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REVIEW

Glycemic index in chronic disease: a review

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Aim: The intent of this review is to critically analyze the scientific evidence on the role of the glycemic index in chronic Western disease and to discuss the utility of the glycemic index in the prevention and management of these disease states.
Background: The glycemic index ranks foods based on their postprandial blood glucose response. Hyperinsulinemia and insulin resistance, as well as their determinants (eg high energy intake, obesity, lack of physical activity) have been implicated in the etiology of diabetes, coronary heart disease and cancer. Recently, among dietary factors, carbohydrates have attracted much attention as a significant culprit, however, different types of carbohydrate produce varying glycemic and insulinemic responses. Low glycemic index foods, characterized by slowly absorbed carbohydrates, have been shown in some studies to produce beneficial effects on glucose control, hyperinsulinemia, insulin resistance, blood lipids and satiety.
Method: Studies on the short and long-term metabolic effects of diets with different glycemic indices will be presented and discussed. The review will focus primarily on clinical and epidemiological data, and will briefly discuss *in vitro* and animal studies related to possible mechanisms by which the glycemic index may influence chronic disease.
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Introduction

Until recently carbohydrates have been classified as 'simple' and 'complex' based on their degree of polymerization; however, their effects on health may be better described on the basis of their physiological effects (ie ability to raise blood glucose), which depend both on the type of constituent sugars (eg glucose, fructose, galactose) and the physical form of the carbohydrate (eg particle size, degree of hydration). This classification is referred to as the glycemic index (GI). The GI is a quantitative assessment of foods based on postprandial blood glucose response (Jenkins *et al*, 1981, 1984), expressed as a percentage of the response to an equivalent carbohydrate portion of a reference food (white bread or glucose; Wolever *et al*, 1991). Carbohydrate foods consumed in isoglucidic amounts produce different glycemic responses (Jenkins *et al*, 1981) depending on the nature of the food and type and extent of food processing. The principle is that the slower the rate of carbohydrate absorption the lower the rise of blood glucose and the lower the GI value. Several health benefits exist for reducing the rate of carbohydrate absorption by means of a low GI diet. These include: reduced insulin demand, improved blood glucose control, and reduced blood lipid levels, all factors that may play important roles in the prevention or management of several chronic Western diseases including diabetes, coronary heart disease (CHD) and possibly certain cancers.

High GI foods are characterized by fast-release carbohydrate and higher blood glucose levels, resulting in greater insulin demand. Hyperinsulinemia is a characteristic condition of insulin resistance and could be seen as a way of coping with reduced insulin sensitivity which has *per se* the purpose of maintining circulating glucose levels. For the

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purpose of this review the two terms 'insulin resistance' and 'hyperinsulinemia' will be combined since they are often observed concomitantly.

A similarity has been noted between the lifestyle risk factors for insulin resistance (eg obesity, lack of physical activity, high intakes of refined carbohydrates) and the major chronic Western diseases, suggesting the hypothesis that hyperinsulinemia may be one of the promoting factors for these conditions (McKeown-Eyssen, 1994; Giovannucci, 1995). Epidemiological evidence suggests direct associations between GI (expressed as glycemic load, a measure of quality as well as quantity of total carbohydrate intake and thus an indirect measure of dietary insulin demand) and risk of diabetes (Salmeron *et al*, 1997a,b) as well as CHD (Liu *et al*, 2000) and obesity (Ludwig *et al*, 1999; Table 1). Evidence is also emerging of a possible link with cancers of the colon (Franceschi *et al*, 2001) and breast (Augustin *et al*, 2001; Table 1).

This review will focus on the GI and its relation to the etiology and clinical management of diabetes, CHD, obesity and the prevention of cancer.

Glycemic index and the slow-release carbohydrate

The rate of hydrolysis of food in the gastrointestinal tract and the rate of gastric emptying determine the absorption rate which, in turn, determines the extent and duration of the glucose rise after a meal. Circulating insulin levels are determined directly by β-cell stimulation by absorbed products of digestion (ie glucose and amino acids) and indirectly by their action on incretins (eg gut inhibitory peptide) released from gut cells. Neural and endocrine stimuli also play a role. The system is therefore responsive to the amount of carbohydrate and its rate of absorption.

The dietary GI provides an indication of the rate at which carbohydrate foods are digested (Jenkins *et al*, 1981; Englyst *et al*, 1999). It allows ranking of foods from those which give rise to the highest blood glucose and insulin responses (high glycemic food) to those associated with the lowest blood glucose and insulin responses (low GI foods). The reference food is white bread with a GI set at 100 (Table 2). Low-GI foods can therefore be viewed as a dietary tool to reduce glucose absorption rate and insulin output (Table 3). The implications of prolonging absorption time (Table 4) may be

Table 1 Relationship between dietary glycemic index and chronic disease in epidemiological studies

Reference	*Disease state*	*Study design*	n	*Difference in GI*	*Association OR or RR (95% CI)*	*Comments*
Salmeron *et al*, (1997a)	Diabetes (type 2)	Cohort	42 759	Quintiles GI 65–79	1.37* (1.02–1.83), GI 1.25 (0.90–1.73) GL	Significance for 5th quintile of GI after fiber adjustment; for 5th quintile of GL after fiber adjustment. No GL association
Salmeron *et al*, (1997b)	Diabetes (type 2)	Cohort	65 173	Quintiles GI 64–79	1.37* (1.09–1.71) GI 1.47* (1.16–1.86) GL	Significance for 5th quintile of GI after fiber adjustment; significance for 5th quintile of GL after fiber adjustment
Meyer *et al*, (2000)	Diabetes (type 2)	Cohort	35 988	Quintiles GI < 58 > 80	0.89 (0.72–1.10) GI 0.95 (0.78–1.16) GI	For 5th quintile of GI after multiple adjustments. For 5th quintile of GL after multiple adjustments. No GI or GL associations
Liu *et al*, (2000)	CHD	Cohort	75 521	Quintiles GI 72–80	1.31* (1.02–1.68) GI 1.98* (1.41–2.77) GL	Significance for 5th quintile of GI after multiple adjustments. Significance for 5th quintile of GL after multiple adjustments
van Dam *et al*, (2000)	CHD	Cohort	646	Tertiles GI 77–85	1.11 (0.66–1.87)	For 3rd tertile of GI after multivariate adjustments. No GI association
Slattery *et al*, (1997)	Colon cancer	Case-control	1993 (cases) 2410 (controls)	Not reported	1.37* (1.04–1.82) M 1.34* (1.00–1.81) F	Significance for 5th quintile of GI after multiple adjustments. GI was calculated differently from other studies. GL was not calculated
Franceschi *et al*, (2001)	Colon cancer	Case-control	1953 (cases) 4154 (controls)	Quintiles GI < 71 > 80	1.9* (1.5–2.4) GI 1.9* (1.5–2.4) GL	Significance for 5th quintile of GI after multiple adjustments. Significance for 5th quintile of GL after multiple adjustments
Augustin *et al*, (2001)	Breast cancer	Case-control	2569 (cases) 2588 (controls)	Quintiles GI < 70 > 79	1.36* (1.14–1.64) GI 1.34* (1.10–1.61) GL	Significance for 5th quintile of GI after multiple adjustments. Significance for 5th quintile of GL after multiple adjustments

*Significantly different from reference category (eg 1st percentile).
GI = glycemic index; GL = glycemic load; F = female; M = male.

important in the etiology of chronic disease and will be discussed in relation to the major chronic conditions.

Factors affecting the rate of glucose absorption from starchy food and therefore the GI value include (1) the nature of the food and (2) the type and extent of food processing (Table 5). The former includes the ratio of amylose to amylopectin present in the raw food (Behall *et al*, 1988) and the type of monosaccharide components, the amount and type of dietary fiber (Jenkins *et al*, 1978), the presence of large amounts of fat or protein (Nuttall *et al*, 1984; Wolever *et al*, 1985; Collier *et al*, 1986; Bornet *et al*, 1987), antinutrients such as phytic acid, lectins and tannins (Yoon *et al*, 1983; Thompson *et al*, 1984; Rea *et al*, 1985) and nutrient–starch interactions in carbohydrate-containing foods, such as in wheat products (Jenkins *et al*, 1987a). Extrusion, flaking, grinding, canning, storing and cooking of the carbohydrate-containing foods can affect the particle size and the integrity of the starch granules (Jenkins *et al*, 1988a) and plant cell walls (Ellis *et al*, 1991), making the carbohydrate portion more accessible to digestive enzymes (Wolever, 1990; Collins *et al*, 1981).

Fat and protein may modify the glycemic response to a carbohydrate food by slowing gastric emptying (Welch *et al*, 1987) and increasing insulin secretion, respectively (Nuttall *et al*, 1984; Gannon *et al*, 1988). However, it has been shown that neither fat nor protein in the amounts found in most foods (with the exception of peanuts and most nuts)

Table 2 Glycemic indices of some common foods

Food	*GI_{wb}*	*GI_g*
Sucrose	92	67
Glucose	138	100
Fructose	32	23
Honey	104	75
Milk	39	28
Beans	40–60	30–43
Lentils	30–40	22–30
Pasta	50–70	36–51
Pizza	86	62
Cornmeal/cornflakes	100–120	72–87
White bread	100	72
Pumpernickel	58	42
Potatoes	120	87
Banana, ripe	85	62
Banana, underripe	43	31
Oranges	62	45
Grapefruit	36	26
Cherries	32	23
Tomatoes	13	9

GI_{wb}, standard food: white bread. GI_g, standard food: glucose ($GI_g = GI_{wb}/1.38$).

