Determining the relationship between dietary carbohydrate intake and insulin resistance

Neville H. McClenaghan

School of Biomedical Sciences, University of Ulster, Cromore Road, Coleraine BT52 1SA, UK

Insulin resistance underlies type 2 diabetes, CVD and the metabolic syndrome, driven by changes in diet, lifestyle, energy over-consumption and obesity. Nutritional recommendations for insulin resistance remain an area of controversy, particularly the quantity and types of dietary carbohydrate. The present review gives an overview of insulin resistance, its relationship to impaired insulin secretion and the metabolic syndrome, research methodologies used to measure insulin action and the epidemiological and intervention studies on the relationship between dietary carbohydrate and insulin resistance. Epidemiological studies provide little evidence to suggest that total dietary carbohydrate predicts risk of type 2 diabetes, and high-carbohydrate, high-fibre diets with low-glycaemic index (GI) may even contribute to diabetes prevention. Despite inherent limitations associated with techniques used to measure insulin resistance and dietary assessment, most intervention studies reveal an increase in glucose tolerance or insulin sensitivity with high-carbohydrate, low-fat diets in non-diabetic and diabetic individuals. When energy is restricted the source or reduced content of carbohydrate does not appear to be as important as fat for body weight. Thus, low energy intake is key to weight loss and augmentation of insulin sensitivity. Given this, widespread adoption of popular low-carbohydrate high-fat diets highlights the necessity to evaluate dietary interventions regarding safety and metabolic effects. While current evidence supports FAO/WHO recommendations to maintain a high-carbohydrate diet with low-GI foods, the relationships between carbohydrate and insulin sensitivity remains an important research area. Emerging technologies should further enhance understanding of gene–diet interactions in insulin resistance, providing useful information for future nutrition policy decisions.

Diet: Carbohydrate: Human studies: Insulin resistance

Introduction

Diet and lifestyle modifications are widely regarded as the cornerstones of treatment of insulin resistance and management of other diseases of the metabolic (insulin resistance) syndrome. The major aims of this approach are to reduce body weight, improve glycaemic control and reduce the risk of cardiovascular and other complications, which may account for up to 80 % of deaths of individuals with diabetes (National Institutes of Health, 1995). Modern dietary strategies to prevent or overcome the hyperglycaemia of insulin resistance often advise complex carbohydrates or starches and avoidance of simple carbohydrates or sugars. However, this approach assumes that simple sugars are digested and absorbed more quickly, thus inducing a more rapid postprandial glucose response and does not take into account metabolic evidence that many starchy foods (including baked potatoes and white bread) can produce even higher glycaemic responses than simple sugars (Kalergis *et al.* 1998). Conceptual confusion regarding dietary carbohydrate and the increasingly widespread use of low-carbohydrate diets for weight loss has led to generalisations regarding carbohydrate intake and the development or progression of insulin resistance, obesity and diabetes. The following sections aim to provide a comprehensive and balanced overview of the nature of insulin resistance, its relationship to impaired insulin secretion and diseases of the metabolic syndrome, the research methodologies used to measure insulin action and, given the above, a review of the literature on epidemiological and intervention studies investigating the relationship between dietary carbohydrate and insulin resistance.

Abbreviations: EHC, euglycaemic–hyperinsulinaemic clamp; GI, glycaemic index; HOMA, homeostasis model assessment; IRS, insulin receptor substrate.

Corresponding author: Dr Neville H. McClenaghan, fax +44 28 7032 4965, email nh.mcclenaghan@ulster.ac.uk

Insulin in health and disease

Insulin plays a pivotal role in whole-body metabolism, and insufficient insulin production, secretion or action significantly alters the homeostatic regulation of numerous metabolic processes. Insulin resistance was first described in diabetes mellitus, which has been defined by the American Diabetes Association Expert Committee recommendations (Anonymous, 1997) as 'a group of metabolic disorders characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action or both', covering a range of heterogeneous diseases of the metabolic syndrome (Haffner & Cassells, 2003). While the mechanisms regulating insulin production, secretion and in particular action are fundamental to understanding the role of insulin in health and disease, in-depth consideration of this complex area is beyond the scope of the present review. The following provides a brief overview of insulin secretion and insulin resistance in health and disease.

Regulation of insulin secretion

Insulin is exclusively produced by pancreatic β-cells of the islets of Langerhans, small clusters of exocrine tissue scattered throughout the pancreas, by enzymic cleavage of its precursor molecule, proinsulin. Much insight into the mechanisms controlling insulin production and secretion has been derived from studies of freshly isolated pancreatic islets and constituent β-cells or bioengineered insulin-secreting cell lines (McClenaghan & Flatt, 1999a). The pancreatic β-cell acts a nutrient fuel sensor, monitoring minute-to-minute circulating levels of glucose (Fig. 1) and other important classes of nutrient (including amino, keto and fatty acids) and responding with modulation of insulin secretion and β-cell function (Flatt, 1992; McClenaghan & Flatt, 1999b). Glucose is the principal regulator of insulin secretion and β-cell function which is internalised by GLUT1 (in man, GLUT2 in rodents), after which is it is rapidly metabolised by glucokinase (Fig. 1). Metabolically derived ATP and other metabolites mediate a number of so-called K_{ATP} channel-dependent and -independent actions of glucose, raising intracellular Ca concentrations and modulating other important events regulating insulin exocytosis (McClenaghan & Flatt, 1999a,b). There has been much debate as to the relative contribution of impaired insulin secretion or action to the onset and pathogenesis of diabetes, but it is clear that there is interplay between these two fundamental features in the onset and progression of the
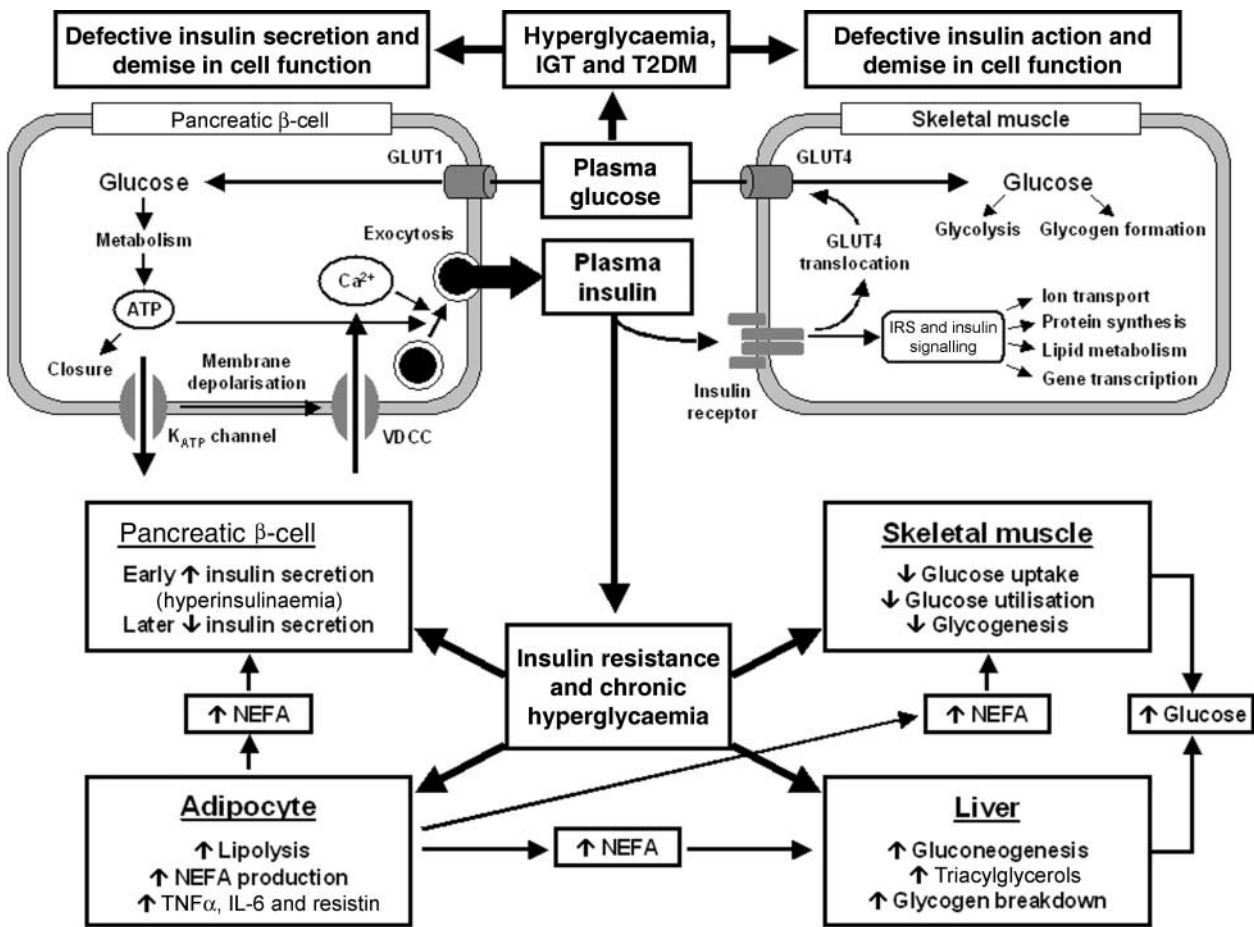

