ARTICLE

Some health benefits of low glycaemic index diets – a systematic review

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Background. Controversy exists regarding practical use of the glycaemic index (GI), often with reference to the responsibility of health professionals to advise consumers only when scientific evidence supports their recommendations. There are indications that low-GI diets may improve health, but the strength of the evidence is not known.

Objectives. The objective of this systematic review was to determine the strength of scientific evidence encouraging dieticians to incorporate the GI concept when planning diets.

Design. A meta-analysis was performed as part of the systematic review. We searched for randomised controlled trials with a cross-over or parallel design published in English between 1981 and 2003, investigating the effect of low-GI versus high-GI diets on markers of carbohydrate and lipid metabolism. The main outcomes were fructosamine, glycosylated haemoglobin (HbA_{1c}), high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), total cholesterol (TC) and triacylglycerols (TGs).

Results. Literature searches identified 13 studies that met strict inclusion criteria. Low-GI diets significantly reduced fructosamine by –0.1 mmol/l (confidence interval (CI): –0.20, 0.00, $p = 0.05$), HbA_{1c} by 0.27% (CI: –0.5, –0.03; $p = 0.03$), LDLC in type 2 diabetics by –0.24 mmol/l (CI: –0.45, –0.04; $p = 0.02$) and TC by –0.33 mmol/l (CI: –0.47,–0.18; $p < 0.0001$) compared with high-GI diets. No effects were observed for HDLC and TGs.

Conclusion. This systematic review presents convincing evidence to recommend the use of the GI as a scientifically based tool when choosing carbohydrate-containing foods to reduce TC and LDLC concentrations and to improve overall metabolic control of diabetes.

There is controversy in the literature on the practical use of the glycaemic index (GI) concept,[1] often with reference to the responsibility of health professionals to advise consumers only when the scientific evidence supports their recommendations. The evidence-based approach has recently been implemented as an objective framework for gathering and reviewing all available evidence when setting nutrition policy and practice.[2] This article is a systematic review of the results of studies that compared the effects of low-GI versus high-GI diets on markers of carbohydrate and lipid metabolism.

Egger and Smith[3] regard a systematic review as being 'most appropriate for denoting any review of a body of data that uses clearly defined methods and criteria', while a meta-analysis is defined as a statistical technique used to combine the results of studies addressing the same question into a one number summary.[4] According to the definition of Egger and Smith,[3] a meta-analysis can, if appropriate, be part of a systematic review. As such we have included the results of a meta-analysis performed on the data gathered.

Scientific evidence was assessed with regard to the benefits of lowering dietary GI as a basis for dietary recommendations designed to improve serum lipid profile and overall metabolic control of diabetes. The terminology suggested by the *Journal of the American Medical Association* was used.[5] The hierarchy of evidence includes: systematic reviews and meta-analyses, randomised controlled trials (RCTs), cohort studies, case-control studies, cross-sectional surveys and case reports.[5]

Scientific evidence

The ultimate purpose of applied health research is to improve health care. Summarising the literature to adduce recommendations for clinical practice is an

important part of the process. It is therefore important to differentiate between strong and weak evidence because recommendations based on inadequate evidence often require reversal when sufficient data become available. Furthermore, it is time consuming and expensive to replace old recommendations and implement new ones. This systematic review presents the most recent evidence, including epidemiological evidence and a meta-analysis conducted on RCTs regarding the health benefits of low-GI diets.

Epidemiological studies

Diabetes mellitus

Table I summarises the findings of cross-sectional and cohort studies on the relationship between GI and the risk of diabetes and coronary heart disease (CHD) (adapted from Jenkins *et al.*[6]).

Considering epidemiological evidence, the cross-sectional EURODIAB Complications Study[10] reported that the lower-GI diet of European outpatients with type 1 diabetes was associated with significantly lower ($p = 0.0001$) glycosylated haemoglobin (HbA_{1c}) concentrations. Compared with the highest GI quartile (GI 89), HbA_{1c} concentrations in the lowest quartile (GI 75) were 11% lower in patients from southern European centres and 6% lower in patients from the rest of the European centres. Furthermore, the Framingham cohort[15] showed a strong positive association between prevalence of CHD and increased HbA_{1c} concentrations, suggesting the importance of hyperglycaemia in the development of CHD.