Table 3 Factors that can reduce the rate of glucose absorption and insulin levels

Soluble fiber
Increased meal frequency
Amylase inhibitors (acarbose)
Low glycemic index foods

Table 4 Possible effects of prolonging carbohydrate absorption time

Lower postprandial glucose rise (Jenkins *et al*, 1990,1992; Bertelsen *et al*, 1993; Jones *et al*, 1993)
Reduced daily mean insulin levels (Jenkins *et al*, 1990,1992; Bertelsen *et al*, 1993; Jones *et al*, 1993)
Flatter gastric inhibitory polypeptide response (Jenkins *et al*, 1990,1992; Bertelsen *et al*, 1993)
Decreased 24 h urinary C-peptide output (Jenkins *et al*, 1989,1992)
Prolonged suppression of plasma free fatty acids (Jenkins *et al*, 1990)
Reduced urinary catecholamine output (Jenkins *et al*, 1990)
Lower total and LDL cholesterol levels (Jenkins *et al*, 1989,1995; Arnold *et al*, 1993; Cohn 1964)
Reduced hepatic cholesterol synthesis (Jones *et al*, 1993)
Decreased serum apolipoprotein B levels (Jenkins *et al*, 1989)
Decreased serum uric acid levels (Jenkins *et al*, 1995)
Raised urinary uric acid excretion (Jenkins *et al*, 1995)

Adapted from Jenkins *et al* (1995).

Table 5 Factors that infuence the glycemic response and the glycemic index

Factors that affect GI	*Factors that decrease GI*	*Factors that increase GI*
Nature of starch	↑ Amylose/amylopectin	↓ Amylose/amylopectin
Nature of monosaccharide components	Fructose	Glucose
	Galactose	
Viscous fiber	↑ Guar	↓ Guar
	↑ β-glucan	↓ β-glucan
Cooking/food processing	Parboiling	Extruding
	Cold extrusion	Flaking
		Popping
Particle size	Large particles	Grinding (small particles)
Ripeness and food storage	Unripeness	Ripeness
	Cooling	
α-Amylase inhibitors	↑ Lectins	↓ Lectins
	↑ Phytates	↓ Phytates
Nutrient-starch interactions	↑ Protein	↓ Protein
	↑ Fat	↓ Fat

↑ = high levels.
↓ = low levels.

significantly alters the glycemic response (Wolever *et al*, 1994). Protein levels of 30 g and fat levels of 50 g per 50 g of available carbohydrate may decrease the GI (Wolever *et al*, 1994).

Thus far more than 500 foods have been tested for assessment of their GI, and values are summarized in GI tables (Foster-Powell & Brand Miller, 1995). Low GI foods include vegetables, fruit, legumes and wholegrain breads such as pumpernickel, while high-GI foods include most refined grain products such as white bread, potatoes and rice (Table 2). The GI tables may have various applications, for instance in designing diets aimed at long-term blood glucose control, as some researchers have found that the GI may be applied not only to single foods but also to mixed meals (Wolever *et al*, 1985; Chew *et al*, 1985; Collier *et al*, 1986; Bornet *et al*, 1987; Le Floch *et al*, 1991). The GI of mixed meals has also been shown to correlate positively with the insulinemic index (a measure of postprandial insulin rise; Bornet *et al*, 1987). However, the debate on the clinical utility of the GI concept has not been resolved. Some investigators have criticized the usefulness of the GI in mixed meals, suggesting the GI of each component of a meal cannot predict the glycemic response to that meal (Coulston *et al*, 1987). Despite the authors' conclusions, their study indeed showed that mixed meals based on high- and low-GI foods produce completely different glycemic effects (Figure 1 in Coulston *et al*, 1987). The discrepancies between studies may be explained partly by methodological differences, principally the method of calculation of the glycemic response area (eg total area above and below baseline *vs* area above baseline), the method of blood sampling (arterial *vs* venous blood) and the length of the study (ie the time between the meal and the last glycemic measurement; Wolever *et al*, 1991). When using the same methodology the GI of mixed meals can be predicted consistently by calculating the mean GI value of their components weighted by the carbohydrate content of each component and by the fact that the correlation between the GI of mixed meals and the mean GI value for their components ranges from 0.84 to 0.99 (Wolever & Jenkins 1986, Wolever *et al*, 1991; Truswell, 1992).

The glycemic index in diabetes

Relatively few prospective studies assessed the association of GI and type 2 diabetes risk (Salmeron *et al*, 1997a,b). Salmeron and collegues have looked at this and found that diets with a high GI increased the risk of type 2 diabetes by 37% (highest *vs* lowest quintiles) after correcting for known risk factors, in a cohort of over 42 000 men during a 6 y follow-up (Salmeron *et al*, 1997a). Similar results were observed in the Nurses cohort ($n = 65\ 173$), where a positive association betweeen type 2 diabetes and glycemic load (GL) was also shown (the product of the average dietary GI and total carbohydrate intake and therefore a measure of total insulin demand; Salmeron *et al*, 1997b). The GI and GL were not associated with type 2 diabetes in the Iowa Women's Health Study (Meyer *et al*, 2000). This study, however, included an elderly cohort which could introduce a selection bias.

The link between high GI and high GL diets and diabetes may relate to glucose peaks and increased insulin demand. High GI foods lead to rapid rises in blood glucose and insulin levels. Hyperinsulinemia, in turn, may downregulate insulin receptors and therefore reduce insulin efficiency, resulting in insulin resistance (Virkamaki *et al*, 1999). This condition may act in a vicious circle by increasing blood glucose concentrations and insulin secretion as shown in Figure 1. Insulin resistance is a risk factor for type 2 diabetes (Reaven, 1993; Nijpels, 1998). Also, poor glucose control has been shown to result in a greater incidence of long term macrovascular and microvascular complications in both type 1 and 2 diabetic patients (The Diabetes Control and Complications Trial Research Group, 1993; UK Prospective Diabetes Study Group, 1998; Stratton *et al*, 2000). Each 1% reduction in mean hemoglobin-A_{1c} (HbA_{1c}) was associated with a 21% reduction in risk for severe end points related to diabetes (eg mortality, myocardial infarction, heart failure, stroke, amputation, retinopathy, cataract extraction; Stratton *et al*, 2000).

Low-GI foods tend to delay glucose absorption thereby resulting in reduced peak insulin concentrations and overall insulin demand. Several studies have found improvements in glycemic control with low-GI diets. In a group of 32 patients with CHD fed a low-GI diet for 4 weeks, significant improvements in insulin sensitivity were reported as suggested by lower insulin requirements necessary to handle a standard glucose load and by the enhanced insulin-induced glucose uptake in adipocytes (Frost *et al*, 1996). Low-GI diets have been shown in other studies to reduce blood glucose levels and urinary C-peptide output, as a measure of insulin secretion, also in healthy subjects (Burke *et al*, 1982; Jenkins *et al*, 1987b). Low-GI diets also improved glycemic control in diabetic patients, as indicated by reductions in glycosylated

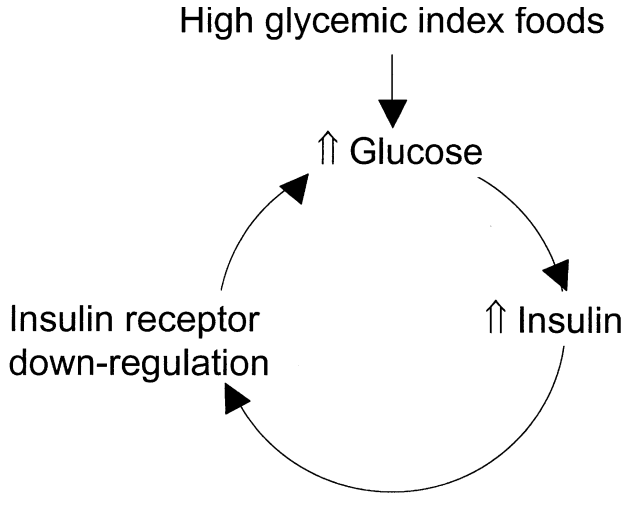

Figure 1 Potential mechanism for the relationship between high glycemic index foods and insulin resistance. (Adapted from Jenkins *et al*, 2000).

proteins (serum fructosamine or HbA_{1c}) in 10 of the 14 studies that measured these variables (Table 6). It should be noted that changes in HbA_{1c} levels tend to be seen after 3 months of dietary intervention. In most of these studies diets were balanced for macronutrient intake and on average they resulted in a 20% difference of dietary GI. One study achieved a 31% GI difference between the test and control group by altering the structure of the starchy food by using the same foods processed differently (eg whole *vs* milled grain or seeds, whole *vs* ground beans, parboiled rice *vs* sticky rice), thereby avoiding alterations in the proportions of macronutrients, micronutrients and phytochemicals. In this trial a decrease in both fasting glucose and insulin levels was achieved in the low GI group (between- and within-group differences), as well as significant reductions in fructosamine levels (within-group difference; Jarvi *et al*, 1999). Generally, cross-sectional data appear to support the results of clinical trials (Wolever *et al*, 1999, Buyken *et al*, 2001).

A cross-sectional study on 272 type 1 diabetic patients found a significant positive correlation between HbA_{1c} and dietary GI, as assessed by a 3-day food record (Wolever *et al*, 1999).