Fig. 1. Overview of the key mechanisms underlying insulin secretion, insulin action and insulin resistance in man. IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus; IRS, insulin receptor substrate proteins; K_{ATP} channel, ATP-sensitive K^+ channel; VDCC, voltage-dependent Ca^{2+} channel.

condition (Fig. 1). Indeed, insulin secretion can be regarded as defective at the time of diagnosis and declines with progression of the type 2 diabetes, often paralleled with a worsening of insulin resistance (Yki-Jarvinen, 1992; Kitano *et al.* 2004). Furthermore, various peptides (including bradykinin and oxytocin) that stimulate insulin release and hormones or mediators (including growth hormone and prolactin) may exert long-term effects on β-cell growth and function. This in turn may influence insulin secretion, and, together with other factors (such as excess cortisol and parathyroid hormone) and physiological and pathophysiological states (such as pregnancy or obesity), may induce insulin resistance (Pickup & Williams, 2003).

Regulation of insulin action

The overarching action of insulin is to control the storage and release of energy during feeding and fasting. Insulin plays a key metabolic role through suppressing gluconeogenesis and promoting lipogenesis (hepatocytes), promoting storage of glucose as glycogen (liver and muscle) and storage of amino acids (muscle) and triacylglycerols (adipose tissue) (Fig. 1). The principal actions of insulin are mediated through its binding to insulin receptors on target tissues, regulating membrane expression of GLUT4 and thus cellular glucose uptake (Fig. 1). Insulin binding activates receptor tyrosine kinase activity and promotes autophosphorylation essential for receptor and post-receptor insulin signalling events mediated by tyrosine phosphorylation of intracellular proteins associated with the insulin receptor including insulin receptor substrate (IRS)-1 and -2. As illustrated in Fig. 1, IRS and insulin signalling pathways represent a complex cascade of events, which regulate a number of processes including ion transport, protein synthesis, lipid metabolism and gene transcription (see White, 2003). However, the physiological insulin signalling system is linked with other receptors and pathways that regulate gene expression in numerous tissues (Pessin & Saltiel, 2000). Thus, defective insulin signalling and uncompensated insulin resistance is closely associated with the diverse disorders comprising the metabolic syndrome. The lack of evidence for a common mechanism explaining the occurrence of acute and chronic insulin resistance highlights the complexity of the insulin signalling system, although prime molecular targets include the IRS proteins, pro-inflammatory cytokines (including TNF-α) and phosphorylation (serine and tyrosine) pathways (White, 2003). Post-receptor defects include decreased activation of IRS-1 and phosphatidylinositol 3-kinase or impaired translocation of GLUT4 (muscle).

Insulin and the metabolic syndrome

Although impaired insulin action and defective glucose regulation and disposal are fundamental features of insulin resistance and diseases of the metabolic syndrome, insulin resistance reflects changes in the biological actions of insulin on carbohydrate, lipid and protein metabolism and other actions of insulin on tissues (including vascular and endothelial cells) and mitogenic processes (including growth, differentiation and gene transcription) (see Pickup & Williams, 2003). As such, insulin resistance is characterised by impaired ability of insulin to (i) inhibit hepatic glucose production, (ii) stimulate glucose uptake by muscle, (iii) inhibit assembly and production of VLDL (despite suppressing NEFA concentrations), and (iv) suppress lipolysis in adipose tissue. As illustrated in Fig. 1, the latter results in an increase in circulating NEFA concentrations, which stimulates gluconeogenesis, triacylglycerol synthesis and glucose production in the liver and further impedes glucose uptake by skeletal muscle. Notably, NEFA, deposition of triacylglycerol in insulin-sensitive tissues, and humoral factors produced by adipose tissue may act directly or indirectly to impair insulin action (Fig. 1). Obesity and diabetes are associated with increased circulating NEFA, at least partly attributable to altered sympathetic nervous system activity, and NEFA may exert a detrimental influence in insulin-sensitive target tissues mediated by a mechanism involving enhanced IRS-1 serine phosphorylation coupled with decreased IRS-1 tyrosine phosphorylation and decreased activity of IRS-1-associated phosphatidylinositol 3-kinase activity (Yu *et al.* 2002). This may contribute to hepatic and peripheral tissue insulin resistance and appears to be further compounded by other factors related to the metabolic (insulin resistance) syndrome, such as excess cortisol and altered activity of the hypothalmo−pituitary−adrenal axis (Bjorntorp, 1997; Pickup & Williams, 2003). The metabolic syndrome is described by a cluster of cardiovascular risk factors linked to insulin resistance (Beck-Nielsen, 1999). Characterisation of data from the European Group for the Study of Insulin Resistance and Danish Twin Register databases revealed that insulin resistance correlates closely with various components of the metabolic syndrome and estimated prevalence in 1999 at about 16 % of Caucasians (Beck-Nielsen, 1999). Furthermore, genetically determined and environmentally induced insulin resistance may precipitate onset of the metabolic syndrome which is probably driven by inappropriate diet and lifestyle leading to energy over-consumption and truncal obesity.

Genes, environment and the mechanisms of insulin resistance

Insulin resistance and the prevalence of diseases of the metabolic syndrome, including type 2 diabetes, vary throughout continents and across the globe (see Pickup & Williams, 2003). There are many hypotheses that attempt to explain these differences, but among the most intriguing lies in the impact of the environment (acquired factors including a diabetogenic Westernised lifestyle) superimposed on a genotype susceptible to energy storage (so-called 'thrifty' genes). Genetic predisposition to the polygenic disorder type 2 diabetes including thrifty genes may count for up to 80 % of susceptibility. According to the 'thrifty genotype' hypothesis, certain 'thrifty' genes promote energy (particularly fat) storage and insulin resistance (see Chakravarthy & Booth, 2004). Malnutrition *in utero* or during early life, resulting in low birth weight and/or inappropriate development, may also predispose to type 2 diabetes in adulthood (see Hales & Barker, 2001) by inherent 'programming' of insulin resistance and/or reduced β-cell mass (so-called 'thrifty phenotype').

It is widely regarded that a genetic background that determines a reduction in insulin sensitivity would promote progressive insulin resistance in the liver and the peripheral tissues, skeletal muscle and fat. In an evolutionary context, thrifty genes determining insulin resistance may be favourable under conditions of starvation, providing a metabolic advantage through ensuring that a ready supply of glucose is available and averting the immediate danger of hypoglycaemia (DeFronzo, 1997). However, exposure of individuals with this genetic background to a Westernised lifestyle of high energy intake and reduced physical activity may result in development of diseases of the metabolic syndrome including obesity-related type 2 diabetes (Chakravarthy & Booth, 2004). The metabolic consequences of insulin in normal and insulin-resistant states in muscle, liver and other tissues are illustrated in Fig. 1.