The Nurses' Health Study,[7] the Health Professionals Study[8] and the Iowa Women's Health Study[9] investigated the long-term effects of GI on the development of type 2 diabetes. Salmeron *et al.*[7] found a positive association between GI and the development of type 2 diabetes in women after adjustment for age, body mass index (BMI), smoking, physical activity, family history of diabetes, alcohol and cereal fibre intake and total energy intake. Comparing the highest with the lowest GI quintile of the diet, the relative risk (RR) of diabetes was 1.37 (95% confidence interval (CI): 1.09, 1.71, p trend = 0.05). A similar association was observed in men after adjusting for the same factors.[8] Comparing the highest and lowest quintiles, the RR of diabetes was 1.37 (95% CI: 1.02, 1.83, p trend = 0.03). However, in the Iowa Women's Health Study[9] no association was reported between GI and the risk of developing diabetes (Table I). The pattern of risk across GI quintiles was inconsistent since the RR first rose to 1.22 in the 3rd quintile and then dropped to 0.84 in the 5th quintile.

Coronary heart disease

A low high-density lipoprotein cholesterol (HDLC) concentration is a strong independent predictor of CHD and has several causes, many of which are associated with insulin resistance, elevated triacylglycerols (TGs), overweight and obesity, physical inactivity and type 2 diabetes.[16]

The Third National Health and Nutrition Examination Survey (NHANES III)[13] (1988 - 1994), found an inverse relationship between GI and HDLC concentrations (13 907 participants). Ford and Liu[13] reported a statistically significant change in HDLC concentration of –0.6 mmo/l per 15-unit increase in GI, after adjusting for covariates such as gender, BMI, smoking status, alcohol intake, physical activity and energy intake derived from fat and carbohydrate. HDLC concentrations for the lowest and highest GI quintiles were 1.36 mmol/l and 1.27 mmol/l, respectively.

Frost *et al.*,[14] reporting data from the Survey of British Adults (1986 - 1987), found a significant negative relationship between serum HDLC concentration and dietary GI in both men ($p = 0.02$) and women ($p < 0.0001$). In women, the improvement in HDLC concentrations between the lowest and highest GI quintile was 0.25 mmol/l, representing a possible 29% reduction in CHD morbidity. In men, the potential decrease in CHD morbidity was found to be 7% reflecting a 0.09 mmol/l difference in HDLC concentration between the lowest and the highest GI quintiles.

In the EURODIAB Complications Study,[10] higher HDLC concentrations were observed in patients from the northern, eastern and western European centres who consumed low-GI diets. The observed relations between GI and HDLC concentrations were independent of dietary fibre intake.[10] However, in the Zutphen Elderly Study,[12] conducted on elderly male subjects, no associations were found between GI and HDLC concentrations. These differences in findings between the epidemiological studies could possibly be attributed to the age and gender differences between study populations.[12] In contrast to these findings, epidemiological evidence failed to prove a significant relationship between low-density lipoprotein cholesterol (LDLC), total cholesterol (TC), TG and low-GI diets.[10,12,14] Furthermore, Liu *et al.*[11] found a positive association between high-GI diets and the development of CHD, while Van Dam *et al.*[12] could not find any relationship (Table I).

Clinical intervention studies

In a recent meta-analysis by Opperman *et al.*[17] of RCTs, we analysed the effect of low-GI diets on markers of carbohydrate and lipid metabolism in healthy subjects as well as subjects with CHD and type 1 and 2 diabetes. Significant improvements were observed in HbA_{1c}, fructosamine, LDLC and TC suggesting that low-GI diets improve blood glucose control as well as

Table I. **Cross-sectional and cohort studies of the relationship between GI and the risk of diabetes and cardiovascular disease and its association with HDL and glycated haemoglobin (HbA_{1c}) (adapted from Jenkins *et al.*[6])**