The health benefits of a low-GI diet is also supported by a number of investigations on meal frequency which was used as a model for a reduced rate of carbohydrate absorption. Increasing meal frequency in isocaloric diets in diabetic and non-diabetic subjects has been shown to reduce postprandial glucose rise (Jenkins *et al*, 1992, Bertelsen *et al*, 1993; Jones *et al*, 1993), daily insulin levels (Jenkins *et al*, 1992; Bertelsen *et al*, 1993; Jones *et al*, 1993) and 24 h urinary C-peptide output (Jenkins *et al*, 1989,1992). Increasing meal frequency is now included in the recommendations given for the management of diabetes by the American Diabetes Association (1994). While the use of the GI is not universally accepted, several health organizations throughout the world now recommend consuming low-GI foods in the management of type 2 diabetes (European Association for the Study of Diabetes, 1995; Buchhorn, 1997) and as part of the healthy diet recommended to the general population (FAO/ WHO report, 1998).

Two main mechanisms of action could be involved in the regulation of insulin sensitivity and glucose levels by low-GI diets: (1) free fatty acid levels; and (2) oxidative stress. In general, rapidly absorbed carbohydrates stimulate a large insulin rise, followed by a rapid blood glucose fall, often below baseline values. This could result in a counter-regulatory response with the release of free fatty acids, creating an insulin-resistant environment (Piatti *et al*, 1991; Boden *et al*, 1991) and reduced glucose tolerance. Ingestion of a slow release carbohydrate food (eg uncooked cornstarch) at bedtime was shown to produce a substantial suppression of nocturnal free fatty acid levels and postprandial improvements in breakfast glucose levels possibly due to reduced nocturnal lipolysis (Axelsen *et al*, 1997,1999a). A slow-release carbohydrate food taken in the evening can also prevent nocturnal hypoglycemia in patients with insulin-dependent diabetes mellitus (Axelsen *et al*, 1999b).

Oxidative stress defined as a disturbance in the balance between free radical production and antioxidant capacity, may play a major role in the micro- and macro-angiopathic complications of diabetes (Baynes, 1991). Diabetes has been associated with enhanced oxidative stress in several studies (Cominacini *et al*, 1994; Tsai *et al*, 1994; Beaudeux *et al*,

Table 6 Effect of low GI foods on glycosylated proteins in type 1 and 2 diabetes

Diabetes type	*Study design*	n	*Duration (weeks)*	*Change in diet GI value*[a]	*Change in glycosylated proteins (%)*	*Type of glycosylated proteins*	*Reference*
1	Clinical trial	7	6	−12	−19†*	HbA_{1c}	Collier *et al* (1988)
1	Clinical trial	8	3	−14	−18†*	Fructosamine	Fontvieille *et al* (1988)
1	Clinical trial	9	2	−27	−6.5††	Fructosamine	Lafrance *et al* (1998)
1	Clinical trial	54	24	−20	−5.5††	HbA_{1c}	Giacco *et al* (2000)
1	Clinical trial	104	52	−1.2	−6.5††*	HbA_{1c}	Gilbertson *et al* (2001)
1	Cross-sectional	2054	—	−14	−7.6* (highest *vs* lowest quartile)	HbA_{1c}	Buyken *et al* (2001)
2	Clinical trial	8	2	−23	−6.6†* −2.6††	HbA_{1c}	Jenkins *et al* (1988b)
2	Clinical trial	16	12	−14	−11†*	HbA_{1c}	Brand *et al* (1991)
2	Clinical trial	6	6	−28	−8††*	Fructosamine	Wolever *et al* (1992a)
2	Clinical trial	15	2	−27	−3.4††*	Fructosamine	Wolever *et al* (1992b)
2	Clinical trial	25	12	−5	−11†*	Fructosamine	Frost *et al* (1994)
2	Clinical trial	20	3	−31	−5.9†* −2.5††*	HbA_{1c} Fructosamine	Jarvi *et al* (1999)
2	Clinical trial	28	4	−20	−1.8††	Fructosamine	Luscombe *et al* (1999)
1 and 2	Clinical trial	18	5	−26	−13††*	Fructosamine	Fontvieille *et al* (1992)
1 and 2	Clinical trial	24	4	−5	−3††	HbA_{1c}	Calle-Pascual *et al* (1988)

*Significant effect ($P < 0.05$). †Treatment difference from baseline (within low GI treatment); ††end-point difference (between treatments).
[a]From high GI diet (reference food: white bread).

1995), although not in all (Jenkins *et al*, 1996; Sanchez-Quesada *et al*, 1996) and with reduced blood levels of antioxidants (Maxwell *et al*, 1997; Ceriello *et al*, 1998b). Recent findings suggest that metabolic processes following a meal may increase oxidative stress (Ceriello *et al*, 1999; Rao & Agarwal, 1999). A direct link has been found between postprandial glycemia and the induction of oxidative stress (Ceriello *et al*, 1998a,1999) that can be reversed by antioxidants (Paolisso *et al*, 1993,1994; Sharma *et al*, 2000). In this respect, possible mechanisms of action of low-GI diets include reduction of: (i) glucose toxicity, ie the effect of high glucose levels in depressing pancreatic function through free radical damage of pancreatic β cells; and (ii) glycosylation of proteins and key enzymes responsible for metabolic processes (advanced glycosylation end products — AGE, Paolisso *et al*, 1992; Ceriello, 2000). No studies thus far have tested the effects of various GI isocaloric diets on oxidative stress in diabetic patients or healthy individuals.

The glycemic index in coronary heart disease

Epidemiological evidence suggests that low-GI diets may decrease the risk of CHD independently (Liu *et al*, 2000) and as part of a healthy lifestyle (Stampfer *et al*, 2000). One study looked at the relationship between GL and CHD in a cohort of 75 521 women followed for 10 y (Liu *et al*, 2000). A direct association emerged after adjusting for known and suspected risk factors (OR = 1.98; CI 1.41 – 2.77, highest *vs* lowest quintile). These findings were not confirmed by the Zutphen Elderly Study which, however, included a very small GI range and an elderly cohort, thereby introducing a possible element of selection bias (van Dam *et al*, 2000).

The possible beneficial effects of a low-GI diet in the prevention of CHD may be explained by improvements in blood lipid profiles, insulin levels, thrombolitic factors and endothelial function.

Hyperlipidemia is a risk factor for CHD and it is one of the most common metabolic dysfunctions associated with diabetes, a disease responsible for a two-fold increase in mortality due to vascular disease (Stamler *et al*, 1993; Lotufo *et al*, 2001). Long-term studies, aimed at determining the metabolic effects of isocaloric macronutrient-balanced diets with high- *vs* low-GI foods, have been shown to significantly reduce serum cholesterol and triglyceride levels in hyperlipidemic and diabetic patients (Jenkins *et al*, 1987c; Wolever *et al*, 1992a,b). Significant reductions were seen in total cholesterol (-8.8%), low-density lipoprotein cholesterol (LDL-C; -9.1%) and triglyceride (-19.3%) with no change in high-density lipoprotein cholesterol (HDL-C; Jenkins *et al*, 1987c). Total cholesterol reductions of 7% were also found in diabetic patients (Wolever *et al*, 1992a,b). More recently Jarvi *et al* (1999) were able to obtain lipid reductions comparable to those of statins (20 – 30% from baseline), after 3 weeks on a low-GI diet.

Studies on high meal frequency (eg nibbling *vs* gorging) have been conducted to simulate slow absorption and thus to mimic the effects of a low-GI diet. The 'nibbling' *vs* 'gorging' paradigm has shown that increasing meal frequency (from 3 to >9 meal/day) reduced total and LDL cholesterol, apolipoprotein-B and serum uric acid levels in healthy subjects, after a period of 2 weeks (Arnold *et al*, 1993; Jenkins *et al*, 1989, 1995; Jones *et al*, 1993). Significant lipid reductions in total and LDL cholesterol (0.23, 0.16 mmol/l, respectively) were also reported in the Rancho Bernardo trial on more than 2000 men and women aged 50 – 89 y, when meal frequency was increased from 1 – 2 meals per day to 4 meals per day (Edelstein *et al*, 1992).

There have been concerns that high carbohydrate intakes at the expense of fat, particularly monounsaturated fat (Coulston *et al*, 1989; Mensink and Katan, 1987; Garg *et al*, 1994) could result in a rise in triglycerides and very-low-density lipoproteins and a suppression of HDL levels, which could translate into a higher risk of heart disease (Gordon *et al*, 1989; Stampfer *et al*, 1996; Vega & Grundy, 1996; Hokanson & Austin, 1996). However, not all carbohydrate-rich diets may produce the same effects on HDL levels, as low-GI diets may confer a more favorable lipid profile compared with high-GI diets. Lowering the dietary GI by at least 12 points reduced triglycerides by approximately 9% in 10 out of 11 studies (Brand Miller, 1994) and recent data showed that a high carbohydrate diet made of low-GI foods significantly increased HDL levels by 5.4% compared to an isocaloric high carbohydrate/high GI diet (Luscombe *et al*, 1999). In addition, cross-sectional data (Frost *et al*, 1999; Ford & Liu, 2001) showed that dietary GI was inversely related to HDL cholesterol levels, which in turn were inversely related to triglycerides, and that GI was a stronger predictor of serum HDL levels than dietary fat (Frost *et al*, 1999). Other investigators have shown that the unwanted HDL reductions seen with some high carbohydrate diets may be transient (Heilbronn *et al*, 1999).

