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Symposium on 'Dietary management of disease'

Session 4: CVD, diabetes and cancer
Diet, insulin resistance and diabetes: the right (pro)portions

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Excess energy intake and positive energy balance are associated with the development of obesity and insulin resistance, which is a key feature underlying the pathophysiology of type 2 diabetes. It is possible that dietary macronutrient intake may also be important, in particular increased levels of sugar and fat. High-fat energy-dense diets contribute to energy excess and obesity. Fat type is also a factor, with evidence suggesting that saturated fat intake is linked to insulin resistance. However, controversy exists about the role of carbohydrate in the development of diabetes. Epidemiological studies suggest that the risk of diabetes is unrelated to the total amount of carbohydrate, but that fibre intake and glycaemic load are important. Common dietary advice for the prevention of diabetes often advocates complex carbohydrates and restriction of simple carbohydrates; however, sugars may not be the main contributor to glycaemic load. Evidence continues to emerge in relation to the influence of dietary sugars intake on insulin resistance. In broader dietary terms fruit and vegetable intake may influence insulin resistance, possibly related to increased intake of fibre and micronutrients or displacement of other food types. There is also considerable debate about the most effective diet and appropriate macronutrient composition to facilitate weight loss. Recent evidence suggests comparable effects of diets with varying macronutrient profiles on weight loss, which is predominantly related to energy restriction. However, based on the results of diabetes prevention trials focusing on lifestyle measures, evidence favours low-fat diets as the preferred approach for weight loss and diabetes prevention.

Macronutrient intake: Carbohydrate: Insulin resistance: Diabetes prevention

Diet and lifestyle modifications are considered to be the cornerstone of prevention of type 2 diabetes[1,2]. The major aims of this approach are to reduce body weight, improve insulin resistance and modify cardiovascular risk factors, which collectively contribute to the twofold to threefold increased mortality as a result of CVD in patients with diabetes. The present review focuses on research that has examined macronutrient intake and in particular on the controversy and confusion about the role of carbohydrate and especially consumption of sugar on the development and treatment of insulin resistance and subsequent risk of diabetes, both in the context of isoenergetic and also weight-reduction diets. Evidence will be reviewed from epidemiological and clinical investigation studies examining macronutrient intakes in relation to insulin resistance and diabetes as well as recent landmark diabetes prevention trials.

The idea that energy overconsumption results in weight gain leading to obesity and ill health dates back to ancient times. In 460 BC Hippocrates wrote that 'when more food than is proper is eaten, it results in disease'[3]. In approximately 400–500 BC Charuka and Susruta also wrote about diabetes that 'the disease was more prevalent in those who were indolent, overweight and gluttonous, and who indulged in sweet and fatty foods' suggesting that even at that time certain food types or macronutrients were believed to exert greater diabetogenic effects[3]. Hyperglycaemia and abnormal glucose metabolism is the defining feature of diabetes and there is still a widely-held belief that a high intake of sugar is a particular risk factor.

Abbreviation: DASH, Dietary Approaches to Stop Hypertension.

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However, it is also now established that excess fat intake and disturbances in fat metabolism, including raised fatty acid levels resulting in lipotoxicity, are associated with insulin resistance and diabetes[4]. The current epidemic of overweight and obesity and diabetes has stimulated substantial research into the role of diet and macronutrient intake on the development of diabetes.

Insulin resistance

The concept of insulin resistance initially emerged following the discovery of insulin. It was noted that patients with diabetes could be divided into two groups based on their response to insulin, i.e. insulin-sensitive and insulin-resistant, which broadly equates to the modern definitions of type 1 and type 2 diabetes[5]. One of the earliest experiments that examined the role of diet on insulin resistance investigated the effect of altering the relative amounts of carbohydrate and fat on insulin action, reporting that the blood glucose-lowering effect of insulin is enhanced as dietary carbohydrate increases[6]. However, this early study highlights that reciprocal changes in macronutrients make interpretation of the causality of effects difficult, as the increase in carbohydrate is accompanied by a reduction in fat intake. Later, following the development of the insulin radioimmunoassay[7], the term insulin resistance became applied to the setting in which insulin is not being administered and hyperinsulinaemia occurs in the context of normal or increased blood glucose levels. The modern definition of insulin resistance is a condition in which 'a normal concentration of insulin produces a less than normal biological response'[8].