Author	Subjects	Main outcome	Type of study	Duration	Difference in GI	Main effect
Salmeron *et al.*[7]	Nurses' Health Study subjects aged 45 - 65 yrs (N = 65 173)	Diabetes	Cohort	6 years	Quintiles, GI: 64 - 79	Positive association between GI and development of type 2 diabetes in women
Salmeron *et al.*[8]	Health Professionals Study	Diabetes	Cohort	6 years	Quintiles, GI: 65 - 79	Positive association between GI and development of type 2 diabetes in men
Meyer *et al.*[9]	Iowa Women's Health Study subjects aged 55 - 69 yrs, N = 35 988	Diabetes	Cohort	6 years	Quintiles, GI: < 58 to > 80	No association between GI and development of diabetes in older women
Buyken *et al.*[10]	EURODIAB Complications study, type 1 diabetics aged 33 yrs, BMI 26.7 kg/m^2, N = 2 810	HbA_{1c}	Cross-sectional	Not reported	Quartiles, GI: 74.9 - 88.55	Low-GI diets associated with (p = 0.0001) HbA_{1c} concentrations
Liu *et al.*[11]	Nurses' Health Study, subjects aged 38 - 63 yrs, BMI 25.7 kg/m^2, N = 75 521	CHD risk	Cohort	10 years	Quintiles, 72 - 80 (by glycaemic load)	CHO with high GI associated with increased risk of CHD
Van Dam *et al.*[12]	Zutphen Elderly Study, subjects aged 65 - 84 yrs in 1955, BMI 25.57 kg/m^2 (555 of 1 088 men still alive from original survey plus 711 new men of same age)	CHD risk	Cohort and cross-sectional	10 years 1985 - 1995	Quintiles, 74 - 85	No association between GI and HDLC concentrations as well as risk of developing CHD
Ford and Liu [13]	NHANES III 20-yr survey, N = 6 825 M, 7 052 F, BMI 26.57 kg/m^2	HDLC	Cross-sectional survey	Not reported	Quintiles, GI: ≤ 75 to ≥ 88	Inverse relationship between GI and HDLC concentrations
Frost *et al.*[14]	British Adults (1986 - 1987), subjects aged 16 - 64 yrs, N = 699 M, 721 F	HDLC	Cross-sectional survey	Not reported	Quintiles, mean GI: 86	Inverse relationship between GI and HDLC concentrations
Buyken *et al.*[10]	EURODIAB Complications Study, type 1 diabetics aged 33 yrs, BMI 26.77 kg/m^2, N = 2810	HDLC	Cross-sectional	Not reported	Quartiles, GI: 74.9 - 88.55	Inverse relationship between GI and HDLC concentrations

CHD = coronary heart disease; HDLC = high-density lipoprotein cholesterol; NHANES III = Third National Health and Nutrition Examination Survey; CHO = carbohydrate; M = male; F = female.

lipid metabolism. No effects were found on HDLC and TG. Some of the results will be reported here, supported by plausible biological mechanisms to explain the outcomes of the meta-analysis.

Carbohydrate metabolism

Figs 1 and 2 present the effects of low- versus high-GI diets on carbohydrate metabolism. This meta-analysis investigated fructosamine and HbA_{1c}.

Fructosamine

There was an overall statistically significant reduction in fructosamine levels in subjects receiving the low-GI diet compared with the high-GI diet (change –0.1 mmol/l, 95% CI: –0.20, 0.00, $p = 0.05$). However, when studies were subgrouped into those involving diabetic and healthy subjects, a non-significant improvement was observed in each group (diabetic subjects: change –0.11 mmol/l, 95% CI: –0.25, 0.03, $p = 0.12$), healthy subjects: change –0.09 mmol/l, 95% CI: –0.24, 0.06, $p = 0.25$). The GI reduction for the included studies was 24 ± 9 units (mean ± standard deviation (SD)).

