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Dietary carbohydrates and insulin action in humans

Thomas M. S. Wolever

Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Canada and Division of Endocrinology and Metabolism, and Clinical Nutrition and Risk Factor Modification Centre, St Michael's Hospital, Toronto, Canada

The metabolic syndrome represents a vicious cycle whereby insulin resistance leads to compensatory hyperinsulinaemia, which maintains normal plasma glucose but may exacerbate insulin resistance. Excess insulin secretion may eventually reduce β-cell function due to amyloid deposition, leading to raised blood glucose and further deterioration of β-cell function and insulin sensitivity via glucose toxicity. Reducing postprandial glucose and insulin responses may be a way to interrupt this process, but there is disagreement about the dietary approach to achieve this. Glucose and insulin responses are determined primarily by the amount of carbohydrate consumed and its rate of absorption. Slowly absorbed, low glycaemic-index (GI) foods are associated with increased HDL cholesterol and reduced risk of type 2 diabetes. There is some evidence that low-GI foods improve insulin sensitivity in humans, although studies using established techniques (glucose clamp or frequently sampled intravenous glucose tolerance test) have not been done. Low carbohydrate diets have been suggested to be beneficial in the treatment of the metabolic syndrome because of reduced postprandial insulin. However, they may increase fasting glucose and impair oral glucose tolerance – effects which define carbohydrate intolerance. The effects of low carbohydrate diets on insulin sensitivity depend on what is used to replace the dietary carbohydrate, and the nature of the subjects studied. Dietary carbohydrates may affect insulin action, at least in part, via alterations in plasma free fatty acids. In normal subjects a high-carbohydrate/low-GI breakfast meal reduced free fatty acids by reducing the undershoot of plasma glucose, whereas low-carbohydrate breakfasts increased postprandial free fatty acids. It is unknown if these effects occur in insulin-resistant or diabetic subjects. Thus further work needs to be done before a firm conclusion can be drawn as to the optimal amount and type of dietary carbohydrate for the treatment of the metabolic syndrome.

Diet: Humans: Carbohydrate: Insulin sensitivity: Insulin secretion: Glycaemic index

The metabolic syndrome represents a vicious cycle whereby insulin resistance leads to compensatory hyperinsulinaemia which maintains normal plasma glucose, but may lead to hypertension, dyslipidaemia and artherosclerosis, and may exacerbate insulin resistance leading to further hyperinsulinaemia. In addition, the metabolic syndrome is believed to be an early step in the development of type 2 diabetes. The exact reason why the metabolic syndrome deteriorates to become type 2 diabetes is not known, but one hypothesis is illustrated in Fig. 1. Excess insulin secretion may eventually reduce β-cell function due to amyloid deposition (Porte, 1991), leading to raised blood glucose and further deterioration of β-cell function and insulin sensitivity via glucose toxicity (Rossetti *et al.* 1990).

Weight reduction (Goodpaster *et al*. 1999) and increased exercise (Dengel *et al*. 1996; Oppert *et al*. 1997) improve insulin sensitivity and have been shown to delay the conversion of impaired glucose tolerance to diabetes (Pan *et al*. 1997). There is almost universal agreement that weight loss and regular exercise should be part of the treatment of the metabolic syndrome. Altering the composition of the diet, independent of weight loss, may also influence insulin sensitivity. The hypothesis illustrated in Fig. 1 would suggest that reducing postprandial glucose and particularly insulin responses may interrupt the progression of the metabolic syndrome. However, there is vigorous disagreement about what kind of diet is most appropriate for management of insulin resistance (Reaven, 1997; Purnell & Brunzell, 1997). This paper reviews the role of dietary carbohydrate in the treatment of the metabolic syndrome.