Insulin acts on a range of target tissues including: skeletal muscle, to stimulate glucose uptake and formation of glycogen; the liver, where insulin suppresses hepatic gluconeogenesis; adipose tissue, causing suppression of lipolysis. At a cellular level, following its secretion from the pancreatic β-cells, insulin travels in the bloodstream to its target tissues where it binds to specific cell-surface receptors. Binding of insulin to its receptor activates receptor tyrosine kinase activity promoting receptor autophosphorylation, which initiates a cascade of post-receptor signalling events that ultimately influence membrane expression of GLUT4. Translocation of GLUT4 to the cell membrane enables cellular glucose uptake. In common insulin-resistant states binding of insulin to its receptor is normal; although the downstream effects are attenuated, consistent with a post-receptor effect, the precise molecular mechanism has not been identified[9].

The pathophysiology of type 2 diabetes involves impairment of insulin action or insulin resistance combined with defects in insulin secretion[10]. Insulin resistance is felt to be a key factor that precedes the onset of glucose intolerance, although subtle defects in insulin secretion kinetics also coexist before the development of diabetes, including a disturbance of pulsatile secretion[11]. Hyperinsulinaemia occurs initially as a response to insulin resistance in order to maintain glucose homeostasis. However, as insulin resistance progresses this compensatory mechanism is overwhelmed and can no longer maintain euglycaemia, resulting in impaired glucose tolerance. Subsequently, a vicious cycle evolves in which hyperglycaemia leads to glucose toxicity, which further exacerbates insulin resistance. One example of this process is the glycation of insulin, which reduces its biological activity[12]. As diabetes develops, the relationship between insulin secretion and insulin resistance becomes disconnected and β-cell function declines, the so-called 'Starling curve' of the pancreas. Type 2 diabetes therefore reflects the 'tip of the iceberg' in terms of abnormalities of insulin action and secretion and altered glucose metabolism. Clearly, understanding the effects of macronutrient intake on the development of diabetes requires a knowledge of the effects of diet on insulin resistance even before hyperglycaemia develops.

Although diabetes is defined based on the level of blood glucose, which is associated with a steep rise in the risk of microvascular complications, including retinopathy, it is well recognised that a substantial proportion of the excess cardiovascular risk attributed to diabetes is already present in patients with impaired glucose tolerance[13,14]. Various clinical studies have also shown that treatments aimed at glucose lowering have little or no effect on macrovascular events[15,16]. It is also recognised that insulin resistance is associated with a cluster of abnormalities that collectively constitute the insulin resistance or metabolic syndrome, which include obesity, glucose intolerance, hypertension, dyslipidaemia (hypertriacylglycerolaemia and low HDL-cholesterol) and abnormalities of coagulation and fibrinolysis[17]. This evidence has led to the identification of insulin resistance not only as a mechanism contributing to the development of diabetes, but also as an independent cardiovascular risk factor.

The rising global prevalence of diabetes is often linked to changing patterns of diet and exercise and the epidemic of overweight and obesity[18]. However, there is marked variation between different ethnic groups that has stimulated a focus on genetic factors causing insulin resistance and diabetes. These two theories are, however, not mutually exclusive and indeed may be linked by the so-called 'thrifty genotype' hypothesis[19]. This theory proposes that certain 'thrifty' genes promote storage of energy and development of insulin resistance. These genes may have conferred a survival advantage historically during times of food scarcity, but when exposed to the excesses of a modern Westernised lifestyle result in obesity, insulin resistance and diabetes. While the identification of diabetes susceptibility genes may enhance the understanding of the mechanisms causing diabetes and ultimately lead to new therapeutic options, prevention of the development of diabetes achieved through dietary modification remains an attractive and perhaps more readily-achievable goal.