Fructosamine is measured as a short-term (2-week) index of glycaemic control. Glycosylated albumin is the main constituent of fructosamine and has a half-life of only 12 days, explaining the usefulness of fructosamine as a short-term marker.[32] Although fructosamine is a shorter-term marker for blood glucose control than HbA_{1c}, it seems that the longer low-GI diets are followed, the larger the observed decreases in fructosamine concentrations. According to Jones *et al*.[33] maximum changes in fructosamine take 4 - 6 weeks to occur. More profound decreases were documented in diabetic than healthy subjects. Results would probably be more representative if all available studies

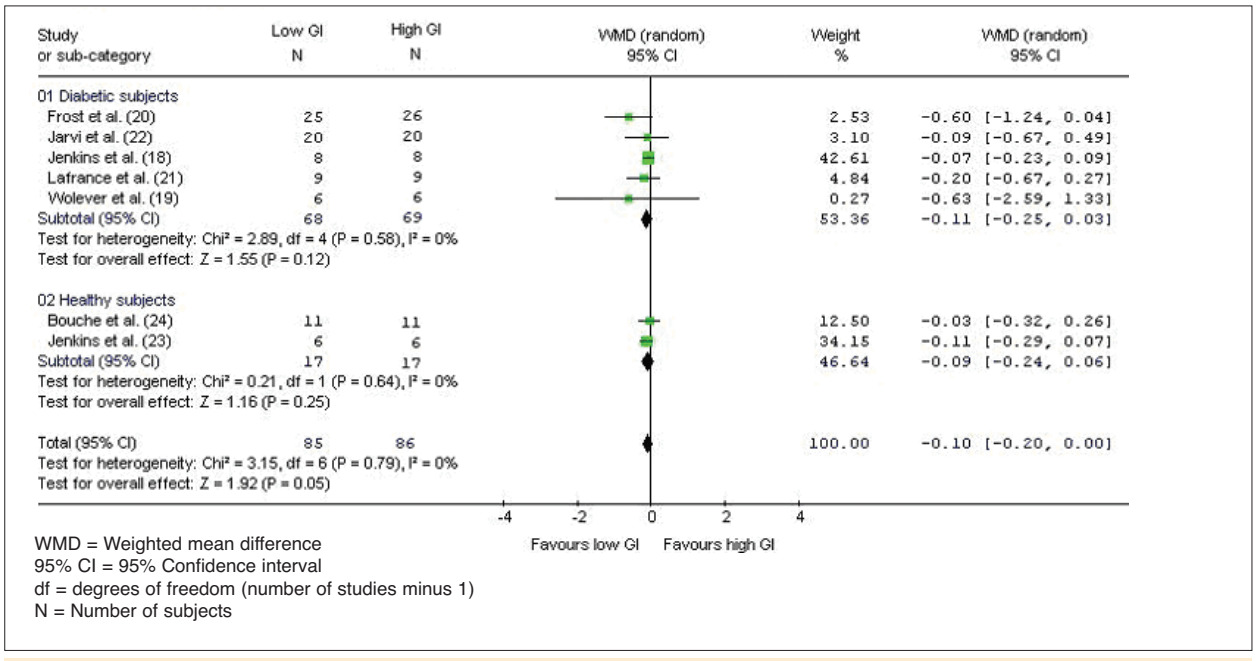

Fig. 1. Net changes in fructosamine.