Dietary determinants of postprandial insulin

The amount, type (glucose versus fructose) and rate of digestion of dietary carbohydrate are the primary determinants of postprandial glucose and insulin responses. Large amounts of protein and fat added to glucose have been demonstrated affect postprandial responses: protein

Corresponding author: T. M. S. Wolever, fax +1 416 978 5882, email thomas.wolever@utoronto.ca

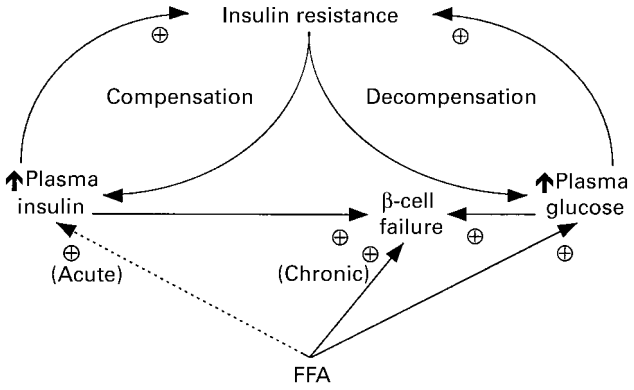

Fig. 1. Proposed model for the role of insulin resistance, pancreatic β-cell function and plasma free fatty acids (FFA) in the development of diabetes.

increases insulin and decreases glucose (Gannon *et al*. 1988) and fat is generally considered to reduce glucose and insulin because of reduced upper gastrointestinal motility (Welch *et al*. 1987). However, fat also potentiates gastric inhibitory polypeptide (GIP) secretion which may have an acute effect in increasing insulin secretion (Collier *et al*. 1988). Nevertheless, I believe that the range of protein and fat contents found in normal meals is not large enough to have a detectable effect on postprandial glucose and insulin, at least in normal subjects. The evidence for this is that when five realistic unmatched mixed meals (cheese omelette; spaghetti, cheese-and-tomato sauce; barley and lentils with cheese; cornflakes and toast; oatmeal) which varied in energy (395–610 kcal), fat (8–24 g or 15–47 % of energy), protein (12–25 g, 11–20 % energy), carbohydrate (38–104 g, 33–69 % energy) and glycaemic index (43–99) were fed to normal subjects, 90 % of the variance of postprandial insulin responses was explained by the amount and glycaemic index (GI) of the meal carbohydrate (Wolever & Bolognesi, 1996).

Fructose produces much lower glucose and insulin responses than glucose because it is slowly converted to glucose in the liver, and only some of this glucose is released into the circulation (Wolever & Brand Miller, 1995). Large amounts of fructose fed to laboratory animals (Thorburn *et al*. 1989) and humans (Beck-Nielsen *et al*. 1980) reproduce the features of the metabolic syndrome, and fructose and sucrose may, at least in some individuals, raise serum triglycerides (Frayn & Kingman, 1995) and LDL cholesterol (Swanson *et al*. 1992). Therefore the use of large amounts of fructose as a way of reducing postprandial insulin is unlikely to be a prudent approach to management of the insulin resistance syndrome. However, the few studies in human subjects suggest that moderate amounts of sucrose and fructose compared to starch have no deleterious effects on insulin resistance (Daly *et al*. 1997).

Considering dietary starch, if it is true that the amount and rate of absorption of dietary carbohydrate are the primary determinants of postprandial insulin, it follows that postprandial insulin can be reduced either by reducing the amount of carbohydrate in the diet, or by reducing the rate of absorption using low-GI foods. What I aim to demonstrate below is that these two methods of reducing plasma insulin do not have the same effects on insulin sensitivity.

Effect of low-GI foods on insulin sensitivity

There are an increasing number of studies in a variety of groups of human subjects which are consistent with the hypothesis that reducing diet GI improves insulin sensitivity.

Frost and co-workers have done several studies examining the role of GI in individuals with, or at risk of developing, coronary heart disease. In their first study (Frost *et al.* 1996) it was shown that 4 weeks of a low-GI diet tended to reduce the area under the glycaemic response curve in response to oral glucose, and significantly reduced the insulin-response area. Although this is clearly a beneficial effect, it is more difficult to know why it occurred. Such a change could represent improved insulin sensitivity, but could also be due to a reduced rate of absorption of the oral glucose due to altered gut morphology. For example, it is known that certain types of dietary fibre alter the morphology of absorptive villi of experimental animals (Tasman-Jones, 1993). Thus in their next study, Frost *et al.* (1998) showed that a low-GI diet improves *in vitro* insulin responsiveness of adipocytes from women at risk for cardiovascular disease, and improves *in vivo* insulin sensitivity as measured by the rate of fall of plasma glucose after an intravenous insulin injection. However, these studies could be criticized because they did not use a validated test such as the euglycaemic, hyperinsulinaemic clamp or the frequently sampled intravenous glucose tolerance test.