The proposed mechanisms for lipid modulation by low-GI foods compared to high GI foods may include: (1) lower insulin-stimulated HMG-CoA reductase activity (the rate-limiting enzyme in cholesterol synthesis; Rodwell *et al*, 1976), as a result of a reduced rate of carbohydrate absorption; (2) impaired bile acid and cholesterol reabsorption from the ileum due to the typically high fibre content of low-GI foods (Kritchevsky & Story 1974; Jenkins *et al*, 1993); (3) inhibition of hepatic cholesterol synthesis by the short chain fatty acid propionate, a by-product of colonic fermentation (Illman *et al*, 1988; Wolever *et al*, 1988; Wright *et al*, 1990); (4) reduced inflammatory response. Some evidence suggests a possible role of insulin in stimulating acute-phase proteins (O'Riordain *et al*, 1995; Thompson *et al*, 1991) which have been directly related to intra-abdominal fat and inversely related to insulin-stimulated glucose disposal (Sites *et al*, 2002). HDL is considered a negative acute-phase protein (Malle *et al*, 1993) and has been found to be negatively associated to C-reactive protein (CRP) and acute and

chronic inflammatory states (Bausserman *et al*, 1988; Rossner, 1978; Hardardottir *et al*, 1994). HDL may reduce the inflammatory response by binding to stimulated T cells thus blocking their interaction with monocytes and consequently inhibiting TNF-α and IL-1β (Hyka *et al*, 2001). A possible mechanism could therefore be that lower glucose raises after low-GI foods may reduce the inflammatory response and raise HDL levels, when compared to high-GI foods.

Regulating insulin levels may be important not only in diabetic patients, but also in healthy subjects as hyperinsulinemia has been directly associated with CHD in previously healthy populations (Ducimetiere *et al*, 1980; Pyorala *et al*, 1985; Despres *et al*, 1996). Hyperinsulinemia has recently been found to moderately increase cardiovascular mortality in middle-age men (Lakka *et al*, 2000) and insulin resistance, a risk factor for CHD (Reaven, 1993) has been shown to respond to manipulations of the dietary GI (Frost *et al*, 1998). Patients with a history of CHD were randomized to either a low- or a high-GI diet (15% GI difference). After the 4 week treatment period an oral glucose tolerance test was performed following an overnight fast and a fat biopsy was obtained to assess *in vitro* glucose uptake in adipocytes. Less insulin was needed to handle a standard glucose challenge and increased insulin-stimulated glucose uptake was observed in the low-GI group, hence suggesting an improvement in insulin resistance (Frost *et al*, 1996).

Finally, when looking at thrombolytic factors Jarvi *et al* (1999) showed a significant reduction of 54% in plasminogen activator inhibitor-1, a marker of increased coagulation, after 3 weeks on a low-GI diet compared to a high-GI diet where energy, macro- and micro-nutrients were balanced in all subjects. Although the mechanisms need to be elucidated some evidence suggests that hyperglycemia and hyperinsulinemia may lead to impaired fibrinolysis and thrombosis as shown by clinical (Calles-Escandon *et al*, 1998) and correlational studies (Juhan-Vague *et al*, 1989; Meigs *et al*, 2000), thereby increasing the risk of CHD (Gerstein & Yusuf, 1996; Ruige *et al*, 1998).

In relation to endothelial function there is some evidence for a role of hyperglycemia in endothelial cell dysfunction possibly through increased generation of oxygen free radicals (Tesfamariam & Cohen 1992; Graier *et al*, 1996; Cosentino *et al*, 1997). Endothelium-dependent vasodilation impaired by dietary glucose ingestion seemed to be restored by consumption of antioxidant vitamins (Levine *et al*, 1996; Title *et al*, 2000; Skyrme-Jones *et al*, 2000). Diabetic patients (type 1 and 2) tend to be more prone to endothelial dysfunction (eg decreased endothelium-dependent vasodilation) and to have higher levels of oxidative stress than healthy populations (Clarkson *et al*, 1996; Williams *et al*, 1996; Akkus *et al*, 1996; Santini *et al*, 1997; Ceriello *et al*, 1998b) and in healthy individuals postprandial hyperglycemia appears to result in increased oxidative stress (Koska *et al*, 1997; Ceriello *et al*, 1998a; Kawano *et al*, 1999).

Also, fasting and postprandial glucose levels were related to CHD in a metaregression analysis of 20 studies including almost 100 000 people, followed for at least 12 y (Coutinho *et al*, 1999).

The glycemic index in obesity

Obesity is a risk factor for several chronic diseases including NIDDM, CHD and some types of cancer (Must *et al*, 1999). The prevalence of overweight (body mass index (BMI) $> 25\,kg/m^2$) and obesity (BMI $> 30\,kg/m^2$) are estimated to be 63 and 55% among American middle-aged men and women, respectively (Must *et al*, 1999), and the increase in prevalence of obesity in the last two decades is 8% (Kuczmarski *et al*, 1994).

Of the dietary factors, fat has been considered by some the main culprit (Astrup & Raben, 1992; Golay & Bobbioni, 1997); however, at the same time as the prevalence of overweight increased there has been a reduction in fat intake in the United States from 42 to 34% of total energy (Lenfant & Ernst, 1994; Nicklas, 1995), with a concomitant increase in carbohydrate intake. In highly industrialized countries the major sources of carbohydrates are refined foods which tend to be quickly absorbed and have high GI values.

Generally, low-GI foods are associated with greater satiety compared to high-GI foods or meals (Haber *et al*, 1977; Leathwood & Pollet, 1988; Rodin *et al*, 1988; Holt *et al*, 1992; Holt & Miller, 1994; Van Amelsvoort & Weststrate, 1992; Liljeberg *et al*, 1999). Recently Ludwig *et al* (1999) have studied the effect of high-, medium- or low-GI breakfast meals on subsequent *ad-libitum* food intake in obese teenage boys. They observed reductions in energy intake of 53 and 81% in the medium- and low-GI groups, respectively, compared to the high-GI group, 5 h after breakfast. These results suggest that in isoenergetic meals, slowly digested carbohydrate-rich foods may allow a sense of satiety to last longer than rapidly digested foods. The characteristic effects of high-GI foods, such as fast carbohydrate absorption, large blood glucose and hormonal (insulin/glucagon) fluctuations, together with reduced satiety, could favour overnutrition in the long run (Haber *et al*, 1977). In particular, the hypoglycemic undershoot, a characteristic effect of high-GI foods, may induce hunger. This may be explained by high-insulin and low-glucagon levels, triggered by high-GI foods, inducing glucose storage, inhibiting lipolysis and consequently reducing glucose availability for metabolic oxidation (hypoglycemic undershoot). This metabolic state could be seen as a fasting state and would trigger glucagon release and hunger signals. Low-GI foods, however, tend to maintain glucose and insulin at a moderate level avoiding the hypoglycemic state. Also, low-GI foods that are rich in dietary fiber may produce a distention of the gastrointestinal tract which may further explain the enhanced satiety level. Cholecystokinin (CCK), a gut peptide that induces satiety, is thought to be directly affected by gastric volume. Meal GI has been found inversely proportional to CCK response and satiety (Holt *et al*, 1992), suggesting a possible role of gastric volume and of bulky foods in maintenance of appetite suppression.

Long-term studies on the impact of low-GI diets in the management and prevention of obesity are, however, necessary in order to confirm the promising short-term trials.

Glycemic index and cancer

The amount of evidence on the relationship between GI and cancer is scant at present. Three epidemiological studies have looked at this and found direct associations for colorectal and breast cancer (Slattery *et al*, 1997; Franceschi *et al*, 2001; Augustin *et al*, 2001).

However, several lines of evidence point to a possible role of the GI in the development of cancer. McKeown-Eyssen (1994) and Giovannucci (1995) hypothesized that hyperinsulinemia/insulin resistance may promote colorectal cancer and possibly other types of cancers related to Western lifestyle (Bruning *et al*, 1992). High intakes of energy and refined carbohydrates, low intake of vegetables, fruit and dietary fiber, lack of physical activity, obesity, diabetes, hyperinsulinemia and high levels of insulin-like growth factors (IGFs) have been implicated in the etiology of various types of cancer (Giovannucci, 1999). Evidence supporting a possible role of the GI or the GL in cancer etiology is still limited and will be discussed in this present review by briefly presenting *in vitro*, animal and human studies, including dietary (eg carbohydrates) and non-dietary factors (eg diabetes, growth factors) that may influence the risk of cancer through the insulin hypothesis.

Colorectal cancer

The influence of the GI or GL has been little studied in relation to colorectal cancer. One case–control study suggests a direct association between dietary GI and colon cancer risk of the proximal site, after adjusting for age, BMI, physical activity, use of aspirin or other non-steroidal anti-inflammatory drugs, family history of colorectal cancer, non-carbohydrate energy intake, dietary calcium and fiber (Slattery *et al*, 1997). Dietary GI as well as GL (an indirect measure of dietary insulin demand) were assessed in a large case–control study and found to be directly associated with colorectal cancer risk (OR for GI, highest *vs* lowest quintile = 1.7; and for GL, OR = 1.8). The results were adjusted for sociodemographic factors, physical activity, number of daily meals, and intakes of fiber, alcohol and energy. ORs were especially elevated for cancer of the colon (1.9 for GI and 2.0 for GL; Franceschi *et al*, 2001). These data suggest the more refined the carbohydrates in the habitual diet, the greater the risk for cancer of the colorectum.