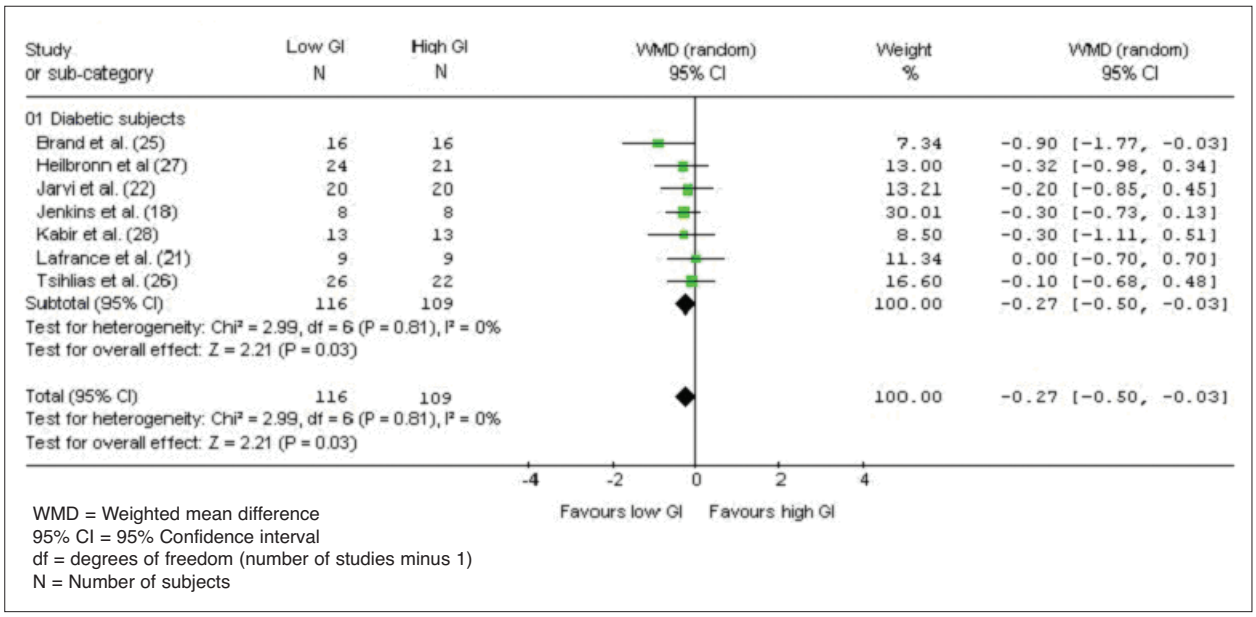

Fig. 2. Net changes in HbA_{1c}.

conducted on fructosamine and the GI could be included, but owing to a lack of complete data (means and SDs of baseline and end values) this was not possible. However, the combined meta-analysis suggests that low-GI diets will reduce mean fructosamine concentrations by 0.1 mmol/l over and above that seen with high-GI diets over a period of 4.6 ± 3 weeks. GI reductions of 24 ± 9 units were achieved.

Glycosylated haemoglobin

There was a statistically significant decrease in mean HbA_{1c} concentrations in subjects receiving low-GI diets (change –0.27%, 95% CI: –0.5, –0.03, $p = 0.03$) (Fig. 2). The difference in GI between the low- and high-GI diets was 21 ± 7 units. All the included studies that measured HbA_{1c} in this meta-analysis were performed on diabetic subjects.

HbA_{1c} is a longer-term marker of carbohydrate metabolism than fructosamine. This test provides an index of the average blood glucose concentration over the half-life of the haemoglobin molecule (approximately 6 weeks).[32] From these results one may conclude that low-GI diets beneficially influenced long-term glycaemic control. A significant reduction of 0.27% in HbA_{1c} concentrations may be expected over a period of 8.5 ± 7 weeks with a GI reduction of 21 ± 7 units. Additionally, more than one type of low-GI food may need to be incorporated into the diet to achieve measurable long-term improvements in glycaemic control.

Poor blood glucose control has been associated with a greater incidence of long-term macrovascular complications in both type 1 and type 2 diabetic patients.[34-37] The UK Prospective Diabetes Study (UKPDS) Group[35] found that each 1% reduction in mean HbA_{1c} concentration was associated with a 21% risk reduction for deaths related to diabetes, 14% for myocardial infarction and 37% for microvascular complications. It is not yet clear precisely how low-GI diets improve the markers of carbohydrate metabolism and prevent the onset of type 2 diabetes. Several mechanisms have been proposed. Briefly, high-GI diets have been associated with high postprandial blood glucose concentrations and increased insulin demands.[38,39] Primary hyperinsulinaemia may cause insulin resistance, which reduces insulin sensitivity. Additionally, habitual consumption of high-GI meals over the long term initiates a cycle of hyperinsulinaemia and insulin resistance leading to a loss of pancreatic beta-cell function[38] that can result in glucose intolerance and an irreversible state of diabetes.[39] Hyperglycaemia also has deleterious effects on counter-regulatory hormone secretion, increases late postprandial serum free fatty acid (FFA) concentrations[38] and leads to the occurrence of oxidative stress.[40] Low-GI diets, on the other hand, tend to delay glucose absorption, therefore resulting in reduced peak insulin concentrations and overall insulin demand.[40]