Most recently, Frost *et al.* (1999) demonstrated an inverse association between serum HDL and diet GI in British men and women: low diet GI was associated with increased HDL cholesterol. Since low HDL cholesterol is a feature of the metabolic syndrome, it was suggested that the relationship between GI and HDL was due to the effect of a low-GI diet in improving insulin sensitivity. This result is consistent with a recent study comparing three diets in subjects with type-2 diabetes; high-carbohydrate/low-GI, high-carbohydrate/high-GI, and low-carbohydrate/high-MUFA (monounsaturated fatty acid). After 1 month on each diet, the only statistically significant effect was that fasting HDL cholesterol was lower after the high-carbohydrate/high-GI diet than after either of the other two diets (Luscombe *et al.* 1999).

Willett's group has shown that a high glycaemic load is associated with increased risk of developing diabetes in both men (Salmerón *et al.* 1997*a*) and women (Salmerón *et al.* 1997*b*). Glycaemic load is calculated by multiplying the amount of carbohydrate in the diet by its GI. However, the protective effect of low glycaemic load was due mainly to the GI part of the equation. The risk for diabetes was not related to the amount of dietary carbohydrate in either study, but in both studies diabetes risk was related to diet GI.

We studied the effect of pharmacological inhibition of carbohydrate absorption on insulin sensitivity in subjects with impaired glucose tolerance (IGT). Subjects with IGT were randomized to receive acarbose or placebo for 4 months, with insulin sensitivity (assessed by the insulin suppression test) measured before and after treatment. Steady-state plasma glucose, the measure of insulin sensitivity, did not

change in the placebo group, but, on acarbose, improved to within 1 SD of the mean of a group of age-matched controls (Chiasson *et al*. 1996). This improvement in insulin sensitivity could have been due to the significant reduction in 12 h mean plasma glucose and insulin. However, there was also an increase in colonic fermentation, as judged by significant increases in serum acetate and butyrate (Wolever & Chiasson, in press). The short-chain fatty acids generated by colonic fermentation have effects on glucose metabolism which might influence insulin sensitivity (Wolever, 1995).

No discussion of GI and insulin sensitivity would be complete without mention of the study by Kiens & Richter (1996). Lean, young men ($n = 7$), all of whom rode bicycles for local transportation and participated in regular physical activity once or twice a week, were given high- and low-GI diets for 4 weeks each in a crossover design. Euglycaemic hyperinsulinaemic clamps were performed at the end of each dietary period. Serum insulin was lower after 3 d of the low-GI diet, but not after 30 d. Whole-body glucose uptake was similar for both diets at a low plasma insulin concentration (370 pmol/L) but was about 9 % lower after the low-GI than the high-GI diet at the high insulin concentration (2400 pmol/L, $P < 0{\cdot}05$). It is amusing that this study has been cited as evidence both in favour of the use of low-GI diets (Brand Miller, 1999) and against them (Beebe, 1999; Pi-Sunyer X, cited by Harris S, Summary of the Third Dietary Guidelines Advisory Committee Meeting, June 16–18 1999, ILSI Research Foundation). The lack of consistency in the insulin sensitivity at the two levels of plasma insulin is confusing. However, the 'low' level of insulin (340 pmol) is much more representative of plasma insulin concentrations in healthy young subjects than the 'high' level (2400 pmol/L). In our hands, average plasma insulin of young, lean subjects over an 8 h period after eating breakfast and lunch is 150 pmol/L (unpublished results). It is also possible that the results in this population of normal, young and physically active subjects may not be applicable to individuals with the metabolic syndrome.

Effects of low-carbohydrate diets on insulin sensitivity

It is difficult to draw conclusions about how low-carbohydrate diets affect insulin sensitivity because the effects may depend on what is used to replace the carbohydrate energy in the diet and on the nature of the subjects studied. A summary of human studies is shown in Table 1. The results of two of these are difficult to interpret because the interventions were not randomized, the results representing a comparison of insulin sensitivity before and after a single period on an experimental high-carbohydrate diet.