As outlined earlier, the hyperglycaemia characteristic of type 2 diabetes results from insulin resistance superimposed over compromised insulin secretion and β-cell function. The hyperinsulinaemia observed early in diabetes is believed to be an attempt to maintain glucose homeostasis under conditions of insulin resistance (Polonsky *et al.* 1996). However, the massive challenge to the β-cells cannot ultimately be sustained and initial hyperinsulinaemia is replaced by hypoinsulinaemia and hyperglycaemia (Polonsky *et al.* 1996). The dynamic relationship between insulin resistance and β-cell function can be seriously impaired by chronic hyperglycaemia through 'glucotoxicity' (Yki-Jarvinen, 1992) which can exacerbate both fundamental defects, aggregated by environmental factors superimposed on genetic predisposition to insulin resistance and type 2 diabetes. Under conditions of glucotoxicity, insulin is glycated in the pancreatic β-cell and may be released into the circulation in this form (Abdel-Wahab *et al.* 1996; Hunter *et al.* 2003). Glycated proteins including HbA_{1c} and insulin do not have the same properties as parental molecules; in the case of glycated insulin, this glycated form is likely to contribute to the progressive deterioration of glucose tolerance in diabetes (Hunter *et al.* 2003; Kaiser *et al.* 2003). The demise of the β-cell in diabetes may arise as a result of glucotoxicity, 'lipotoxicity', overexertion or exhaustion, or dysregulated growth that accompany the insulin-resistant state.

Clinical determination of insulin resistance

As described earlier, the mechanisms underlying insulin resistance are complex. The term 'insulin resistance' is used in a variety of contexts to refer to a generalised impairment of the physiological actions of insulin. Given the diverse metabolic roles of insulin, coupled with different tissue sensitivities to the actions of this hormone in an individual, population or between populations, it is perhaps not surprising that determination of insulin resistance is remarkably difficult. Insulin resistance is generally measured in terms of the glucose-lowering effect of insulin, thus reflecting only the hypoglycaemic effect of insulin in an individual. This is important as impaired glucose-lowering action indicates resistance to insulin's hypoglycaemic action but does not necessarily indicate insensitivity to other actions of insulin. Since the pioneering research by Himsworth (1936), which distinguished insulin-resistant

and insulin-deficient forms of diabetes, various clinical methods have been devised to measure insulin resistance. An overview of the modern methodologies used to determine *in vivo* insulin resistance is given in Table 1; methodologies are briefly described under the three overarching categorisations – 'steady-state', 'dynamic' or 'basal-state' techniques.

Steady-state techniques

Steady-state techniques are based on the principle that to maintain euglycaemia the rate of glucose infusion under hypoglycaemic conditions should match insulin-stimulated glucose disposal in skeletal muscle. The 'euglycaemic–hyperinsulinaemic clamp' (EHC) (DeFronzo *et al.* 1979) and modifications to include measurement of hepatic glucose output (Steele 1959; Chiasson *et al.* 1977) is arguably the best available standard technique (Ferrannini & Mari, 1998). Alternatives are the 'insulin sensitivity (or suppression) test' and 'continuous infusion of glucose with model assessment' both of which correlate well with data from the EHC. The 'insulin sensitivity (or suppression) test' refers to several methods, which rely on infusion of fixed doses of glucose and insulin until a 'steady state' is reached (Shen *et al.* 1970; Harano *et al.* 1977).

Dynamic techniques

Dynamic techniques involve regular plasma sampling for determination of glucose and/or insulin concentrations in response to glucose challenge. Modifications of the most popular diagnostic tool of diabetes, the 'oral glucose tolerance test', can be used to assess insulin sensitivity, although validity depends on normal insulin secretion (Home, 1988). The 'frequently sampled intravenous glucose tolerance test' (Bergman *et al.* 1979) can be modified with a bolus injection of intravenous insulin (Beard *et al.* 1986; Yang *et al.* 1987) or the insulinotropic hypoglycaemic sulfonylurea, tolbutamide (Finegood *et al.* 1990), and so be improved in its sensitivity and reproducibility (Beard *et al.* 1986; Bergman *et al.* 1989; Saad *et al.* 1994). An alternative approach is the 'insulin tolerance test' that determines insulin sensitivity from the glucose-lowering rate of intravenous insulin administration (Bonora *et al.* 1989; Hirst *et al.* 1993).

Basal-state techniques

The widely used 'homeostasis model assessment' (HOMA) devised by Matthews *et al.* (1985) calculates insulin sensitivity (HOMA-R) and β-cell function from fasting measures of plasma glucose and insulin. HOMA measurements correlate closely with EHC measurement of insulin resistance (Hermans *et al.* 1999). Another measure is the 'quantitative insulin sensitivity check index', which is derived from the relationship between fasting plasma insulin and glucose and closely agrees with data derived from HOMA (Katz *et al.* 2000).

Choice of technique to determine insulin resistance

The main factors determining choice of *in vivo* technique relate to precision, nature of information required, and

Table 1. Overview of main methodologies used to assess insulin resistance

	Description	Comments
Steady state		
EHC	Studies insulin kinetics in fasted state. Insulin infused intravenously at constant rate to achieve stable hyperinsulinaemia and maximum peripheral glucose uptake. Glucose infused intravenously to maintain blood glucose at 5 mmol/l. Steady state is when glucose infusion equals rate of glucose disposal	Gold standard for determining insulin sensitivity. Reproducible. Can be modified to examine other aspects including contribution of hepatic *v.* extrahepatic insulin action (i.e. hepatic glucose output)
Insulin sensitivity or suppression test	Co-infusion of fixed doses of insulin and glucose coupled with suppression of endogenous insulin secretion by use of somatostatin. Steady-state plasma glucose is the measured index (i.e. glucose reflects level of insulin resistance)	Easier to perform than EHC. Poor reproducibility. Makes assumptions likely to lead to underestimation of insulin resistance
Continuous infusion of glucose with model assessment	Multivariable computer model evaluating physiological insulin response to infused glucose, with insulin sensitivity and β-cell function calculated from the model	Easy to perform and gives index of insulin secretion. Model makes assumptions but correlates well with EHC data
Dynamic		
OGTT	Plasma glucose and insulin are measured following glucose load. Insulin sensitivity is assessed from endogenous insulin concentrations in response to glucose load. The higher the glucose:insulin ratio, the higher the insulin resistance	Intrinsically poor precision and reproducibility. Glucose:insulin ratio dependent on insulin clearance as well as secretion. Not valid in diabetic subjects
Frequently sampled intravenous glucose tolerance test	Estimation of insulin sensitivity by multi-compartment modelling of changes in plasma insulin and glucose after intravenous glucose bolus. Insulin sensitivity and glucose effectiveness are derived. Accuracy and sensitivity improved by modifications (including tolbutamide bolus or short insulin infusion)	Overcomes some drawbacks of OGTT caused by intestinal glucose absorption. Reproducible and valid for non-diabetic and diabetic subjects
Insulin tolerance test	Determines insulin sensitivity from rate at which blood glucose falls in response to intravenous insulin in fasted subjects. Sampling every 2 min and oral glucose given afterwards to prevent hypoglycaemia	Simple and inexpensive. Reproducible. Occasional risk of hypoglycaemia in more insulin-sensitive subjects (unusual)
Basal state		
HOMA	Fasting plasma glucose and insulin measured for calculation of insulin sensitivity (HOMA-R) and β-cell function using model. Assumes normal-weight subjects >35 years have insulin resistance of 1 and 100 % β-cell function. Error reduced by average of three fasting readings. Increasing HOMA-R values indicate increasing insulin resistance	Simple, inexpensive and widely used. Validated across wide range of insulin sensitivity. Poor reproducibility. Confounded by exogenous insulin and oral glycaemic drugs. Useful for epidemiological research
Quantitative insulin sensitivity check index	Insulin sensitivity derived from relationship between fasting insulin and glucose concentrations. Alternative to HOMA method	Simple and inexpensive. Measures closely compare to similar HOMA method

EHC, euglycaemic−hyperinsulinaemic clamp; OGTT, oral glucose tolerance test; HOMA, homeostasis model assessment.

practical considerations including time, complexity, number and experience of investigators, classification and number of subjects, and cost (Ferrannini & Mari, 1998; Del Prato, 1999). Notably, 'continuous infusion of glucose with model assessment', 'frequently sampled intravenous glucose tolerance test' and HOMA can all give indices of β-cell function, thus generating additional useful research data. While data arising from most of these methods are somewhat comparable, the EHC, despite being laborious and complicated, is still regarded as the 'gold-standard' method of choice in small-scale studies (Ferrannini & Mari, 1998). However, in epidemiological studies with large sample size, HOMA, despite analytical and biological variability, is convenient and thus arguably more appropriate (Wallace & Matthews, 2002). Other methods used to assess insulin resistance are 'insulin-stimulated glucose uptake in

adipocytes' (Kashiwagi *et al.* 1985; Garvey *et al.* 1988) or the 'organ perfusion/catheterisation technique' (Zierler, 1961), but these will not be considered further as they are difficult and invasive and thus not widely adopted.