Role of dietary fat

Studies have shown that high-fat, and therefore energy-dense, diets contribute to hyperenergetic intake and weight gain, which increases the risk of obesity and diabetes[4]. However, there is also evidence that the type of fat is also

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important and that this effect is independent of obesity. The amount of saturated fat and saturated fat:polyunsaturated fat have been shown to influence the risk of diabetes in epidemiological studies and also studies of insulin action, perhaps related to alterations in the fatty acid composition of cell membranes or to lipid storage in muscle[20]. The influence of fat intake on insulin resistance and diabetes risk has been covered in detail elsewhere[21]. However, while the present review primarily focuses on the role of carbohydrates and sugars, evidence should be interpreted with fat amount and subtype as potential confounding factors.

Role of carbohydrates and sugars

Dietary carbohydrate broadly consists of starch, sugars and fibre. The traditional classification separates carbohydrates into simple and complex forms based on their chemical structure. Simple sugars include monosaccharides (glucose, fructose and galactose) and disaccharides (sucrose, maltose and lactose), while complex carbohydrates comprise monosaccharide polymers. Indigestible carbohydrate polymers constitute fibre and are a negligible source of energy. Common dietary advice for the prevention of diabetes often advocates complex carbohydrates and restriction of simple carbohydrates based on the assumption that simple sugars are rapidly digested and absorbed, exerting a more marked glycaemic response that could over time cause detrimental metabolic effects including hyperinsulinaemia, insulin resistance and diabetes. However, despite some persistence of this misapprehension, it has been shown that the chemical structure of carbohydrates poorly predicts the glycaemic response[22].

The concept of glycaemic index was proposed to provide a more physiological classification of carbohydrates compared with the traditional approach based on chemical structure[23,24]. The glycaemic index of a food is defined as the incremental area under the blood glucose response curve for a 2 h period of a standard 50 g portion of the given food[23]. Glycaemic index is expressed as a percentage of the response to a reference standard, typically glucose or white bread. Glycaemic index therefore provides a physiological measure of the postprandial glycaemic response and depends on the rate of digestion and speed of absorption of carbohydrate. However, a number of factors may influence glycaemic response: fat content (because fat retards absorption of a meal's carbohydrate); cooking method and duration; meal timing. The glycaemic response within 2 h after ingestion is also rather arbitrary, with longer postprandial studies showing that sucrose shows a more rapid decline in blood glucose levels in the later postprandial phase (≥ 3 h) compared with starches[25]. As the glycaemic response is determined not only by the glycaemic index but also the amount of carbohydrate in the food, the concept of glycaemic load[26], a function of glycaemic index and carbohydrate content, was introduced. Although an attractive concept there is currently insufficient evidence to make firm recommendations about the influence of glycaemic index or glycaemic load on insulin resistance and the development of diabetes; further research is required.

Various approaches may be utilised to investigate the role of diet and macronutrient composition on the development of insulin resistance and diabetes. FFQ are commonly used in large epidemiological studies. Although they are cost-effective and can be used with relative ease, it can be difficult to estimate usual frequency and consumption. Furthermore, it is only feasible to use simple techniques to assess insulin resistance, such as the frequently-employed homeostasis model assessment (which utilises measurements of fasting glucose and insulin)[27] or the oral glucose tolerance test (which assesses the endogenous insulin response to a glucose load)[28]. While these tests are relatively simple and inexpensive, they lack reproducibility. The design of epidemiological studies is also relevant; if cross-sectional as opposed to prospective it is possible that subjects may have modified their diets before or around the time of diagnosis of diabetes.

Alternatively, smaller intervention studies can have the advantage of being carefully controlled, with detailed assessments to investigate the mechanisms of any potential effects. However, by necessity, they are usually short-term and address surrogate rather than hard clinical end points such as development of diabetes. The euglycaemic hyperinsulinaemic clamp technique[29] is considered to be the gold standard technique for determining insulin sensitivity. This technique involves the constant infusion of insulin to achieve steady-state hyperinsulinaemia. Glucose is infused concomitantly to maintain the ambient or a preset plasma glucose level, with the glucose infusion rate at steady-state providing a measure of *in vivo* insulin sensitivity. While the glucose clamp technique is highly reproducible, it is very time consuming and labour intense, which makes it only suitable for small-scale detailed clinical investigation studies. However, the glucose clamp technique can be combined with other techniques such as isotope-dilution techniques to examine different components of insulin action such as hepatic glucose production. Differing steady-state insulin levels can also be employed to dissect out varying tissue insulin sensitivities[30]. Clearly, both large-scale epidemiological studies and small detailed clinical intervention studies may yield important information relating to the impact of dietary factors on the development of insulin resistance and diabetes.