Less convincing evidence however comes from animal studies where differences in dietary GI did not affect the growth of aberrant crypt foci, a preneoplastic marker of colon cancer (Corpet *et al*, 1998). Also, high-GI diets did not seem to stimulate colon carcinogenesis in an animal model although the investigators found a possible protective effect of pasta which reduced intestinal adenoma incidence when compared to high sucrose and glucose diets (Caderni *et al*, 1997).

Carbohydrates are among dietary factors that influence both glucose and insulin levels and also appear related to colorectal cancer risk. The main carbohydrate classes studied are starch (or polysaccharides) and sugar. Epidemiological observations report a direct association between starch or polysaccharide intake and colorectal cancer although some did not achieve statistical significance (Tuyns *et al*, 1987; Haenszel *et al*, 1980; Slattery *et al*, 1988; Zaridze *et al*, 1993; Franceschi *et al*, 1998; Macquart-Moulin *et al*, 1986). However, when the end point was colorectal adenomatous polyp, a precursor of colorectal cancer, high carbohydrate intake resulted in a lower risk in both cohort (Giovannucci *et al*, 1992) and case–control studies (Hoff *et al*, 1986; Macquart-Moulin *et al*, 1987; Benito *et al*, 1993; Neugut *et al*, 1993; Sandler *et al*, 1993). In two studies the association was found only in women (Neugut *et al*, 1993; Sandler *et al*, 1993). A positive association of sugar intake with colorectal cancer risk has been observed in the majority of cohort and case–control studies that have looked at this relationship (Table 7). Adjustments for energy intake and other possible confounders such as body weight, socio-economic status, smoking and family history of the disease were not possible in all studies. Of the seven studies that did include these adjustments (Bostick *et al*, 1994; Macquart-Moulin *et al*, 1986,1987; La Vecchia *et al*, 1993; Centonze *et al*, 1994; Franceschi *et al*, 1997; Slattery *et al*, 1997), six (Bostick *et al*, 1994; Macquart-Moulin *et al*, 1987; La Vecchia *et al*, 1993; Centonze *et al*, 1994; Franceschi *et al*, 1997; Slattery *et al*, 1997) found a significant increase in risk of colorectal cancer with high sugar consumption, with odd ratios (ORs) ranging from 1.4 to 2.8 for the highest quartile or quintile of intake. The picture is further complicated when food groups were analysed. Starch-rich foods such as rice in Japan (Wynder *et al*, 1969), rice, cereal dishes and potatoes in Southern Europe (Macquart-Moulin *et al*, 1986; Franceschi *et al*, 1997) were found to be directly associated with colorectal cancer risk.

The slightly conflicting results may be partly due to the primary type of carbohydrate consumed by the population under study. In some countries the main sources of carbohydrate may be unrefined bread (eg a low-GI bread such as pumpernickel), while in others it may be high-GI foods such as potatoes or white bread. These foods elicit different glycemic and insulinemic responses and thus could affect the risk of colorectal cancer differently.

Other evidence from non-dietary factors is pointing to a possible promoting role of insulin in colon carcinogenesis. A link between cancer and diabetes mellitus has been suspected for more than 100 y and until the 1920s hyperglycemia was used as a marker in cancer screening (Freund, 1885; Trinkler, 1890; Boas, 1903; Schafer, 1934; Marble, 1934; Ellinger & Landsman, 1944). Type 2 diabetes, a condition resulting from long-term exposure to high insulin levels, has been found to increase significantly colorectal and colon cancer risk by 43 and 49%, respectively, in the cohort of

Table 7 Relationship between carbohydrate intake and colorectal cancer risk

Reference	*Study design*	*Number of cases*	*Site*	*Association OR or RR (95% CI)*	*Comments*
Manousos *et al* (1983)	Case–control	100	Colorectal	—	No OR calculated for sugar and syrups or cereals but results suggest no association
Miller *et al* (1983)	Case–control	171 men	Colon	1.4	Sugar > 17.7 *vs* < 17.7 g/day
		177 women	Colon	1.3	
		194	Rectum	1.3	
Pickle *et al* (1984)	Case–control	58	Colon	1.4	Sweets > 8.5 *vs* < 8.5 servings/week
		28	Rectum	1.6	
Bristol *et al* (1985)	Case–control	50	Colorectal	3.6* (1.2–10.9)	Sugars > 99 *vs* < 57 g/day
Macquart-Moulin *et al* (1986)	Case–control	399	Colorectal	1.28	Highest *vs* lowest quartile of sugar, honey, jam, jelly
La Vecchia *et al* (1988)	Case–control	339	Colon	1.22	Highest *vs* lowest tertile of sugar intake
		236	Rectum	0.51	
Tuyns *et al* (1987)	Case–control	453	Colon	2.31*	Sugar > 175 *vs* < 0 g/week
		365	Rectum	2.73*	
Benito *et al* (1990)	Case–control	286	Colorectal	1.64	H *vs* L quartile
Bidoli *et al* (1992)	Case–control	123	Colon	1.6	Sugar
				1.2	Pasta or rice
				1.1	Pastry
		125	Rectum	1.6	Sugar
				1.2	Pasta or rice
				1.7	Pastry
Peters *et al* (1992)	Case–control	123	Colorectal	1.00	Per 100 kcal sugar or non-sucrose CHO
				1.01	
La Vecchia *et al* (1993)	Case–control	953	Colon	2.0* (1.4–2.9)	Sugar added to hot drinks ≥ 3 *vs* 0 tsp/cup
		633	Rectum	1.4* (0.9–2.1)	
Bostick *et al* (1994)	Cohort	212 (from $n = 35\,004$)	Colon	2.00* (1.21–3.30)	Non-dairy sucrose-containing foods > 18.5 *vs* < 4.5 servings/day
				1.74 (1.06–2.87)	Sucrose-containing foods > 20.5 *vs* > 5.5 servings/day
				1.45 (0.88–2.39)	Sucrose > 62.5 *vs* < 25.8 g/day
				1.30 (0.83–2.06)	Total CHO > 274 *vs* < 152 g/day
Centonze *et al* (1994)	Case–control	119	Colorectal	2.75* (1.26–5.97)	Sugar and syrups > 26 *vs* < 7 g/day
Franceschi *et al* (1997)	Case–control	1953	Colorectal	1.69* (1.36–2.10)	Bread and cereal dishes > 37.8 *vs* < 19.3 servings/week
				1.43* (1.19–1.73)	Refined sugar > 48.5 *vs* 7.5 servings/week
				1.13 (0.93–1.37)	Cakes and dessert > 8.5 *vs* < 0.7 servings/week
Slattery *et al* (1997)	Case–control	1993	Colon	1.59* (1.07–2.37)	Sucrose > 26 *vs* < 13.1 g/1000 kcal/day

H, highest; L, lowest; CHO, carbohydrate. *$P \leq 0.05$.

women from the Nurses' Health Study (Hu *et al*, 1999). Similar associations have been reported by several other investigators (Adami *et al*, 1991; O'Mara *et al*, 1985; Hardell *et al*, 1996; La Vecchia *et al*, 1991,1997; Wideroff *et al*, 1997), albeit not all (Ragozzino *et al*, 1982; Green & Jensen, 1985; Kune *et al*, 1988; Steenland *et al*, 1995; Tables 8 and 9). In summary, these studies suggest a 10–40% increase in risk of colorectal cancer in diabetic patients. Most of the associations appear to be moderately positive, stronger for males than females and for colon than rectal cancer. The associations were not explained by potential confounding factors including BMI and physical activity (La Vecchia *et al*, 1997).

When diabetic populations were followed in prospective studies the increase in colorectal cancer risk was approximately 34% in men and 20% in women (Weiderpass *et al*, 1997a; Will *et al*, 1998) compared to the general population, and it was stronger for colon than rectal cancer, confirming the above findings. However, the progression of colorectal cancer did not seem to be worsened by diabetes (Will *et al*, 1998).

Another way of investigating the insulin–colon cancer hypothesis is by assessing the association between blood glucose levels after glucose challenge and subsequent colorectal cancer mortality. After 12 y follow-up, Levine *et al* (1990) found a positive association in men but not in women. These results, however, were not confirmed by Smith *et al* (1992), who conducted a similar study with a larger cohort and a longer follow-up (18–20 y). More recently Schoen *et al* (1999) found a two-fold increased risk in colorectal cancer after 77 months of follow-up in subjects with high baseline fasting glucose levels and high glucose and insulin levels 2 h after glucose challenge (relative risk, RR = 1.8, 2.4, 2.0, respectively). In this study no associations were found with diabetes although the number of diabetic subjects was very limited ($n = 23$). Further evidence for a possible role of hyperinsulinemia in colorectal cancer is given by a small case–control study where direct associations were found between two risk factors for hyperinsulinemia, plasma triglycerides and glucose, and risk of carcinoma *in situ* (Yamada *et al*, 1998).