The wide variety of techniques used to assess insulin resistance (Table 1) clearly serves to indicate that there is no ideal or universal method to measure this important parameter. As a further complexity, insulin resistance is not the same across all tissues (see Bessesen, 2001) and the various actions of insulin may be implicated to different degrees in the development of insulin resistance. Unfortunately, tissue-specific insulin sensitivities have rarely been assessed in studies with dietary manipulations; thus some caution is required when interpreting studies of the influence of dietary change on insulin resistance. Despite these various shortcomings, coupled with various criticisms regarding

study design and rigour or selection and application of technique, collectively there is a sufficient body of data from these techniques to draw certain useful conclusions.

Dietary factors, energy intake and the development of insulin resistance

The epidemic rise in incidence of type 2 diabetes has fuelled research into the complex interplay between genes and environmental factors in the pathogenesis of the hyperglycaemic diabetic state. Key among the environmental factors is the Western lifestyle typified by high energy intake and low physical activity, driving individuals towards energy storage, overweight and obesity. As outlined earlier, it is generally accepted that energy over-consumption is fundamental to the development of insulin resistance and diseases of the metabolic syndrome, including type 2 diabetes (DeFronzo & Ferrannini, 1991; Haffner & Cassells, 2003; Kitano et al. 2004). Indeed, energy over-consumption driving the deposition of metabolically active abdominal fat has been proposed as a major cause of insulin resistance (Ruderman et al. 1998) and may explain the increasing prevalence of insulin resistance and type 2 diabetes in children (Ehtisham et al. 2000; Bundred et al. 2001). Non-splanchnic adipose tissue from the upper body, from head, neck trunk, and upper extremities also makes a significant contribution to NEFA flux (Jensen & Johnson, 1996). Thus, excess deposition of subcutaneous truncal fat may also cause insulin resistance in non-diabetic subjects and in type 2 diabetes (see Garg, 2004), prompting future research into the relationship between body fat distribution and insulin resistance.

Hyperglycaemia resulting from insulin resistance is a defining feature of type 2 diabetes; however, there has been much debate over the relationship between diet and in particular dietary carbohydrate intake and insulin resistance. The historic link between diet and diabetes hails back to antiquity when Charak and Sushrut (400–500 BC) described sweet-tasting diabetic urine in individuals who were slothful, overweight and gluttonous and gorged on sweet and fatty foods (Pickup & Williams, 2003). While an important role of diet in the pathogenesis of insulin resistance is generally accepted, the relative contribution of individual macronutrients is relatively poorly understood. Disturbances in macronutrient metabolism, particularly carbohydrate and fat metabolism through raised plasma glucose (glucotoxicity) and fatty acids (lipotoxicity), are characteristic of the insulin-resistant state and it is understood that type 2 diabetes is as much defined by defective fat as glucose metabolism (Pickup & Williams, 2003).

Overweight is an extremely important risk factor for insulin resistance and diseases of the metabolic syndrome (see Parillo & Riccardi, 2004). Energy over-consumption and the increase in metabolically active abdominal adipose tissue tends to a greater flux of NEFA to the liver which can impact on glucose oxidation and hepatic extraction of insulin and impair insulin secretion (Fig. 1). Intervention studies have also demonstrated that weight loss can reduce fasting hyperglycaemia in type 2 diabetes, improves insulin sensitivity and increases the capacity of non-oxidative glucose metabolism (Parillo & Riccardi, 2004). Excessive

body-fat deposition results from an imbalance between energy intake and expenditure. With the increase in sedentary lifestyles, energy intake is the main driver of overweight precipitated by high consumption of fat-rich foods (Astrup, 2001).

A large number of clinical studies have shown that high-fat (and thus energy-dense) diets may impact on insulin action, impair glucose tolerance and promote obesity, and cardiovascular and other disorders of the metabolic syndrome (Choudhary, 2004). However, the type of fat also appears important, and while saturated fat intake can worsen metabolic abnormalities, monounsaturated fat may have beneficial effects on lipid profiles. This conclusion comes from epidemiological data that also suggest a particularly adverse affect of *trans* fatty acids on the risk of insulin resistance and type 2 diabetes (Hu et al. 2001). Indeed, while saturated and certain monounsaturated fats are implicated in causing insulin resistance, in general polyunsaturated and *n*-3 fatty acids do not appear to have adverse effects on insulin action (Hu et al. 2001; Lovejoy, 2002). Although dietary fat is linked with type 2 diabetes through increased body weight, the mechanism by which dietary fat intake influences development of diabetes appears to be largely mediated through its effects on insulin sensitivity, and dietary fat can influence insulin sensitivity independently of body weight (Parillo & Riccardi, 2004). Animal and human studies consistently show an association between dietary fat quality and impaired insulin sensitivity and mechanistically this may be mediated through alterations in fatty acid composition of cell membranes (Vessby, 2000).

The total amount of fat intake appears to influence insulin sensitivity only when it exceeds a threshold level of 35–40 % total energy consumption (Parillo & Riccardi, 2004), adding further complexity, and highlighting the requirement for further study. It is also interesting to note that dietary carbohydrate intake primarily affects short-term glycaemic control while long-term glycaemic control is regulated by the total energy consumption. As outlined earlier, although over-consumption of fat-rich energy-dense foods is key to the development of overweight and obesity, dietary carbohydrates can also be converted into fats for storage. While the latter is an energy-requiring process which usually only takes place when carbohydrate intake greatly exceeds daily energy requirements (Franz, 2001), fructose is a better substrate for hepatic fatty-acid synthesis than glucose, and thus excess fructose may be converted into fat in the liver (Pickup & Williams, 2003). Understanding of the differences in satiating effects of macronutrients is also important with regard to energy over-consumption. As high-fat foods have disproportionately weak (joule-for-joule comparing with protein or carbohydrate) satiating effects, this can lead to passive over-consumption driven, in part, by the high palatability of high-fat foods (Blundell & MacDiarmid, 1997). Although both dietary macronutrient and energy intake play a role in obesity and insulin resistance, the quality and quantity of macronutrients, together with diet composition, remain important questions for dietitians and health practitioners, with serious implications in devising new strategies to curb the growing incidence of insulin resistance diseases of the metabolic syndrome.

Dietary carbohydrate, glycaemic index and glycaemic load

The most common forms of dietary carbohydrate are starch, sugars and fibre and current guidelines suggest that 80 % of energy intake for diabetes should be a combination of carbohydrate and monounsaturated fat (for a review, see Choudhary, 2004). The simple sugars include the mono-saccharides (glucose, fructose and galactose) and disacchar-ides (sucrose, maltose and lactose). Complex carbohydrates on the other hand take the form of polymers of monosaccharides. Polymers of glucose can occur in linear (amylose) or branched (amylopectin) forms. Amylopectin is more rapidly digested and absorbed than amylose and the latter may also interact with dietary fat to slow absorption further, which might be beneficial to insulin sensitivity. Starches that are not directly absorbed, but rather fermented in the gut to produce SCFA, are known as 'resistant starch'. Carbohydrate polymers comprising non-glucose monomers are indigestible and are the constituents of soluble or insoluble fibre, including β-glucan, guar gum and hemi-celluloses. Fibre is a nominal energy source but can interact with other nutrients in the gastrointestinal tract.

Traditional classification of carbohydrates purely on the basis of chemical structure does not provide many useful insights into their relative importance to health and disease. Rather, the ability of a carbohydrate to contribute directly or indirectly to the carbohydrate pool (glycaemic carbo-hydrates) coupled with postprandial glycaemic response provides more useful information (Cummings & Englyst, 1987). As different carbohydrate-containing foods generate different glycaemic responses, this led Jenkins *et al.* (1981) to develop a glycaemic index (GI) to rank foods. Using this convention, carbohydrate foods that are rapidly absorbed are high GI, while those that are more slowly absorbed are low GI. The GI is based on the post-ingestion glucose area under the curve in response to ingestion of 50 g carbohydrate in test food compared with 50 g reference carbohydrate (glucose or white bread) and depends on the rate of digestion and rapidity of absorption of carbohydrate (Brand-Miller *et al.* 1999) (Table 2).