Animal studies

Studies in animals have consistently shown that high intakes of sucrose or fructose in rodents cause insulin resistance. For example, in an examination of rats fed equal amounts of high-sucrose or high-starch diets over 4 weeks *in vivo* insulin action was assessed by the euglycaemic clamp technique and a marked impairment following the high-sucrose diet was demonstrated[31]. However, the high-sucrose diet contained 69% total energy from sucrose and the percentage energy from fat was low. This level of sucrose intake is far in excess of levels normally consumed by human subjects and would be unpalatable. Likewise, studies in rodents have shown a detrimental effect on insulin action of high fructose intakes (>35% total

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energy), but again it is difficult to translate this intake to typical levels of consumption by human subjects[25]. Thus, although evidence supports a negative effect of high sucrose or fructose on insulin sensitivity in rodents, the applicability to human subjects is questionable.

Epidemiological studies

Modern Westernised diets contain an increased amount of carbohydrate and sugars and it is widely perceived that such diets may contribute to an increase in insulin resistance and risk of type 2 diabetes. A number of large-scale epidemiological studies have examined diet and the development of diabetes. A prospective study of 42 504 male healthcare professionals who did not have diabetes at baseline has found, using a Western dietary pattern score, a high risk of development of diabetes in those participants with the highest scores, particularly in obese participants[32]. The Western diet included frequent consumption of sweets and desserts, suggesting a high intake of carbohydrate and sugar; however, the definition also included red meat, processed meat, French fries and high-fat dairy products, which are associated with a high saturated fat intake, which is known to be associated with insulin resistance. Given the nature of dietary pattern analysis, it is difficult therefore to determine the effect of sugar and carbohydrate independent of other food types or energy intake.

The Nurses' Health Study[26] and the Health Professionals Study[33] were both large prospective epidemiological studies conducted in the USA that used FFQ to investigate the influence of diet on risk of developing diabetes. The Nurses' Health Study examined 65 173 women aged 40–65 years at outset. During 6 years of follow-up 915 new incident cases of type 2 diabetes were recorded[26]. The results show no association between total carbohydrate intake and risk of type 2 diabetes. However, diets with high glycaemic load and low cereal fibre content were found to be associated with increased risk. The Health Professionals Study examined 42 759 men aged 40–75 years and without diabetes at baseline. During 6 years of follow-up 523 incident cases of type 2 diabetes were recorded[33]. Like the Nurses' Health Study, the results show no association between total carbohydrate content and incidence of type 2 diabetes, although again a positive association with glycaemic load and an inverse association with fibre content were found, suggesting an effect of carbohydrate quality. However, sugars are not the major contributors to the glycaemic load of the diet in these studies. Furthermore, another large US study, The Iowa Women's Health Study, in older subjects has revealed no association with glycaemic load[34]. It is possible that the older subjects without diabetes at baseline in the latter study may have been a selected group with lower inherent risk of adverse effects of diet and development of diabetes.

The San Luis Valley Study, a US prospective epidemiological study that has examined the effect of diet on insulin resistance and risk of diabetes, included 1317 subjects with impaired glucose tolerance who were followed for 1–3 years[35]. Follow-up data included not only the development of diabetes but also measurement of fasting insulin levels as an indirect measure of insulin resistance. Contrary to the Nurses' Health Study[26] and the Health Professionals Study[33], an inverse association was found between total carbohydrate intake and insulin resistance and incidence of diabetes and no association was found between carbohydrate subtype and development of diabetes. However, a relationship was found between dietary fat and progression to diabetes. The reasons for the contradictory results are unclear but it is possible that the effects of diet may vary in subjects with established abnormalities of glucose metabolism, such as impaired glucose tolerance, compared with those at an earlier stage in the natural history of glucose intolerance.