Table 8 Relation between diabetes mellitus, colorectal cancer and adenoma: case–control studies

Reference	*Number of CRC cases*	*Number of cases of diabetes with CRC*	*Cancer site*	*Association OR or RR (95% CI)*	*Comments*
O'Mara *et al* (1985)	1309	53	Colon	1.4* M 1.2* F	Adjusted for age
			Rectal	1.0* M 1.1* F	
Kune *et al* (1988)	715	33	Colorectal	1.28 (0.67–2.47) M 0.75 (0.35–1.61) F	Adjusted for age and sex
La Vecchia *et al* (1991)	1078	83	Colon Rectal	1.6* (1.1–2.3) 1.3 (0.8–2.0)	Adjusted for age, sex, area of residence, education, BMI, and selected indicator foods
La Vecchia *et al* (1994)	1326	92	Colon	1.1 (0.8–1.8) M 1.0 (0.6–1.5) F	Adjusted for age, sex, education, smoking, BMI, specific risk factors for the disease
			Rectal	1.1 (0.7–1.8) M 0.7 (0.3–1.3) F	
Hardell *et al* (1996)	329	28	Colorectal	2.9* (1.4–6.0) M 1.0 (0.4–2.3) F 1.7 (1.0–3.0) All	Adjusted for sex, age, occupational physical activity
Le Marchand *et al* (1997)	1192	204	Colon (left)	1.9 (1.1–3.5) M 3.0 (1.2–7.1) F	Adjusted for age, family history of CRC, alcoholic drinks/week, lifetime recreational physical activity, BMI, energy intake
			Colon (right)	0.9 (0.4–1.8) M 1.3 (0.6–2.7) F	
			Rectal	0.7 (0.3–1.6) M 1.7 (0.7–4.4) F	
La Vecchia *et al* (1997)	1953	116	Colorectal	1.4* (1.1–1.7) >40 y 1.6* (1.1–2.3) >60 y	Adjusted for age, sex, education, smoking, BMI, specific risk factors for the disease
Kono *et al* (1998)	821	49 (new NIDDM)[a]	Adenoma of sigmoid colon	1.4 (1.0–2.0)	Adjusted for BMI, smoking, alcohol use, rank of Self Defense Forces and hospital
		21 (old NIDDM)[b]		1.3 (0.8–2.2)	

CRC, colorectal cancer. CR, colon–rectum. M, male. F, female. [a]Newly diagnosed non-insulin dependent diabetes mellitus. [b]Non-insulin diabetes mellitus under treatment.

Epidemiological studies have found a positive association between colon cancer risk and various determinants of hyperinsulinemia/insulin resistance, particularly obesity and physical inactivity (Vena *et al*, 1987; Severson *et al*, 1989; Ballard-Barbash *et al*, 1990; Potter *et al*, 1993; Giovannucci *et al*, 1995; Schoen *et al*, 1999).

Is there a link between high glucose, high insulin levels and increased risk of cancer? Mechanistic studies have been pointed at insulin-like growth factors (IGFs). Insulin acts as a growth factor for colonic mucosal cells and it has been shown to possess promoting effects in *in vitro* and in animal cancer studies (Koenuma *et al*, 1989; Watkins *et al*, 1990; Bjork *et al*, 1993; Tran *et al*, 1996). Insulin has the ability to stimulate IGFs which are important mitogens, necessary for the cell to progress from G1 to the S phase of the cell cycle (Aaronson, 1991). Ninety-five percent of IGF-1 circulates bound to IGF binding protein-3 (IGFBP-3), which controls the availability of free IGF-1 by modulating its access to the IGF-1 receptor (Jones & Clemmons, 1995; Collett-Solberg & Cohen 1996). IGF-1 promotes cell growth by stimulating tyrosine-specific protein kinase activity both in its own receptors as well as in the insulin receptors. Insulin has been shown to have moderate affinity to the IGF receptors, particularly the IGF-1 receptor (Ullrich *et al*, 1986). IGF-1 has also anti-apoptotic (Baserga, 1995; Remacle-Bonnet *et al*, 2000) and angiogenic properties (Warren *et al*, 1996), two attributes that may favour tumor development. IGFBPs (mainly IGFBP-3 and IGFBP-1) appear to have the opposite effects to IGF-1 (Giovannucci, 1999).

An indirect mechanism postulated for the tumor initiating action of IGFs may include interactions with genetic factors since growth factors are known to activate k-ras proteins (Bos, 1998), which are responsible for promoting cell growth. When mutated, k-ras proteins lose their ability to become inactive and their hyperactivity may increase the risk of generating tumor cells.

Insulin and IGF-1 receptors have been found in both normal and malignant cells of the colonic mucosa and have been shown to stimulate proliferation of human colorectal cells (Lahm *et al*, 1992; McKeown-Eyssen, 1994).

Circulating levels of IGF-1 were related to colorectal cancer risk in a case–control study, after adjustment for known dietary and non-dietary risk factors (Manousos *et al*, 1999). Similarly, two other cohort studies have shown a strong positive association between IGF-1 and colorectal cancer among men of different age groups (Ma *et al*, 1999) and between IGF-1 and intermediate–late stage adenomas as well as colorectal cancer among women, where a more than two-fold increased risk was found (Giovannucci *et al*, 2000). In these two cohorts a negative association was observed for

Table 9 Relationship between diabetes mellitus and colorectal cancer: cohort studies

Reference	*Cohort at baseline*	*Number of cases of diabetics with CRC*	*Cancer site*	*Association OR or RR (95% CI)*	*Comments*
Kessler (1970)	Diabetics 21 447	192	Colon	0.97 M	SMR
				1.16 F	
				1.09 All	
			Rectal	0.64* M	
				0.97F	
				0.81 All	
Ragozzino *et al* (1982)	Diabetics 1135	18	Colorectal	1.3 (0.6–2.4) M	SIR
				1.0 (0.4–2.0) F	
				1.2 (0.7–1.8) All	
Green and Jensen (1985)	Diabetics 1499	17	Colorectal + stomach	1.31 (0.81–2.11)	SIR
Adami *et al* (1991)	Diabetics 51 008	325	Colon	1.2* M	SIR
				1.0* F	
			Rectal	1.3* M	
				0.9* F	
Steenland *et al* (1995)	Healthy 14 407	11	Colorectal	1.43 (0.61–3.31) M	Compared to matched
				1.40 (0.64–3.10) F	non diabetic subjects
Weiderpass *et al* (1997a,b)	Diabetics 153 852	1435	Colon	1.37 (1.24–1.50) M	SIR
				1.42 (1.30–1.55) F	
			Rectal	1.36 (1.21–1.52) M	
				1.10 (0.95–1.26) F	
			Colon	1.63 (1.48–1.79) M	SMR
				1.51 (1.38–1.64) F	
			Rectal	1.61 (1.41–1.82) M	
				1.36 (1.17–1.57) F	
Wideroff *et al* 1997	Diabetics 109 581	1257	Colon	1.3 (1.1–1.4) M	SIR
				1.1 (1.0–1.2) F	
			Rectum	1.0 (0.9–1.2) M	
				1.0 (0.9–1.2) F	
Will *et al* (1998)	Diabetics 15 487	161	Colorectal	1.30 (1.03–1.65) M	IDR
				1.16 (0.87–1.53) F	
Schoen *et al* (1999)	Diabetics 1161	23	Colorectal	1.6 (0.8–3.1) M	IDR
				1.1 (0.5–2.6) F	
				1.4 (0.8–2.4) All	
Hu *et al* (1999)	Healthy 118 403	62	Colorectal	1.43* (1.10–1.87)	Compared to matched
			Colon	1.49* (1.09–2.06)	non diabetic women
			Rectum	1.11 (0.56–2.21)	
			Advanced CR	1.56* (1.07–2.28)	
			Fatal CR	2.39* (1.46–3.92)	
Lund Nilsen and Vatten (2001)	Healthy 75 219	37	Colorectal	0.66 (0.35–1.24) M	Compared to matched
				1.55* (1.04–2.31) F	non diabetic subjects

CRC, colorectal cancer. CR, colon–rectum. M, male. F, female. SMR, standardized mortality ratio (compared to nationwide rates). SIR, standardized incidence ratio (compared to nationwide rates). IDR, incidence density ratio (compared to own cohort).

IGFBP-3 which reduced risk by 72% in men when the highest quintile was compared to the lowest (Ma *et al*, 1999) and in women for both colorectal adenoma and cancer (highest *vs* lowest tertile). Also, high levels of IGF-1 and low levels of IGFBP-3 have been shown to be directly associated with colorectal adenomas (RR = 4.39; 95% CI 1.31–14.7) and to predict adenoma progression, suggesting that both factors could be related to future colorectal cancer risk (Renehan *et al*, 2001).

Other growth factor-related studies suggest a link between IGF-1 and colorectal carcinogenesis. Tall individuals (Hebert *et al*, 1997) and those with acromegaly, characterized by elevated levels of growth hormone and IGF-1 (Ron *et al*, 1992), show an increased risk of colorectal cancer.

Nutrition is a major regulator of IGF-1 (Underwood, 1996). Fasting results in a decrease while overnutrition results in an increase in IGF-1 levels although the exact nature of the dose–response relationship between food intake and levels of IGFs in circulation remains to be determined. In a clinical trial high carbohydrate/high-GI diets increased IGF-1 levels compared to low carbohydrate diets in obese subjects (Prewitt *et al*, 1992). The opposite was shown in a small cross-sectional study in Greece where an independent and negative association was found between circulating IGF-1 levels and energy from carbohydrates (Kaklamani *et al*, 1999). The Mediterranean diet, however, is known to contain several food items with low GI values and it is possible that the dietary GL in this Greek population was lower than in a typical Western diet used in the clinical study by Prewitt *et al* (1992).

Breast cancer

Only one study thus far has reported on the association between dietary GI or GL and risk of breast cancer (Augustin *et al*, 2001). Direct associations with breast cancer risk emerged for GI (OR = 1.4 for highest *vs* lowest quintile; 95% CI 1.1 – 1.6) and GL (OR = 1.3; 95% CI 1.1 – 1.6) after correcting for known risk factors. Interestingly, high-GI foods, such as white bread, increased the risk of breast cancer (OR = 1.3; 95% CI 1.1 – 1.6) while the intake of pasta, a medium – low-GI food, did not influence risk (OR = 1.0; 95% CI 0.8 – 1.2).