Lipid metabolism

This meta-analysis pooled the results of 13 RCTs studying low- versus high-GI diets and their effects on markers of lipid metabolism. In the studies reviewed, low-GI diets showed a statistically significant improvement in TC concentrations, while non-significant improvements were observed in LDLC. No significant change was found in TG and HDLC with low-GI diets, although an inverse relationship was found in epidemiological studies between the GI and HDLC with lower-GI diets.[10,13,14] Contrary to general belief, an inverse relationship was found between low-GI diets and TG. According to Wolever *et al*.[19] insulin regulates both cholesterol and TG synthesis. One would therefore expect an improvement in TG concentrations because the marker for carbohydrate metabolism (HbA_{1c}) in this meta-analysis improved significantly. Furthermore, it appears obvious that improved blood glucose control would reduce insulin resistance accompanied by an improvement in TG concentrations. Nevertheless, intra-individual biological variation in TG concentrations has been well documented.[52,53] According to Nazir *et al*.[52] and Castro Cabezas *et al*.[53] several factors contribute to the variation of TG such as intervention diet (amount of fat and carbohydrate), exercise, alcohol consumption, diurnal and seasonal variation and smoking, and could possibly explain the lack of effects on TG concentrations. A possible explanation for the unchanged HDLC concentrations can be attributed to the length of studies. Intervention periods differed from only 2 weeks to 6 months.[17]

LDL cholesterol

Overall, low-GI diets tended to lower mean LDLC concentrations although not statistically significantly (change –0.15 mmol/l, 95% CI: –0.31, 0.00, $p = 0.06$). The GI of the diets was decreased by 21 ± 10 units. In type 2 diabetics, it seems that mean LDLC concentrations were decreased to a larger extent than in CHD and healthy subjects. Larger decreases in LDLC were reported for longer studies in well-controlled type 2 diabetic subjects[20,25] except for an unexpected non-significant increase in mean LDLC concentrations after 6 months, as reported by Tsihlias *et al*.[26] (Fig. 3).

The study by Tsihlias *et al*.[26] showed a non-significant increase in LDLC concentration over a period of 6 months. However, when this study is excluded from the meta-analysis, the effect of low-GI diets on LDLC is significant in type 2 diabetics (change –0.24 mmol/l, 95% CI: –0.45, –0.04, $p = 0.02$) as well as for the overall effect. The negative results from this study may be attributed to a relatively small GI reduction of 11 units, the fact that GI was lowered for only 1 meal (breakfast), and the possibility of poorer compliance with longer studies. Furthermore, not all available studies conducted on the GI and LDLC could be included. RCTs that showed promising results on low-GI diets and LDLC, but that did not report means and SDs for