However, recommendations associated with low-GI diets are the subject of much debate as they are based on various generalisations, for example the application of exact GI to foods, and the fact that some low-GI foods are high in fat (including ice cream). As such, when evaluating the health effects of individual foods, GI values cannot be used in isolation and nutrient composition of the foods and overall dietary pattern are also important. As there is no exact value of a low-GI or high-GI diet, this can add to consumer confusion, although it appears that the lower the GI the better the effects, and the differences between a low- (<70) and a high- (>80) GI diet should be at least 10 % in order to achieve measurable metabolic effects (Willett *et al.* 2002). The fact that the plasma glucose response to feeding is not only determined by the GI value of a given food but also the amount of carbohydrate in the food led to the concept of the glycaemic load. Glycaemic load is a function of GI and carbohydrate content, thus representing the quality and quantity of carbohydrates consumed (Table 2). Thus, glycaemic load can be altered by changing carbohydrate intake or changing dietary GI and is arguably less restrictive in application than the more simplistic measure of GI.

Dietary carbohydrate and insulin sensitivity

When manipulating diets, a change in any one dietary component is accompanied by reciprocal change in other dietary components. So when the effect of dietary carbohydrates on insulin action is examined, alterations are being made to dietary macronutrients as a consequence of the relative change in carbohydrate. The earliest experiments on human subjects examined the effect of altering relative amounts of carbohydrate and fat on insulin action and Himsworth (1936) reported that the blood glucose-lowering action of insulin was improved as dietary carbohydrate increased. This much-cited study was the first indication of an association between low-fat, high-carbohydrate diets and improvement in insulin's ability to stimulate glucose disposal. Positive effects of high-carbohydrate diets on human insulin sensitivity have

Table 2. Examples of glycaemic index (GI) and glycaemic load (GL) of common foods (Hu *et al.* 2001)

Food	GI*	Serving size†	Carbohydrate per serving (g)	GL per serving (g)
White rice, low-amylose	125	1 cup (225 ml)	53	67
Baked potato	121	1	51	61
Cornflakes (breakfast cereal)	119	1 cup (225 ml)	24	29
Honey	104	1 tablebspoon (15 ml)	17	18
Sucrose	92	1 teaspoon (5 ml)	4	4
Ice cream	87	0·5 cups (112·5 ml)	16	14
White rice, high-amylose	84	1 cup (225 ml)	45	37
Orange juice	81	6 ounces (170·1 g)	20	16
Brown rice	78	1 cup (225 ml)	45	35
Parboiled rice	67	1 cup (225 ml)	43	29
All-bran (breakfast cereal)	60	0·5 cup (112.5 ml)	23	14
Apple juice	58	6 ounces (170·1 g)	22	13
Spaghetti	58	1 cup (225 ml)	40	23
Whole milk	38	1 cup (225 ml)	12	5
Fructose	33	2 tablespoons (30 ml)	31	10
Groundnuts	20	1 ounce (28·35 g)	5	1

* White bread = 100.
† 1 oz = 28·35 g; 1 cup = 225 ml; 1 tablespoon = 15 ml; 1 teaspoon = 5 ml.

remained an area of debate, largely because of the stark contrast between the outcomes of human studies and those in rodents. A large number of studies conducted in rodents suggest that high intakes of fructose (up to 60 % of energy) and sucrose (up to 70 % of energy) result in a decline in insulin sensitivity in the liver and peripheral tissues (for a review, see Storlien *et al.* 2000). These rodent studies demonstrated adverse effects as a function of the dose of sucrose or fructose and duration of exposure, such that to observe an effect the duration of exposure must be longer with lower doses. However, other animal studies have shown that fructose may preserve β-cell mass and prevent diabetes (Orban *et al.* 2001), suggesting that there may be particular effects in different animal strains or species. Studies in human adults with or without type 2 diabetes have consistently shown no effect on insulin sensitivity of isoenergetic substitution of sucrose or fructose for starch (Wolever, 2000). If anything, both fructose and sucrose have been associated with lower glucose excursions after ingestion, and palatability alone would suggest that it is unlikely that humans would ever ingest sugar in the quantities consumed in the aforementioned animal studies.

Epidemiological studies considering dietary carbohydrate intake and insulin resistance

Prospective studies

An overview of outcomes of major prospective studies dating back to the early 1970s on dietary carbohydrate, fibre and incidence of type 2 diabetes is given in Table 3. It is evident that, apart from very early epidemiological studies (Kahn *et al.* 1971; Medalie *et al.* 1974), collectively there is little evidence to suggest that the intake of total carbohydrate predicts the risk of type 2 diabetes. Interestingly, some of these studies support the view that high-carbohydrate, high-fibre diets, with low GI, may even contribute to diabetes prevention (Table 3). Prospective studies that include an evaluation of dietary fibre, or fruit or vegetable consumption consistently reveal an inverse association between these components and incidence of

type 2 diabetes (Feskens *et al.* 1995; Ford & Mokdad, 2001; Stevens *et al.* 2002; Montonen *et al.* 2003). In a study of Swedish adult females, with 12-year follow-up, Lungren *et al.* (1989) reported no significant differences in carbohydrate intake in women who subsequently developed diabetes compared with those who did not. This lack of association between total carbohydrate and diabetes incidence was also observed in the large Nurses' Health Study (Colditz *et al.* 1992) and Health Professionals' Study (Salmeron *et al.* 1997*b*). The former study was conducted in females initially aged 40–65 years, while the latter considered males initially aged between 40 and 75 years, indicating at least in adults that there is no association between total carbohydrate and diabetes incidence regardless of sex. As illustrated in Table 3, data derived from both the Nurses' Health Study (Salmeron *et al.* 1997*a*) and Health Professionals' Study (Salmeron *et al.* 1997*b*) indicated an association between the GI or glycaemic load and risk of developing type 2 diabetes, while the Iowa Women's Health Study (with older participants) did not reveal any association (Meyer *et al.* 2000). When considering the large-population Harvard Group studies (Salmeron *et al.* 1997*a,b*) it is important to note that the reported outcomes have been questioned on the basis of the application of validated food-frequency questionnaires with repeated measures with inherent multiplication of errors (Pi-Sunyer, 2002). On balance it is clear that there are inherent errors with every dietary assessment method, and while food-frequency questionnaires may have poor accuracy, food diaries also provide unreliable estimates of actual nutrient consumption and under-reporting adds further confusion when relating metabolic variables with dietary intake.

Cross-sectional, longitudinal and case–control studies

Table 4 considers the literature on dietary carbohydrate type and incidence of impaired glucose tolerance or type 2 diabetes. In the San Luis Valley Diabetes Study (Table 4), which tracked the development of hyperinsulinaemia over

Table 3. Prospective studies on dietary carbohydrate, fibre and incidence of type 2 diabetes

Study	Reference	Subjects (*n*)	Dietary method	Outcome
Israel Ischemic Heart Study	Kahn *et al.* (1971); Medalie *et al.* (1974)	373	Dietary history	Inverse association with sucrose intake
Study on Swedish adults	Lungren *et al.* (1989)	1462	24 h recall	No association
Zutphen Study	Feskens & Kromhout (1989)	841	Dietary history	No association
Nurses' Health Study	Colditz *et al.* (1992)	84 360	FFQ	No association
Seven Countries Study	Feskens *et al.* (1995)	338	Dietary history	Inverse association with vegetables and legumes
Nurses' Health Study	Salmeron *et al.* (1997*b*)	65 173	FFQ	Inverse association with fibre; positive association with GL
Health Professionals' Study	Salmeron *et al.* (1997*a*)	42 759	FFQ	Inverse association with fibre; positive association with GL
Iowa Women's Health Study	Meyer *et al.* (2000)	35 988	FFQ	Inverse association with fibre; no association with GI or GL
Study on US adults	Ford & Mokdad (2001)	9665	24 h recall	Inverse association with vegetables
ARIC Study	Stevens *et al.* (2002)	12 251	FFQ	Inverse association with cereal fibre
Finnish Mobile Clinic Study	Montonen *et al.* (2003)	4316	Dietary history	Inverse association with cereal fibre
Women's Health Study USA	Janket *et al.* (2003)	39 345	FFQ	No association

FFQ, food-frequency questionnaire; GL, glycaemic load; GI, glycaemic index; ARIC, Atherosclerosis Risk in Communities.