Dietary factors have been shown to play a role in breast cancer. Of the macronutrients that affect the GI starch intake has been directly associated with breast cancer risk in a case – control study after adjustment for confounding factors such as age, energy intake and alcohol consumption (Franceschi *et al*, 1996). Similar results were obtained by Ingram *et al*, (1991) while others did not show a significant relation (Rohan *et al*, 1988; Zaridze *et al*, 1991). Total carbohydrate intake in general was not associated with breast cancer risk (Table 10), although one study showed a significantly positive association (Franceschi *et al*, 1996) and another showed a negative association (Wakai *et al*, 2000). One of the possible explanations for these apparently opposing results could be the different type of carbohydrates used as the staple food in the two different population (Italian and Indonesian, respectively). High-GI foods as white bread and crackers are the main starch consumed by the Italian population representing 39% of total starch intake, followed by pasta and rice which together account for 25% (Favero *et al*, 1997). Starch identified as a food group (eg white bread or refined cereal dishes) has also been found to increase risk of breast cancer in most epidemiological studies (Iscovich *et al*, 1989; Franceschi *et al*, 1995; Favero *et al*, 1998), although some have found no association (Toniolo *et al*, 1989; Rohan *et al*, 1993) and in one study from the Netherlands an inverse association emerged (van't Veer *et al*, 1990). However, in this study the cereal products represented also the main source of dietary fiber suggesting these were not refined cereals. Associations of sugar intake/confectionery with breast cancer have been reported in at least eight studies; two were direct (Franceschi *et al*, 1995; Favero *et al*, 1998), one inverse after adjustment for macronutrient energy (Zaridze *et al*, 1991), while the remaining showed no consistent association (Rohan *et al*, 1988; Iscovich *et al*, 1989, Ewertz & Gill 1990; Ingram *et al*, 1991; Levi *et al*, 1993, Franceschi *et al*, 1996; Table 10).

The European intervention study (DIANA project) has shown that after 4.5 months on a diet rich in low-GI foods postmenopausal women showed reduced levels of circulating estradiol and testosterone, two hormones associated with breast cancer in postmenopausal women (Berrino *et al*, 2001). It should be noted, however, that this randomized controlled trial also included other dietary manipulations (eg soy foods) which could have partly accounted for the results.

Endocrine factors associated with diabetes may influence the growth of neoplastic breast cells. Frequency of breast cancer seems to be increased in diabetic women (Talamini *et al*, 1997) and women with impaired glucose tolerance (Muck *et al*, 1975). A large case-control study on 2569 women with breast cancer and 2588 controls (median age 55 y) showed an increased risk of breast cancer with diabetes mellitus in post-menopausal women after allowance for common risk factors such as parity and BMI (OR = 1.5, 95% CI = 1.1 – 2.0; Talamini *et al*, 1997). In a large retrospective cohort study of 80 005 diabetic women, a 30% increased risk of breast cancer emerged in diabetics compared with the incidence rates of the general Swedish population (Weiderpass *et al*, 1997b). No significant association was found in another study that included over 41 000 women aged 55 – 69 y during a 10 y follow-up (Sellers *et al*, 1998). In the Iowa Study of over 31 000 women, diabetes worsened breast cancer prognosis while it seemed to affect risk only in women with a history of breast cancer; however, obesity was found to account for most of this association (Folsom *et al*, 2000).

Hyperisulinemia/insulin resistance has been hypothesized to play a role in breast cancer development (Kaaks, 1996). Insulin may act as a mitogen in a dose-dependent manner in breast cancer cells through the insulin receptor. Positive associations of insulin with breast cancer were observed in 99 premenopausal non-diabetic women diagnosed with node-negative invasive carcinoma of the breast (first stage) compared to 99 age-matched controls with benign breast disease (Del Giudice *et al*, 1998). The odds ratio between the highest and lowest quintile of insulin levels was 2.83 (95% CI = 1.22 – 6.58) after adjusting for dietary and other risk factors such as obesity. Another study showed that serum C-peptide levels, a measure of insulin secretion, were significantly increased in 223 cases with stage I and II breast cancer (38 – 75 y) compared to 441 age-matched controls (RR = 2.9, 95% CI = 1.7 – 5.1, highest *vs* lowest quartile, C-peptide difference of 1.7 μg/l; Bruning *et al*, 1992). These results were independent of adiposity and body fat distribution. However, in the Malmo Preventive Project, when looking at fasting blood glucose and blood glucose levels after an oral glucose challenge no relationship was found with breast cancer in peri- and postmenopausal women (Manjer *et al*, 2001).

Obesity, in particular central obesity, is one of the major risk factors for insulin resistance and hyperinsulinemia and is positively associated with breast cancer risk in postmenopausal women (Sellers *et al*, 1992; Hunter & Willett, 1993; Ballard-Barbash & Swanson, 1996; Trentham-Dietz *et al*, 1997; Galanis *et al*, 1998). Central obesity was directly associated with breast cancer independently of BMI in at least two studies (Folsom *et al*, 1990; Kaaks *et al*, 1998). Two possible reasons for these associations could be related to hormonal factors: (i) estrogen synthesis from androstenedione, which occurs mainly in adipose tissue, is increased with greater body fat; and (ii) obesity leads often to a status

Table 10 Relationship between carbohydrate intake and breast cancer risk

Reference	*Study design*	*Numbers of cases*	*Association[a] OR or RR (95% CI)*	*Food*	*Comments*
Seely and Horrobin (1983)	Ecological	—	0.9 (cc)	Per capita sucrose and glucose consumption	
Katsouyanni *et al* (1988)	Case–control	120	0.98 (0.43–2.26)	Total CHO	Adjusted for age, years of education, interviewer, parity, age at first birth, at menarche, at menopause, residence, marital status, nutrients
			1.46 (0.84–2.54)	Sucrose	
Rohan *et al* (1988)	Case–control	451	0.92 (0.60–1.39)	Starch > 120.7 *vs* < 62.5 g/day	Adjusted for family history of BC, BBD, BO, age at menarche, at first birth, at menopause, breast self-examination, oral contraceptives, HRT, smoking, years of education
			1.12 (0.74–1.68)	Sugar > 159.9 *vs* < 80.0 g/day	
Iscovich *et al* (1989)	Case–control	151	1.9	Bread	Adjusted for energy intake
			2.3*	Bread and cakes	
			1.2	Sweets	
			1.9	Sugar containing items	
Toniolo *et al* (1989)	Case–control	250	1.1	Bread	Adjusted for age and energy intake
			0.9	Pasta and rice	
			0.8	Sugar	
Ewertz and Gill (1990)	Case–control	1486	1.10 (0.63–1.89)	Sugar added to coffee/tea > 40 *vs* < 20 g/day	Adjusted for age and residence
van't Veer *et al* (1990)	Case–control	133	0.42*	Cereal products	Adjusted for age, history of BBD, family history, smoking, education, HRT, age at menarche and at first pregnancy, BMI, energy and alcohol intake
Ingram *et al* (1991)	Case–control	99	1.4 (0.7–2.8)	Total CHO	Adjusted for parity, first degree family history of BC, age at menarche, BMI
			2.0* (1.0–3.8)	Starches	
			0.9 (0.4–1.7)	Sugar	
			1.1 (0.6–2.1)	Desserts	
Zaridze *et al* (1991)	Case–control	139	2.67 (0.47–15.1)	Starch	Adjusted for age at menarche, education and energy intake
			0.02* (0.002–0.27)	Sugar	
Levi *et al* (1993)	Case–control	107	1.2*	Pasta	Adjusted for age, education and energy intake
			1.6*	Pastry	
			1.3	Sugar	
Rohan *et al* (1993)	Cohort	519 ($n = 56\,837$)	0.95 (0.68–1.33)	Bread	Adjusted for age, age at menarche and at first birth, surgical menopause, years of education, family history of BC, BBD, dietary factors
			0.75 (0.53–1.04)	Pasta	
Katsouyanni *et al* (1994)	Case–control	820	1.03 (0.94–1.12)	Total CHO	Adjusted for demographic and reproductive factors, total energy intake and nutrients
Franceschi *et al* (1995)	Case–control	2569	1.34* (1.08–1.65)	Bread and cereal dishes[b] > 29.5 *vs* < 14.5 servings/week	Adjusted for energy intake
			1.25 * (1.03–1.52)	Sugar and candies > 47.5 *vs* < 7.0 servings/week	
			1.12 (0.92–1.36)	Desserts > 8.5 *vs* < 2.5 servings/week	
Franceschi *et al* (1996)	Case–control	2569	1.30* (1.09–1.54)	Available CHO > 330.1 *vs* < 197.6 g/day	Adjusted for age, centre, education, parity, menopausal status, energy and alcohol intake
			1.39* (1.17–1.66)	Starch > 190.8 *vs* < 105.2 g/day	
			0.89 (0.67–0.93)	Sugars > 127.4 *vs* < 64.9 g/day	
Favero *et al* (1998)	Case–control	2569	1.34* (1.1–1.7)	Bread and cereal dishes[b] > 29.5 *vs* < 14.5 servings/week	Adjusted for age, centre, education, parity, energy and alcohol intake
			1.25* (1.0–1.5)	Sugar and candies > 47.5 *vs* < 7.0 servings/week	
Wakai *et al* (2000)	Case–control	226	0.16* (0.08–0.31)	Total CHO	Incomplete collection of reproductive history

*$P \leq 0.05$. cc, correlation coefficient. BMI, body mass index. BC, breast cancer. BBD, benign breast disease. HRT, hormone replacement therapy. BO, bilateral oophorectomy. CHO, carbohydrate.
[a]Between highest and lowest intake.
[b]Cereal dishes: bread (white and wholemeal), biscuits, rice, pasta.

of hyperinsulinemia with the potential consequences on estrogen and insulin-like growth factors previously mentioned. The latter point is supported by epidemiological evidence showing an inverse correlation between obesity and sex hormone binding globulin (Madigan *et al*, 1998; Newcomb *et al*, 1995).