There have also been a number of epidemiological studies that have examined the association between intake of dietary sugars and markers of insulin resistance[36]. Several studies have shown an inverse relationship between intake of dietary sugars and insulin resistance, others have revealed the opposite effect, while some further studies have revealed no association. It is possible that some of these inconsistencies may relate to methodological differences, including inaccuracy in reporting of dietary intake. It is also interesting to note that the studies showing a positive association are for South Asian adults in the UK and for African-American children in the USA[37,38], which could be explained by a genetic susceptibility to the detrimental effects of dietary sugars given the recognised high prevalence of diabetes in these ethnic groups.

Intervention studies

Studies examining the effect of fructose on insulin sensitivity have generally shown no association or an increase in insulin sensitivity with increased fructose intake across a range of subject groups, including those subjects with and without diabetes[25,36]. However, to the authors' knowledge there is only one study in the literature that has employed optimal assessment of insulin action using the euglycaemic clamp technique; this study has demonstrated an increase in insulin sensitivity in subjects with type 2 diabetes in response to a high fructose intake[39].

Several studies have suggested a detrimental effect of high sucrose intake on insulin resistance. An increase in fasting insulin and insulin response to a sucrose load has been demonstrated in subjects without diabetes in a cross-over trial comparing diets containing 30% energy from sucrose or wheat starch[40]. A further study has demonstrated a detrimental effect of more modest increases in sucrose (18% dietary energy) that more closely approximates intakes that are found in the US population[41]. However, the subjects for these studies were selected based on their insulin resistance at baseline or presence of hypertriacylglycerolaemia, which may limit the generalisability of the conclusions. The studies also utilised measurement of serum insulin levels as an indirect measure of insulin sensitivity. It is possible that chronic over-secretion of insulin may lead to receptor down-regulation and insulin resistance. A more recent study has examined the effects of a high-sucrose *v.* a high-starch diet on 24 h glucose and insulin profiles[42]. The higher immediate postprandial glucose and insulin profiles observed following

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the high-sucrose diet were found to be accompanied by lower troughs in insulin concentrations in the later postprandial period, with the consequence of similar 24 h area-under-the-curves for insulin after both the high-sucrose and high-starch diets despite differing patterns of response.

In order to investigate the effect of varying sucrose intake in the context of a diet with a fixed percentage energy from carbohydrate, a study has been performed to compare low *v*. high sucrose intakes as part of a balanced isoenergetic diet in overweight but otherwise healthy subjects[43]. Comparison of a 10% sucrose intake with a 25% sucrose intake was chosen as current dietary guidelines recommend restriction of sucrose to 10% total energy. The study utilised a two-step hyperinsulinaemic euglycaemic clamp combined with isotope-dilution methodologies to enable assessment of peripheral or whole-body insulin sensitivity as well as hepatic insulin sensitivity. The study also utilised continuous glucose monitoring to examine 24 h glycaemic patterns. Although the study was free living, all food was provided and subjects attended either daily or on alternate days to monitor adherence to the diet. The results show that a high sucrose intake has no detrimental effect on hepatic or peripheral insulin sensitivity or on glycaemic profiles. It is concluded that a high sucrose intake as part of a euenergetic weight-maintaining diet has no detrimental effect on insulin sensitivity in healthy overweight subjects who are not diabetic. However, further studies are required to examine older more-obese subjects and across a wider range of sucrose intakes to determine the generalisability of these results.

Role of fruit and vegetables

Alongside interest in the effect of macronutrients on insulin resistance and diabetes risk, research is also pursuing the effect of individual foods or entire food groups on these variables. Recently, fruit and vegetable intake has attracted substantial interest in this context. A systematic review published in 2007 has examined the association between the intake of fruit, vegetables and antioxidants and the risk of type 2 diabetes[44]. The review does not include dietary pattern studies, of which there are many that generally favour an association between diets rich in fruit and vegetables and markers of glycaemic control, insulin resistance and diabetes risk. Instead, the review focuses on more robust prospective cohort studies (five in total), finding that the consumption of three or more daily servings of fruit or vegetables is not associated with a substantial reduction in the risk of type 2 diabetes.

