of Agriculture, Fisheries and Food. London: Her Majesty's Stationery Office, 1994.
101. Park YK, Yetley EA. Intakes and food sources of fructose in the United States. Am J Clin Nutr 1993;58(suppl):737S–47S.
102. Hollenbeck CB, Coulston AM, Reaven GM. Glycemic effects of carbohydrates: a different perspective. Diabetes Care 1986;9:641–7.
103. World Health Organization. Diet, nutrition, and the prevention of chronic diseases. WHO Tech Rep Ser 1990;.
104. The health of the nation—a strategy for health in England. London: Her Majesty's Stationery Office, 1992.
105. Luo J, Rizkalla SW, Alamowitch C, et al. Chronic consumption of short-chain fructooligosaccharides by healthy subjects decreased basal hepatic glucose production but had no effect on insulin-stimulated glucose metabolism. Am J Clin Nutr 1996;63:939–45.