The studies in non-diabetic subjects generally show beneficial effects of a high-carbohydrate diet on insulin sensitivity, while those in diabetic subjects show a deleterious effect. This could be either because of a true difference between subjects, or because in the non-diabetic studies

Table 1. Effect of high carbohydrate diets on insulin sensitivity: summary of human studies

Diet C : F : P* (% energy)	Subjects	Duration of diet (d)	Comments	Insulin sensitivity (% change)†	Reference
85 : 0 : 15 versus 30 : 55 : 15	Eight normal young	3–5	Liquid formula diets	+44 % ($P < 0{\cdot}05$)	Chen *et al.* 1988
85 : 0 : 15 versus 49 : 37 : 13	10 normal old	3–5	Formula versus *ad libitum* diet	+83 % ($P < 0{\cdot}05$)	Chen *et al.* 1988
68 : 14 : 18 versus 43 : 42 : 18	12 normal: six young, six old	21–28	Dietary fibre also increased	+26 % ($P < 0{\cdot}02$)	Fukagawa *et al.* 1990
55 : 20 : 20 versus 31 : 50 : 14	Eight normal	21		+3 % (ns)	Borkman *et al.* 1991
70 : 15 : 15 versus 30 : 50 : 20	12 Pima and 12 Caucasian	14	Improved oral GTT ($P < 0{\cdot}01$)	+2 % (ns)	Swinburn *et al.* 1991
60 : 20 : 20 versus 40 : 40 : 20	10 with type-2 diabetes	15	High-MUFA diet	−21 % ($P = 0{\cdot}02$)	Parillo *et al.* 1992
60 : 25 : 15 versus 35 : 50 : 15	Eight with type-2 diabetes	21	High-MUFA diet	−11 % (ns)	Garg *et al.* 1992
60 : 20 : 20 versus 50 : 30 : 20	20 with IGT	84	Study non-randomized	+11 % ($P < 0{\cdot}05$)	Hughes *et al.* 1995
51 : 35 : 14 versus 8 : 75 : 17	10 exercise-trained men	21	Study non-randomized	0 % (ns)	Cutler *et al.* 1995

* Carbohydrate : fat : protein.
† A positive value represents improved insulin sensitivity on the high carbohydrate diet.

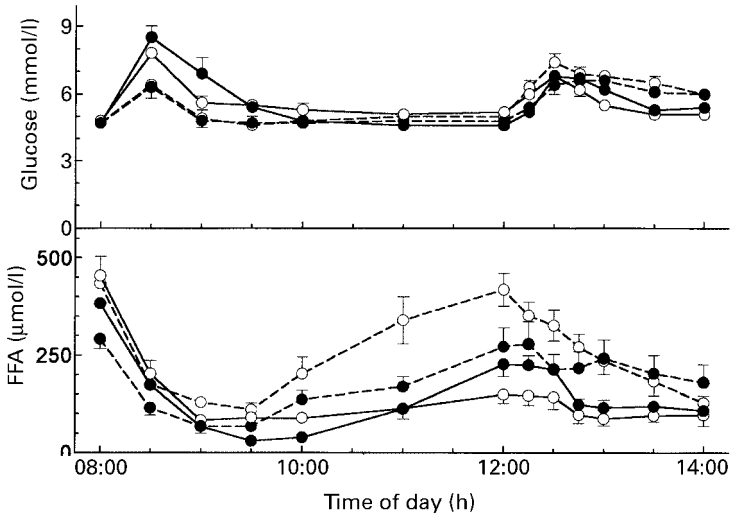

Fig. 2. Responses of plasma glucose and free fatty acids in eight normal subjects after four different isocaloric breakfasts followed by a standard lunch. The breakfast meals followed a 2×2 factorial design and consisted of high carbohydrate (84 g; solid line) or low carbohydrate (41 g; broken line) and high GI (92–102; filled circles) or low GI (70; open circles). The reduction in carbohydrate energy was replaced by non-hydrogenated canola oil margarine. Values are means ± SEM. From Wolever *et al.* (1995).

dietary fat was increased with a combination of saturated and monounsaturated fat, whereas in the diabetic studies the increase in fat was almost entirely accounted for by an increase in monounsaturated fat. The resolution of this issue will require further studies.