Table 4. Cross-sectional, longitudinal and case–control studies on dietary carbohydrate type and incidence of impaired glucose tolerance or type 2 diabetes

Study	Reference	Subjects (*n*)	Methods	Outcome
Cross-sectional				
Study on Japanese-American adults	Tsunehara *et al.* (1990)	229	OGTT; diet history	Inverse association with carbohydrate, energy and sucrose intake
San Luis Valley Diabetes Study	Marshall *et al.* (1991)	1317	OGTT; 24 h recall	Inverse association with total carbohydrate intake; no association between carbohydrate subtype and glucose tolerance
Study of Native Canadian adults	Wolever *et al.* (1997); Gittelsohn *et al.* (1998)	728	OGGT; 24 h recall; FFQ	No association with simple sugar intake; positive association with high-fat 'junk food' intake
Longitudinal				
Study on Dutch adults	Feskens *et al.* (1991)	175	OGTT; dietary history	No association between monosaccharide or disaccharide intake and development of IGT
San Luis Valley Diabetes Study	Marshall *et al.* (1994)	123	OGTT; 24 h recall	No association between sucrose, total carbohydrate or starch intake and development of diabetes
Case–control				
Study of adults in Papua New Guinea	Hodge *et al.* (1996)	285	OGTT; FFQ	No association, no differences between cases and controls for any carbohydrate

OGTT, oral glucose tolerance test; FFQ, food-frequency questionnaire; IGT, impaired glucose tolerance.

1–3 years in individuals with pre-existing impaired glucose tolerance, no relationship between dietary carbohydrate and either hyperinsulinaemia or onset of diabetes was described (Marshall *et al.* 1994); rather, the study reported a trend for an inverse relationship. This strong, well-conducted prospective study, however, revealed a significant relationship between dietary fat and newly diagnosed cases of diabetes (Marshall *et al.* 1994). Earlier cross-sectional studies suggest a decreased prevalence of diabetes with high carbohydrate intake. Indeed, Tsunehara *et al.* (1990) found lower intakes of refined carbohydrates in diabetics compared with non-diabetics, although it is unclear whether these subjects were aware of their diagnosis at the time of dietary assessment. So, consistent with the prospective studies described earlier (Table 3), the studies described in Table 4 collectively support the view that high carbohydrate intake does not affect incidence of impaired glucose tolerance or type 2 diabetes.

Epidemiological studies of dietary sugars intake

As illustrated in Table 5, there is less consistency in the patterns arising from epidemiological studies on non-diabetic and diabetic subjects when assessing dietary sugars intake and insulin resistance. While inverse associations between intake of simple carbohydrates and measures of glycaemia and insulin resistance were observed in four of the larger cross-sectional studies (Keen *et al.* 1979; Feskens & Kromhout, 1990; Buyken *et al.* 2000; Williams *et al.* 2000), five other cross-sectional (Mooy *et al.* 1995; Boeing *et al.* 2000; Rosell *et al.* 2003; Yang *et al.* 2003) and longitudinal (Marshall *et al.* 1997) studies revealed no association. A weak positive association between simple carbohydrate intake and fasting insulin levels was reported in the 'Coronary Artery Risk Development in Young Adults' study of young black and

white Americans (Manolio *et al.* 1991; Archer *et al.* 1998). Similarly, in a study by Sevak *et al.* (1994), which had the advantage of a 7 d weighed intake, total carbohydrate and sucrose intake was positively correlated with insulin resistance but only for postprandial and not fasting insulin measures (Sevak *et al.* 1994). Interestingly, these latter studies that demonstrated a positive relationship between dietary sugars and insulin resistance involved South Asian adults in London and black American children (Manolio *et al.* 1991; Archer *et al.* 1998). Thus, when considering these studies, the possible influence of genetic factors, which may predispose to insulin resistance, should not be overlooked as illustrated by the impact of 'thrifty' insulin resistance genes in South Asian (Lindquist *et al.* 2000) and Westernised Native American Pima Indian populations (Weyer *et al.* 1999).

Intervention studies considering dietary carbohydrate intake and insulin resistance

Intervention studies comparing effects of high and low carbohydrate intake

Table 6 gives an overview of dietary intervention studies comparing high with low carbohydrate intake in non-diabetic and diabetic individuals. In these intervention studies, various solid or liquid diets were combined with different techniques to yield measures of glucose tolerance or insulin sensitivity. As shown, in non-diabetic subjects most studies revealed an increase of glucose tolerance (Anderson *et al.* 1973; Swinburn *et al.* 1991) or insulin sensitivity (Chen *et al.* 1988; Fukagawa *et al.* 1990; Vidon *et al.* 2001; Sunehag *et al.* 2002). Exceptionally, in one study by Jeppesen *et al.* (1997) that indicated a lowering of insulin sensitivity with a high-carbohydrate diet, a number of women, although

Table 5. Epidemiological studies on dietary sugars intake and insulin resistance

Study	Reference	Subjects (n)	Methods	Outcome
Cross-sectional				
Study of English professional adults	Keen *et al.* (1979)	3554	OGTT; diet record	Inverse association
Zutphen Study	Feskens & Kromhout (1990)	418	OGTT; diet history	Inverse association
CARDIA Study	Manolio *et al.* (1991); Archer *et al.* (1998)	4734	Fasting insulin; diet history	Weak positive association
Hoorn Study	Mooy *et al.* (1995)	2484	OGTT; FFQ	No association
Study of UK South Asian and white adults	Sevak *et al.* (1994)	173	OGTT; weighed record	Positive association
EPIC Study (Potsdam cohort)	Boeing *et al.* (2000)	1773	HbA_{1c}; FFQ	No association
EURODIAB Study	Buyken *et al.* (2000)	2079	HbA_{1c}; diet record	Inverse association
Study of African-American and white children	Lindquist *et al.* (2000)	95	IVGTT; 24 h recall ($\times$ 3)	Inverse association
Ely Study	Williams *et al.* (2000)	802	OGTT and insulin; FFQ	Inverse association
Study of Swedish adults	Rosell *et al.* (2003)	301	Fasting insulin; diet record	No association
NHANES III Study	Yang *et al.* (2003)	11 855	HbA_{1c}, glucose, insulin; 24 h recall	No association
Longitudinal				
San Luis Valley Diabetes Study	Marshall *et al.* (1997)	1069	Fasting insulin; 24 h recall	No association

OGTT, oral glucose tolerance test; CARDIA, Coronary Artery Risk Development in Young Adults; FFQ, food-frequency questionnaire; EPIC, European Prospective Investigation into Cancer; HbA_{1c}, glycated Hb; IVGTT, intravenous glucose tolerance test; NHANES, National Health and Nutrition Examination Survey.

non-diabetic, had high degrees of insulin resistance. However, it would be difficult to conceive that subjects with the greatest degrees of initial insulin resistance would show positive responses to short-term intervention with a high-carbohydrate diet.

The trend of improved glucose tolerance or increased insulin sensitivity after high-carbohydrate, low-fat diets was also recorded with diabetic subjects (Table 6) (Brunzell *et al.* 1971, 1974; Anderson, 1977; Hjollund *et al.* 1983; Hughes *et al.* 1995). Other studies reported no difference between diabetics consuming high- and low-carbohydrate diets (Coulston *et al.* 1987; Garg *et al.* 1992). The latter studies, reporting a lack of effect of a high-carbohydrate diet on insulin resistance in diabetes, may reflect differences in the degree of initial insulin sensitivity (and thus lack of effect of short-term high-carbohydrate intervention in severe insulin resistance) in population or age groups and perhaps also different genetic backgrounds. As noted above, there are also differences in initial insulin sensitivity in studies on non-diabetic subjects. In this regard, it is also interesting that lower levels of insulin sensitivity have been reported in adolescent compared with pre-pubertal children (Sunehag *et al.* 2002). This is consistent with the view that there may be recordable differences in insulin sensitivity between adults and children, thus emphasising the importance of population, ethnic background and age when interpreting insulin resistance data.