A few prospective studies, published since the systematic review, do however provide evidence of an inverse association between fruit and vegetable intake and diabetes risk. The EPIC-Norfolk Study has recently reported results of a 12-year follow-up of approximately 22 000 individuals[45]. A high consumption of fruit and vegetables was shown to be associated with a 22% reduction in risk of type 2 diabetes. Furthermore, the association with vitamin C was shown to be even stronger, equating to a 62% reduction in diabetes risk for the top quintile of plasma vitamin C. The authors contend that measurement error when assessing dietary intake may have attenuated the association between fruit and vegetable intake in their study and in previously published studies. A further prospective study from China has reported that in a cohort of 64 191 women vegetable, but not fruit, intake is inversely associated with risk of type 2 diabetes (relative risk 0·72 (95% CI 0·61, 0·85); $P<0·01$)[46]. However, in the EPIC-Norfolk study the association with diabetes risk was stronger for fruit than for vegetables[45].

Consistent with the observation of a strong association between plasma vitamin C and reduced risk of diabetes in EPIC-Norfolk[45], other studies in the literature have reported an association between intake or status of carotenoids, which are also considered to be potential markers of fruit and vegetable intake, and glucose metabolism. In the Botnia Dietary Study of participants at high risk of type 2 diabetes (182 first- and second-degree relatives of patients with type 2 diabetes) it was found that dietary carotenoid intake in men is inversely associated with fasting plasma glucose concentrations, whilst plasma β-carotene concentrations are inversely associated with insulin resistance, assessed by homeostasis model assessment[47]. An inverse association between serum carotenoids (particularly β-carotene and lycopene) and fasting serum insulin concentrations has also been noted in the third National Health and Nutrition Examination Survey[48] and inverse correlations between steady-state plasma glucose (calculated from insulin suppression test) and plasma concentrations of α-carotene, β-carotene and lutein have been found in a small study of thirty-six healthy volunteers who were not diabetic[49].

Randomised controlled trials will, of course, provide the most convincing evidence for a favourable effect of fruit and vegetable intake on insulin resistance. Some data do exist in this area, but only in the context of whole-diet interventions in which fruit and vegetable intake has been augmented as one component of a broader dietary intervention rather than being the single target of the intervention. Specifically, the Dietary Approaches to Stop Hypertension (DASH) diet and the Mediterranean diet have both been shown to have beneficial effects on insulin resistance and features of the metabolic syndrome[50–52]. The Tehran Lipid and Glucose Study studied the effect of a 6-month randomised controlled outpatient intervention on features of the metabolic syndrome[50]. Participants (approximately forty per group) were randomised to receive a control diet, a weight-reducing diet or the DASH diet (rich in fruits, vegetables, low-fat dairy products and whole grains and low in saturated fat and total fat) with reduced energy. Relative to the control diet the DASH diet was found to be associated with reductions in weight and fasting blood glucose. The weight-reducing diet was also found to result in a reduction in weight but not fasting blood glucose. The PREMIER randomised controlled trial has determined the effects of multi-component lifestyle interventions on blood pressure. The effect of the PREMIER interventions on insulin sensitivity was examined in a small subset of fifty-two participants (sixteen to eighteen per group) in the USA[51]. Participants with above-optimal blood pressure (systolic blood pressure 120–159 mmHg, diastolic blood pressure 80–95 mmHg)

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were randomised to one of three groups for 6 months: standard advice to follow the National High Blood Pressure Education Programme recommendations (weight loss if overweight, limiting alcohol and dietary Na intake, regular physical activity and eating a healthful diet; advice only); behavioural intervention in combination with standard advice (established); behavioural intervention, standard advice and specific guidance on the DASH diet (established + DASH). Insulin sensitivity, assessed by intravenous glucose tolerance test with minimal model analysis, was found to improve in the established + DASH group compared with the advice-only group. A Mediterranean diet study has reported a decrease in insulin resistance (assessed by homeostasis model assessment) and a reduction in the prevalence of the metabolic syndrome following a 2-year intervention in 180 patients with the metabolic syndrome[52]. A randomised controlled trial is currently underway to examine the effect of increased fruit and vegetable consumption, under weight-maintaining conditions, on insulin resistance using the gold standard euglycaemic hyperinsulinaemic clamp technique (NCT00874341).