The study of Swinburn *et al*. (1991) raises the interesting and important question of what is the physiologic relevance of changes, or lack of changes, in measured insulin sensitivity. In this study, consistent with the older literature, there was a marked and significant improvement in oral glucose tolerance and a significant reduction in fasting plasma glucose on the high- versus the low-carbohydrate diet. Although this was not accompanied by any significant change in insulin sensitivity, there were significant improvements in glucose effectiveness (the ability of glucose to stimulate its own removal) and in pancreatic responsiveness (plasma insulin response after intravenous glucose injection). The metabolic syndrome is related to defects in both insulin sensitivity and β-cell function. The results of the study by Swinburn *et al*. (1991) suggest that dietary carbohydrate may have more important effects on pancreatic function, or on a combination of factors, than insulin sensitivity alone.

Effect of dietary carbohydrate on post-prandial free fatty acids

Dietary carbohydrates may mediate their effects on insulin sensitivity, at least in part, by altering plasma FFA concentrations. Elevated serum FFA concentrations are associated with diabetes and insulin resistance (Randle *et al*. 1963; Fraze *et al*. 1985; Paolisso *et al.* 1995). Free fatty acids raise plasma glucose by reducing insulin-stimulated glucose uptake, increasing hepatic glucose output, and reducing glucose-induced insulin secretion (Boden *et al*. 1994; Zhou & Grill, 1994). Free fatty acids in plasma are derived from two sources: release from adipose tissue when the supply of carbohydrate as a fuel is exhausted (e.g. after an overnight fast), and release from chylomicrons under the influence of lipoprotein lipase.

Under fasting conditions FFA are elevated, indicating that adipose tissue fatty acids are being released and used as fuel by muscle. In normal subjects the rise in plasma insulin after an oral glucose load rapidly suppresses plasma FFA. However, the high rise in insulin causes the blood glucose to undershoot, which is followed by a rebound in plasma FFA. About 4 h after a 50 g glucose load, plasma FFA have rebounded to levels which are similar to fasting. Sipping the glucose slowly over 3 h prevented the undershoot of plasma glucose and hence prevented the rebound of FFA (Jenkins *et al*. 1989). Altering the GI and amount of dietary carbohydrate in a breakfast test meal markedly influenced the rebound of FFA in normal subjects. Four hours after an

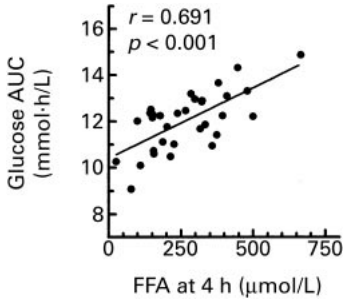

Fig. 3. Relationship between the total area under plasma–glucose response curve after the standard lunch and the concentration of plasma free fatty acids 4 h after four different breakfast meals in eight healthy subjects. The composition of the breakfast meals is described in the legend to Fig. 2. From Wolever *et al.* (1995).

84 g carbohydrate/low-GI breakfast, plasma FFA was significantly lower than after an 84 g carbohydrate/high-GI meal. The FFA rebound was even higher after a 41 g carbohydrate/high-GI meal, and highest after a 41 g carbohydrate/low-GI meal (Wolever *et al*. 1995; Fig. 2). Mean plasma glucose for 2 h after a standard lunch was directly related to the plasma FFA concentration just before lunch (Fig. 3). It should be emphasized that these results were obtained in normal subjects. It is not known whether differences in the type and amount of dietary carbohydrate affect FFA in subjects with insulin resistance or diabetes who have high fasting and postprandial plasma FFA concentrations (Fraze *et al*. 1985).

Conclusions

Further work needs to be done before a firm conclusion can be drawn as to the optimal amount and type of dietary carbohydrate for the treatment of the metabolic syndrome.

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