Intervention studies comparing effects of different carbohydrates on insulin sensitivity

Dietary intervention studies on fructose, sucrose, and simple carbohydrates *v.* complex carbohydrates are summarised in Table 7. While some studies revealed an increase in insulin sensitivity during fructose diets (Crapo & Kolterman, 1984; Crapo *et al.* 1986; Koivisto & Yki-Jarvinen, 1993), others revealed no association (Turner *et al.* 1979; Sunehag *et al.*

2002), or even a decrease in insulin sensitivity (Beck-Nielsen *et al.* 1980; Hallfrisch *et al.* 1983). The study by Beck-Nielsen *et al.* (1980) represented an over-feeding or supplementation study in which healthy subjects were given an extra 4180 kJ (1000 kcal)/d of fructose in water and cannot really be compared with other studies due to lack of an effective control. Furthermore, this study, when related to others in non-diabetic subjects, suggests that much higher intakes of fructose are required to significantly reduce insulin sensitivity, and is arguably too short to be of metabolic significance (Bantle *et al.* 1986). The Beltsville study (Hallfrisch *et al.* 1983) recruited men with abnormally high insulin responses to sucrose load, and noted very high insulin and glucose responses to consumption of a 15 % fructose diet (although fasting insulin levels were not affected by the fructose diets). This was particularly the case in the hyperinsulinaemic men, who may or may not be insulin resistant, which is confusing particularly as the other studies (Table 7) would suggest that fructose increases insulin sensitivity in type 2 diabetes (Crapo *et al.* 1986; Koivisto & Yki-Jarvinen, 1993).

When considering sucrose a different pattern emerges, with either no association (Bossetti *et al.* 1984; Jellish *et al.* 1984; Colagiuri *et al.* 1989; Thorburn *et al.* 1990; Raben *et al.* 2001; Brynes *et al.* 2003) or a decrease in insulin sensitivity (Reiser *et al.* 1981*a,b*; Coulston *et al.* 1985). In the studies by Reiser *et al.* (1981*a,b*) on non-diabetics, the 'gorging' meal pattern may at least partly have been responsible for the outcome, as it is known that this eating style is in itself associated with higher fasting serum insulin and lipid values (Jenkins *et al.* 1989). The study by Coulston *et al.* (1985) assessed the metabolic effects of sucrose in subjects with type 2 diabetes, only demonstrating a decrease in insulin sensitivity-related postprandial parameters, and did not undertake direct measures of insulin sensitivity.

Indeed, the studies denoted in Table 7 emphasise the diversity in techniques employed to determine insulin

Table 6. Dietary intervention studies comparing a high with low carbohydrate (CHO) intake

	Reference	Subjects (n)	Methods	Outcome
Non-diabetic				
Liquid (20–80 % glucose)	Anderson et al. (1973)	13	OGTT	Glucose tolerance improved with increasing glucose
Normal v. 85 % CHO v. 30 % CHO	Chen et al. (1988)	10	IVGTT	High CHO increased insulin sensitivity
68 % CHO–high fibre v. 43 % CHO–low fibre	Fukagawa et al. (1990)	12	GC	High CHO increased insulin sensitivity
>50 % CHO v. <40 % CHO (high fat)	Borkman et al. (1991)	8	GC	No difference
Normal v. 70 % CHO v. 30 % CHO	Swinburn et al. (1991)	24	OGTT	Glucose tolerance improved with high CHO
51 % CHO–low fat v. 8 % CHO–high fat	Cutler et al. (1995)	10	EHC	No difference
60 % CHO v. 40 % CHO	Jeppesen et al. (1997)	10	IST	High-CHO diet decreased insulin sensitivity
55 % CHO v. 45 % CHO–high MUFA	Thomsen et al. (1999)	16	IVGTT	No difference
Liquid (2–85 % CHO plus 0–83 % fat)	Bisschop et al. (2001)	6	EHC	No dose–response differences
40 % CHO–45 % fat v. 55 % CHO–30 % fat	Vidon et al. (2001)	7	OGTT	High CHO increased insulin sensitivity
30 % CHO–55 % fat v. 60 % CHO–25 % fat	Sunehag et al. (2002)	24	IVGTT	High CHO increased insulin sensitivity
Diabetic				
Liquid (45 % CHO v. 85 % CHO)	Brunzell et al. (1971)	22	GTT; fasting insulin	High CHO increased insulin sensitivity
Liquid (45 % CHO v. 85 % CHO)	Brunzell et al. (1974)	15	GTT; fasting insulin	High CHO increased insulin sensitivity
Liquid 44 % CHO v. 75 % CHO)	Anderson (1977)	11	GTT	Glucose tolerance improved with high CHO
High fibre, high starch, low fat	Hjollund et al. (1983)	18	ITT	Test diet increased insulin sensitivity
60 % CHO–20 % fat v. 40 % CHO–40 % fat	Coulston et al. (1987)	9	Fasting, day-long glucose, insulin	No difference
60 % CHO v. 30 % CHO	Garg et al. (1992)	8	GC	No difference
60 % CHO–low fat v. 40 % CHO–high MUFA	Parillo et al. (1992)	10	GC	Low CHO–high MUFA improved insulin sensitivity
60 % CHO (with or without exercise)	Hughes et al. (1995)	10	GC	Small improvement in insulin sensitivity

OGTT, oral glucose tolerance test; IVGTT, intravenous glucose tolerance test; GC, glucose clamp; EHC, euglycaemic–hyperinsulinaemic clamp; IST, insulin sensitivity and suppression test; GTT, glucose tolerance test; ITT, insulin tolerance test.

Table 7. Dietary intervention studies of effects of different carbohydrates (CHO) on insulin sensitivity

	Reference	Subjects (n)	Methods	Outcome
Simple sugars – fructose				
20 % CHO energy fructose	Turner et al. (1979)	6 HTG	Fasting/post-load glucose and insulin	No association
Normal diet plus 4180 kJ (1000 kcal) fructose	Beck-Nielsen et al. (1980)	15 ND	ITT	Decrease in insulin sensitivity
0–15 % CHO energy fructose	Hallfrisch et al. (1983)	12 ND; 12 HI	Fasting, post-load glucose and insulin	Decrease in insulin sensitivity (particularly in HI)
24 % CHO energy fructose	Crapo & Kolterman (1984)	11 ND	OGTT	Increase in insulin sensitivity
24 % CHO energy fructose	Crapo et al. (1986)	7 T2DM	OGTT	Increase in insulin sensitivity
20 % energy fructose	Koivisto & Yki-Jarvinen (1993)	10 T2DM	EHC; GTT, HbA$_{1c}$	Increase in insulin sensitivity
12 or 24 % total energy fructose	Sunehag et al. (2002)	12 ND	IVGTT	No association
Simple sugars – sucrose				
5–33 % energy sucrose	Reiser et al. (1981a,b)	24 ND	Fasting insulin	Decrease in insulin sensitivity
33 % CHO energy sucrose	Bossetti et al. (1984)	8 ND	Fasting glucose and insulin	No association
Isoenergetic diet with 3–220 g sucrose	Jellish et al. (1984)	24 T2DM	Fasting/post-load glucose	No association
1 or 16 % energy sucrose	Coulston et al. (1985)	11 T2DM	Fasting, day-long glucose and insulin	Decrease in insulin sensitivity (day-long only)
Diet with 3 or 220 g sucrose	Abraira & Derler (1988)	18 T2DM	Fasting, post-load glucose, insulin, HbA$_{1c}$	No association
Diet with 45 g sucrose or 16 mg asp	Colaguiri et al. (1989)	9 T2DM	EHC; HbA$_{1c}$; plasma glucose	No association
Fructose replaced sucrose	Thorburn et al. (1990)	6 T2DM	EHC	No association
23 % sucrose v. 2 % sucrose	Raben et al. (2001)	18 ND	HOMA	No association (HOMA-R unchanged)
Diet with 90 g sucrose	Brynes et al. (2003)	17 ND	HOMA	No association
Simple sugars v. complex CHO				
20 % energy as sucrose, fructose or starch	Bantle et al. (1986)	12 T1DM; 12 T2DM	Plasma and urinary glucose	Increase in insulin sensitivity (fructose only)
Sucrose replaced 45 g complex CHO	Peterson et al. (1986)	23 DM	HbA$_{1c}$; fasting glucose	No association
CHO as 35 % complex v. 35 % simple	Reiser et al. (1986)	19 ND	GTT; Fasting insulin	Decrease in insulin sensitivity (35 % simple only)
20 % fructose or 20 % starch energy	Reiser et al. (1989)	10 ND; 10 HI	Fasting, day-long insulin	Increase in glucose tolerance (fructose)
20 % fructose plus/minus starch	Bantle et al. (1992, 1993)	6 T1DM; 12 T2DM	Plasma glucose	Increase in insulin sensitivity (fructose minus starch)