In terms of possible explanations for a beneficial association between fruit and vegetable intake and insulin resistance, no clear mechanism exists as yet. Such a relationship may be mediated by the high fibre content of fruit and vegetables, as dietary fibre may be able to favourably modulate glucose homeostasis or insulin sensitivity[53]. However, results of a recent meta-analysis are not consistent with this theory[54]. The antioxidant properties of fruits and vegetables may also be important, as it is postulated that oxidative stress may impair insulin action[55] and an association between increased free radical production and reduced glucose disposal has been reported in an elderly group[56]. In reality, it may be a synergistic effect of the many phytochemicals found within fruit and vegetables that is responsible for any protective effect of fruit and vegetables on diabetes risk, and such effects are difficult to disentangle.

Weight-loss diets and insulin resistance

The risk of developing diabetes is strongly related to measures of adiposity rising exponentially as BMI increases in the overweight and obese range[57]. Combined with the rising prevalence of overweight and obesity this finding has resulted in intense interest in diets promoting weight loss. However, there is considerable debate about the most effective type of diet and the appropriate macronutrient composition to facilitate weight loss[58]. Traditionally, a hypoenergetic low-fat diet has been the most widely recommended. These diets supply balanced fat : carbohydrate : protein in reduced quantities to produce an energy deficit. Although low in fat, there is little evidence that low-fat diets cause weight loss independent of energy restriction. The success of this approach is strongly linked to adherence, although it is well recognised that this factor often declines over time[58].

Recently, a number of diets have been advocated that provide an alternative to challenging diet and lifestyle modification[59]. These options include diets that focus on carbohydrate restriction, the best known of which is the Atkin's diet[60]. It has been proposed that restriction of carbohydrate leads to metabolism of fat resulting in ketogenesis, which produces an unintentional reduction in energy intake as a result of suppression of appetite[58,59]. However, restriction of carbohydrate may be associated with an increase in fat intake and there is concern that this outcome may be associated with adverse effects on the risk of diabetes and CVD, particularly if there is an increase in saturated fat intake[58,59]. Similarly, high-protein weight-reduction diets are also claimed to reduce hunger and satiety.

When comparing different weight-loss diets it is important to consider a range of features in addition to the effectiveness for weight reduction. Diets should contain a broad range of foods to ensure nutritional adequacy and promote compliance. Low-carbohydrate diets may be deficient in micronutrients, including vitamins, minerals and fibre, and the monotonous nature of these diets may reduce their sustainability. The composition of weight loss is also important, i.e. the reduction in fat *v.* lean body mass. In the short term, low-carbohydrate diets are associated with a greater reduction in body water than body fat. It is also possible that differing macronutrient profiles may have varying effects on metabolic profiles and cardiovascular risk. Low-carbohydrate diets may adversely affect lipid levels if they contain high levels of saturated fat and also increase serum uric acid levels, whereas high protein intake may be harmful to renal function.

Although many alternative diets are portrayed as scientifically sound, there is limited evidence in relation to their long-term safety and efficacy, and in particular in relation to their effects on insulin resistance and development of diabetes and CVD. Several trials have shown that low-carbohydrate high-protein diets result in more weight loss over 3–6 months than conventional high-carbohydrate low-fat diets but this effect is not sustained at 1 year[61,62]. However, the novelty of the diet, media attention and the enthusiasm of the researchers could affect the adherence of participants to any type of diet. A key question is the long-term response to diets that emphasise a specific macronutrient profile. In a recent large trial 811 overweight adults were assigned to one of four diets to enable comparisons of low fat *v.* high fat, average protein *v.* high protein and over a range of carbohydrate intake[63]. Across the 2 years of follow-up the subjects were offered group and individual dietary instructional sessions. The participants were reported to have lost a maximal amount of weight after 6 months, with subsequent gradual weight regain after 12 months. Average weight loss at 6 months was reported to be 6 kg and at 2 years 4 kg, with no difference between diets. Satiety, hunger, satisfaction with the diet and attendance at group sessions were also found to be similar between diets. The diets were also shown to improve lipid-related risk factors and, with the exception of the diet with the highest carbohydrate content (65% total energy), decrease fasting serum insulin.