Estrogen has long been shown as a promoting agent in breast cancer and several risk factors for breast cancer such as nulliparity, late age at first pregnancy and late natural menopause are also associated with life-long exposure to sex hormones. The most active form of estrogen is free, unbound estradiol. The influence of estrogens on the breast is related to estrogen receptors which may be activated, among others, by insulin-like growth factors (Yee & Lee, 2000). Sustained high insulin levels may increase the risk of breast cancer by at least two possible routes: (1) suppression of sex hormone-binding globulin (SHBG) thereby rendering free circulating estradiol more available for action at the tissue level; (2) suppression of IGFBP-I, thus increasing free IGF-1 levels (Plymate *et al*, 1990; Nestler *et al*, 1991).

In vitro and animal studies have shown mitogenic and anti-apoptotic effects of IGFs in mammary cell lines (Bhalla *et al*, 2000; Helle & Lonning, 1996; Pilichowska *et al*, 1997; Foekens *et al*, 1989; Huff *et al*, 1986, Ng *et al*, 1997). Transgenic mice overexpressing growth hormone have a higher frequency of breast cancer (Bates *et al*, 1995; Hadsell *et al*, 1996) and disruption of the IGF-1 gene seems to prevent breast tumor formation by viral oncogens (Sell *et al*, 1993). Human mechanistic studies of the effect of estrogen antagonist drugs on breast carcinogenesis have shown a direct link with IGF-1. Tamoxifen is used in the prevention and therapy of breast cancer and has been found to reduce serum levels of IGF-1 and raise IGFBP-1 in postmenopausal breast cancer patients (Ho *et al*, 1998). This has been proposed as one of the mechanisms through which the antiestrogenic drug tamoxifen and more recently fenretinide, a vitamin A analog, may inhibit growth of mammary tumor cells (Ho *et al*, 1998; Kelloff *et al*, 1999).

Epidemiologic evidence is suggesting a possible role of IGFs in promoting and IGFBPs in suppressing breast carcinogenesis. Higher levels of IGF-1 were associated with breast cancer both in pre- and post-menopausal women in one study (Peyrat *et al*, 1993) and only in premenopausal women in two other studies (Bruning *et al*, 1995; Bohlke *et al*, 1998) where lower levels of IGFBP-3 were also found in premenopausal cases compared to controls. No associations were observed for these variables and breast cancer in postmenopausal women in two other investigations (Bruning *et al*, 1995; Hankinson *et al*, 1997) and in one study on premenopausal women (Del Giudice *et al*, 1998), although in the latter the control group chosen, potentially at high risk. In a small case–control study IGF-1 and IGFBP-3 were found, respectively, directly and indirectly associated with premenopausal ductal carcinoma *in situ* (Bohlke *et al*, 1998). Similar results were obtained in a nested case–control study based on the American Nurses Cohort where the positive association between plasma IGF-1 levels and breast cancer risk reached significance in premenopausal women younger than 50 and the relative risk increased after adjustment for plasma IGFBP-3 concentrations (Hankinson *et al*, 1998). Most of these studies did not include analysis on free IGF-1 which may be the most active fraction of total IGF-1, except in one small case-control study (Li *et al*, 2001) where a significant positive association was found with breast cancer risk (OR = 6.31).

As for colorectal cancer, other growth factor related studies may support a role of IGFs in breast cancer. Acromegaly increased the risk by four-fold (Nabarro, 1987) with a two-fold increase in mortality from breast cancer (Orme *et al*, 1996). Also height has been directly associated with breast cancer (van den Brandt *et al*, 1997). Although modest, positive associations have been found between height and breast cancer in several prospective studies where approximately two-fold increase in risk was observed with a difference in height of 15 cm (de Ward *et al*, 1974; Swanson *et al*, 1988; van den Brandt *et al*, 1997) or with 8 cm increment (Tornberg *et al*, 1988, Tretli, 1989; Vatten & Kvinnsland 1990, 1992; Manjer *et al*, 2001).

Prostate cancer

Some evidence suggests a promoting effect of refined carbohydrates in prostate carcinogenesis. Diets rich in fat, refined sugars and excess calories, all factors that favour the development of hyperinsulinemia, increase risk of prostate cancer (Talamini *et al*, 1992; Franceschi, 1994). Conversely, a low-fat/high-fiber diet plus daily exercise has been shown to decrease insulin and increase SHBG levels in obese men (Tymchuk *et al*, 1998).

Androgens are necessary hormones for the development and progression of prostate cancer. Testosterone is regulated by SHBG and also by insulin and insulin-like growth factors (Plymate *et al*, 1988; Singh *et al*, 1990; Pasquali *et al*, 1995; Katsuki *et al*, 1996). As with breast cancer, insulin may increase prostate cancer risk by suppressing SHBG levels. Insulin has also been shown to act as a mitogen in prostate adenocarcinoma cell lines (Polychronakos *et al*, 1991; Kimura *et al*, 1996). Insulin-like growth factors, particularly the IGF-1 family, have mitogenic and antiapoptotic activity in normal as well as in transformed prostate epithelial cells (Cohen *et al*, 1991; Rajah *et al*, 1997) and stimulate prostate growth in rodents (Torring *et al*, 1997). Epidemiological studies have shown a positive correlation between IGF-1 levels and prostate cancer risk (Chan *et al*, 1998; Mantzoros *et al*, 1997; Wolk *et al*, 1998). A four-fold increased risk was observed in the highest quartile of IGF-1 levels compared to the lowest level in a nested case-control study of 152 paired subjects (Chan *et al*, 1998). The results were independent from baseline prostate-specific antigen levels and remained statistically significant after adjusting for potential confounders such as weight, height, BMI, lycopene, androgen receptors and plasma hormone levels. The design of the study allowed the inference that high levels of circulating IGF-1 were not a consequence of disease progression as suggested also by other investigators who found no association between IGFs and prostate cancer stage (Wolk *et al*, 1998). IGFBPs have also been considered in relation to prostate cancer, particularly IGFBP-3 in epidemiological studies

(Chan *et al*, 1998; Wolk *et al*, 1998). Most investigators have reported an inverse association between IGFBP-3 and prostate cancer risk (Chan *et al*, 1998; Thrasher *et al*, 1996; Kanety *et al*, 1993), although others have found no association (Wolk *et al*, 1998).

A possible role of IGFs in prostate carcinogenesis is also suggested by mechanistic studies on Suramin, a drug used in the treatment of advanced prostate cancer, which was shown to suppress IGF-levels (Miglietta *et al*, 1993; Sartor *et al*, 1994).

Furthermore, height, as a surrogate of growth factors and IGF activity, has been shown to be positively associated with prostate cancer risk in two cohort studies (Andersson *et al*, 1997; Giovannucci *et al*, 1997) and in a case–control study where a moderate direct association was observed with advanced prostate cancer (Norrish *et al*, 2000).

It is not yet clear whether diabetes may be a risk factor for prostate cancer. Some epidemiological studies have shown a 34% lowered risk (Giovannucci *et al*, 1998), while in another there was a 56% increased risk only in men with a diagnosis of diabetes of 5 y or more (Will *et al*, 1999).

Obesity is also directly associated with prostate cancer (Gann *et al*, 1995). Compared to normal weight ($BMI < 23\,kg/m^2$), men moderately overweight ($BMI = 23–28\,kg/m^2$) showed a two-fold elevated risk while severely overweight men ($BMI > 28\,kg/m^2$) showed a four-fold greater risk of prostate cancer after correcting for confounding factors (Talamini *et al*, 1986).

Although scant, some evidence points towards a role of insulin in prostate carcinogenesis. At present no studies have been conducted on the relationship between dietary GI or GL risk of prostate cancer.

Conclusion

Low-GI diets include foods such as beans, vegetables, pasta, parboiled rice and wholegrain breads and they may have clinical implications in the prevention and management of chronic Western diseases, particularly type 2 diabetes, CHD and possibly cancer. High and low GI diets may be a better measure for assessing the physiological effects of dietary carbohydrates than the traditional 'simple' and 'complex' carbohydrate definition. Overall, GL may be a better measure of the association between dietary carbohydrate and disease in epidemiological studies.

The literature suggests that the low-fat/high-carbohydrate diets advocated by health organizations in Western countries could be further improved by switching from high-GI to low-GI food choices. When introduced *ad-libitum* in the diet, low-GI foods would often confer an array of advantages with their low energy density and discrete content of dietary fiber, vitamins, minerals and phytochemicals. Studies looking at dietary (eg carbohydrates) and non-dietary factors (eg diabetes, growth factors) in relation to cancer may suggest an important role of insulin in carcinogenesis. There may be a place for low-GI diets in disease prevention and management particularly in populations characterized by already high incidences of obesity, insulin resistance and glucose intolerance; however, more studies are necessary to confirm the possible role of high glucose and insulin in disease development in order to rule out any possible confounding factor and to better understand potential mechanisms of action.

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