HTG, hypertriacylglycerolaemia; ND, non-diabetic; ITT, insulin tolerance test; HI, hyperinsulinaemic; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes; EHC, euglycaemic–hyperinsulinaemic clamp; GTT, glucose tolerance test; HbA$_{1c}$, glycated Hb; IVGTT, intravenous glucose tolerance test; asp, aspartame; HOMA, homeostasis model assessment; T1DM, type 1 diabetes mellitus; DM, diabetes mellitus.

sensitivity and prompt further long-term intervention studies using the EHC or other well-validated techniques to measure insulin resistance. This is highlighted by the studies comparing simple sugars and complex carbohydrate, which tended to show that fructose increases insulin sensitivity (Bantle *et al.* 1986, 1992, 1993) and glucose tolerance (Reiser *et al.* 1989), without actual measurements of insulin sensitivity before and after dietary intervention. Such studies, not using the 'gold-standard' EHC, do not add greatly to our understanding of the effects of simple sugars compared with complex carbohydrate in the development or progression of insulin resistance.

Intervention studies comparing effects of glycaemic index on metabolic control

As is the case with the studies reported in Table 7, those given in Table 8, which study the effects of GI, largely rely on indirect measures of insulin resistance and thus only really provide an estimate of overall metabolic control. However, despite this limitation, these data largely support an association between low-GI diets and improved metabolic control (Table 8). When interpreting this overall outcome it is important to emphasise again that low GI does not mean low carbohydrate, rather reflecting the features or quality of dietary carbohydrate in particular foods (Table 2). Although an increasing body of evidence would suggest merit in adopting high-carbohydrate, low-GI diets, the charge that high-GI diets result in insulin resistance is

Table 8. Dietary intervention studies of effects of glycaemic index (GI) on metabolic control

	Subjects (*n*)
Studies in which low-GI diet was associated with improved metabolic control	
Fontvieille *et al.* (1988)	8 T1DM
Brand *et al.* (1991)	16 T1DM
Fontvieille *et al.* (1992)	18 DM
Wolever *et al.* (1992)	6 T2DM
Frost *et al.* (1994)	51 T2DM
Behall & Howe (1995)	10 ND and 14 HI
Howe *et al.* (1996)	9 ND and 13 HI
Frost *et al.* (1996)	28 HD
Frost *et al.* (1998)	28 ND
Jarvi *et al.* (1999)	20 T2DM
Wolever & Mehling (2002, 2003)	34 IGT
Brynes *et al.* (2003)	17 ND
Goff *et al.* (2003)	21 ND
Studies in which low-GI diet was associated with worsening of metabolic control	
Kiens & Richter (1996)	7 ND
Studies in which low-GI diet had no association with metabolic control	
Calle-Pascual *et al.* (1988)	35 DM
Luscombe *et al.* (1999)	21 T2DM
Tsihlias *et al.* (2000)	91 DM
Herrmann *et al.* (2001)	9 ND

T1DM, type 1 diabetes mellitus; DM, diabetes mellitus; T2DM, type 2 diabetes mellitus; ND, non-diabetic; HI, hyperinsulinaemic; HD, heart disease; IGT, impaired glucose tolerance.

unproven on the basis of current experimental data arising from the use of well-validated measures of insulin resistance (see Pi-Sunyer, 2002).

Conclusions

While intake of dietary fat, particularly saturated fat, shows clear associations with insulin resistance in animals (Storlien *et al.* 1996) and human subjects (Marshall *et al.* 1997) and could predispose to development of diabetes (Marshall *et al.* 1994), the effects of carbohydrate on insulin sensitivity are not so clear. While simple sugars have been shown to cause insulin resistance in some rodent strains, most literature on human subjects would not support this view. Indeed, sugars are both normal and important dietary components, sourced from cane or beet sugar (sucrose), 'high-fructose' syrups (found in soft drinks in the USA), and most fruits, where they can comprise up to 8 % of their weight or more. However, in a recent article, Mann (2004) draws attention to the fact that the source of dietary sugars (such as fructose and sucrose) may be important when considering the impact of intake on human health. This may be particularly important when considering the apparent increase in daily intake of drinks rich in non-milk extrinsic sugars in the UK and USA (Henderson *et al.* 2003; Mann, 2004). In this regard, while fructose has hyperlipidaemic properties, these are short-lived in humans (Grigoresco *et al.* 1988), thus averting any fears over the current recommendations for increased fruit consumption in healthy eating programmes. It is also important to note that many products with high saturated fat content (such as pre-prepared meals, confectionery and chocolate) also contain dietary sugars and excessive consumption of such products is associated with weight gain and may thus contribute significantly to obesity. Indeed, when considering the dietary patterns and current obesity–type 2 diabetes epidemic, it is imperative that diets are viewed in terms of ability to promote regulated weight loss and ameliorate insulin resistance. Important in this regard was the observation that a low-fat, high-carbohydrate diet may lead to gradual and sustained weight loss while preventing fat gain in individuals who are not overweight (Kirk *et al.* 2000). In addition, there is evidence that eating frequently and often (so-called 'grazing') on low-fat, low-energy foods such as fruits and cereal bars may be the best way of achieving a healthy body weight (Green *et al.* 2000).

When energy is restricted the source of carbohydrate does not appear to be important for body weight (Vermunt *et al.* 2003), nor indeed does the reduced carbohydrate content (Bravata *et al.* 2003). Interestingly, in a recent intervention study of subjects with impaired glucose tolerance, significantly more weight was lost with a high-GI diet than with low-GI or MUFA diet which does not support the view that reducing glycaemic load, either by reducing GI or carbohydrate intake, necessarily results in weight loss (Wolever & Mehling, 2003). Indeed, a very recent systematic review of low-carbohydrate diets found that weight loss is associated with the duration of the diet and restriction of energy intake, but not the restriction of carbohydrates (Astrup *et al.* 2004). Also, when considering the literature on dietary intervention studies it is important to consider that

manipulation of carbohydrate content in a given diet cannot conclusively demonstrate the effects of carbohydrate independent of other dietary factors. As an example, studies comparing the effects of a high-fat, high-carbohydrate diet with a low-fat, high-fibre diet do not allow for separation of effects of a high-carbohydrate diet from the effects of a high-fat diet. This adds to the complexity, as does the consequences of long-term adherence to radical low-carbohydrate diets, which has been associated with an increased prevalence of halitosis, muscle cramps, constipation and headache and, perhaps more importantly, may increase risk of CVD and cancer (Astrup *et al.* 2004).

Collectively, the data described in the present paper support the view that high-carbohydrate diets do not adversely affect insulin sensitivity, and may in fact offer some beneficial effects. While epidemiological studies play an essential role in helping devise prevention strategies for diseases of the metabolic syndrome, in order to get a more convincing picture, future intervention studies need to research the effects of sugars, complex carbohydrate or fibre in different populations including those presumed to be most susceptible to their actions. As emphasised earlier, these studies should cover both short- and long-term adherence to these diets and employ direct measures of insulin resistance, preferably using the EHC. Standardisation of approach and global multi-centre studies would certainly provide more convincing data. This is also true for the measures of insulin resistance, which should expand on the rather simplistic approach of measuring insulin and glucose levels, perhaps to cover other important genetic markers and metabolic variables. Indeed, research application of emerging genomic, proteomic and metabolomic approaches should increase understanding of the complex mechanisms underlying insulin resistance. Adopting these new tools also offers considerable opportunities to unravel the complex relationships between carbohydrate and other dietary components and risk or pathogenesis of insulin resistance and the metabolic syndrome.

Although genetic predisposition and advancing age cannot be directly modified, clearly other risk factors driving the diabetes–obesity epidemic including physical inactivity and energy over-consumption can potentially be changed through targeted lifestyle modification programmes. While current evidence supports the FAO/WHO recommendations to maintain a high-carbohydrate diet with low-GI starchy foods (Wolever & Mehling, 2002), the relationships between dietary carbohydrate and insulin sensitivity remain an important area of research focus, in order to provide the most useful information for future nutrition policy decisions.

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