To investigate the effect of weight-loss diets with differing macronutrient profiles on insulin resistance a study has been performed to investigate the effects of a low-carbohydrate hypoenergetic diet (20% energy from

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carbohydrate, 60% energy from fat) with a low-fat hypoenergetic diet (60% energy from carbohydrate, 20% energy from fat, with equivalent protein intake to exclude this factor as a confounding variable) in overweight and obese subjects without diabetes[64]. Although the study was free living, all food was weighed and distributed and intake calculated to ensure a 2092 kJ (500 kcal)/d deficit on calculated energy requirements. Weight loss was found to occur in both groups across 8 weeks, with both groups losing approximately 7% of baseline weight, which is similar to the magnitude seen in diabetes prevention studies and is important in terms of disease prevention. Both diets were found to promote weight loss from the central body region and to be associated with comparable effects on insulin sensitivity assessed using the euglycaemic clamp technique. However, a difference in augmentation index (a measure of vascular compliance) between the two diets was demonstrated, which could not be explained by changes in conventional vascular risk factors. This observation is potentially of concern and if confirmed may suggest a potentially negative effect of a low-carbohydrate diet on long-term vascular health.

Diabetes prevention trials

Recently, two randomised controlled trials have specifically examined the effect of a lifestyle intervention in preventing type 2 diabetes[65,66]. In the Finnish Diabetes Prevention Study 522 overweight and obese subjects with impaired glucose tolerance were randomised to either a lifestyle intervention or a control group with follow-up over 3·2 years[65]. The lifestyle intervention included individualised counselling focused on achieving and maintaining healthy body weight, reducing fat intake, increasing fibre intake and increasing physical activity. The intervention was reported to be associated with a 58% reduction in the relative risk for development of type 2 diabetes. Each component of the intervention (weight loss, increase in physical activity, reduction in total and saturated fat intake and an increase in dietary fibre) was found to contribute to the risk reduction. Subjects who were diagnosed with diabetes were reported to show a tendency to consume a diet with lower carbohydrate and fibre content. A subset of subjects underwent assessment of insulin sensitivity, which was found to show a tendency to be higher in the intervention group compared with the control group, with a strong correlation between the improvement and weight loss.

In the US Diabetes Prevention Program 3234 obese adults with impaired glucose tolerance were randomised to a lifestyle intervention, metformin or placebo over 2·8 years[66]. The goals of the lifestyle intervention were to achieve and maintain a weight reduction of ≥7% initial body weight through a healthy low-fat diet and to engage in physical activity of moderate intensity, such as brisk walking, for ≥150 min/week. The lifestyle programme was reported to result in a 58% reduction in the incidence of diabetes, which is remarkably similar to the results of the Finnish Diabetes Prevention Study[65]. The lifestyle intervention was found to be more effective than metformin therapy, which reduced the incidence of diabetes by 31%. The study was not designed to test the relative contributions of dietary changes, increased physical activity and weight loss on the reduction in the risk of diabetes.

Conclusion

In conclusion, avoidance or delay in progression to type 2 diabetes has major benefits to patients in terms of increasing life expectancy and quality of life and potentially also in economic terms. Obesity is the single most important risk factor for type 2 diabetes. Currently, evidence from large-scale diabetes prevention trials, supported by smaller intervention studies focusing on effects on insulin resistance, suggest that weight loss achieved through a combination of exercise and diet is key to prevention of type 2 diabetes and amelioration of insulin resistance. In this setting evidence supports the use of weight-reduction diets that are low in fat and saturated fat and high in carbohydrate and fibre. However, when weight loss cannot be achieved with this approach, alternative diets centred on restriction of carbohydrate can be effective for weight loss, at least in the shorter term. The influence of dietary macronutrient intake on insulin resistance appears to be of secondary importance to the effect of weight loss. However, there is a lack of evidence relating to the effectiveness of low-carbohydrate diets in terms of diabetes prevention and cardiovascular risk. While the total amount of dietary carbohydrate does not appear to influence the risk of diabetes, the type of carbohydrate may be important. In the context of a euenergetic weight-maintenance diet in normal and overweight subjects dietary sugar or its restriction has no effect on insulin resistance, and it would appear that 'more is known about the adverse effects of sugar than is true'. Further studies examining the physiological effects of differing dietary carbohydrate intakes in relation to glycaemic index and their effects on insulin resistance and development of diabetes are needed, particularly in at-risk populations.

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