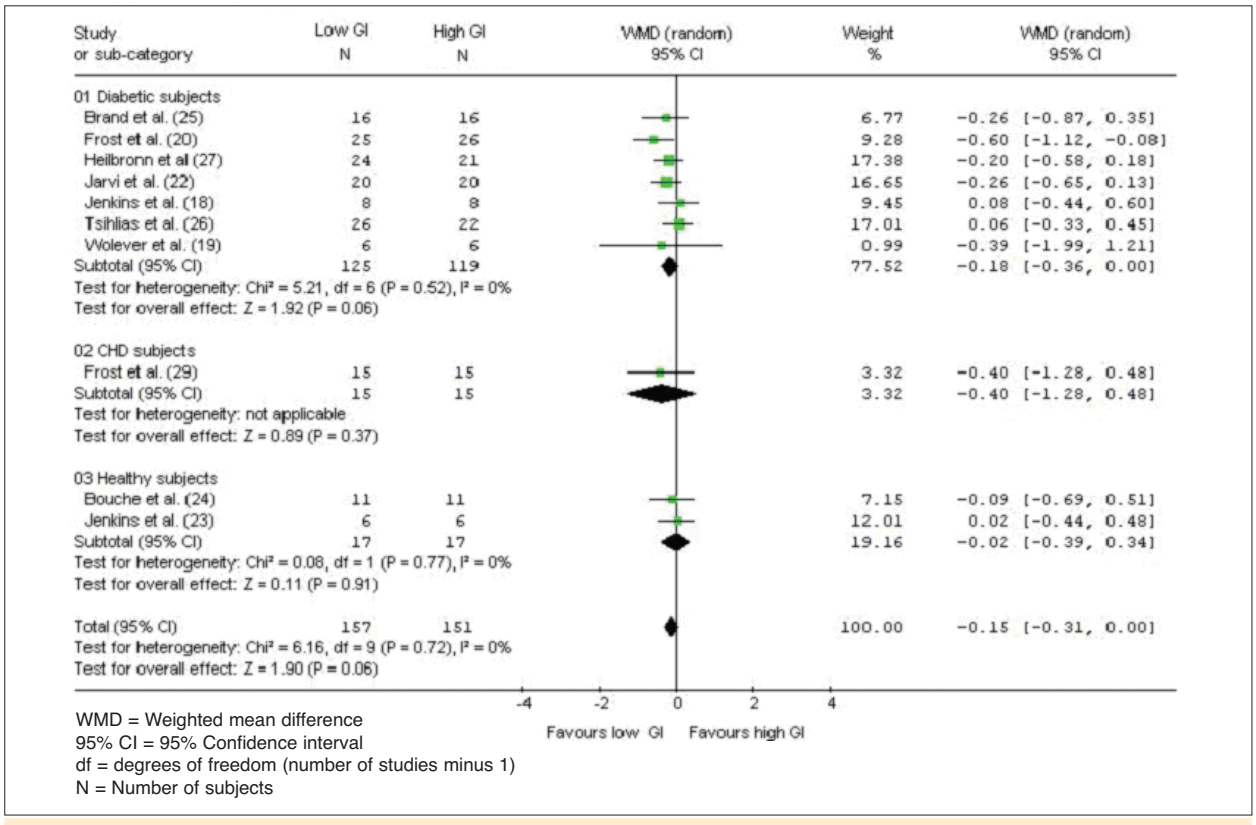

Fig. 3. Net changes in LDLC.

the change, were those by Jenkins *et al*.[41,42] Both these studies found significant improvements in LDLC concentrations with low-GI diets.

When comparing corresponding studies that measured markers of carbohydrate metabolism and LDLC,[22,25,27] improvements in LDLC concentrations were observed where decreases in fructosamine and HbA_{1c} were perceived. But how can low-GI diets contribute to lower LDLC concentrations? A possible mechanism may be that insulin resistance may occur with consumption of a high-GI diet because of the direct effects of hyperglycaemia.[38] Insulin resistance impairs normal suppression of FFA release from adipose tissue in the postprandial state.[43] According to Timar *et al*.[44] increased FFA released from abdominal adipose tissue, delivered to the liver, offers an efficient substrate for enhanced synthesis of TG and very-low-density lipoprotein cholesterol (VLDLC), resulting in elevated cholesterol concentrations.

Furthermore, with the prevalence of insulin resistance as seen in type 2 diabetics, LDL-receptor activity is reduced resulting in less LDLC removal from the blood, therefore contributing to higher LDLC concentrations.[45] Barakat *et al*.[46] explain that reduced receptor activity may be attributed to glycosylation of the LDL particle in the presence of hyperglycaemia. Glycosylated LDLC cannot bind as efficiently as non-glycosylated LDLC because of impairments in the binding of the LDL particles to LDL receptors and therefore glycosylated LDL particles will remain longer in circulation.

From these results, excluding the study by Tsihlias *et al*.,[26] it seems that low-GI diets have favourable effects on LDLC concentrations of type 2 diabetic subjects. A reduction of 0.20 mmol/l in LDLC concentration can be expected over a period of 10 ± 7 weeks with a GI reduction of 28 ± 8 units.

Total cholesterol

There was an overall statistically significant improvement in TC in subjects receiving low-GI diets compared with high-GI diets (change –0.33 mmol/l, 95% CI –0.47, –0.18, $p < 0.001$). This improvement was achieved by lowering the GI of the intervention diet by 22 ± 8 units. Larger decreases in TC concentrations were observed in patients with elevated TC baseline concentrations (> 5.2 mmol/l).[18-20,22,24,25,27-30] Two studies showed that mean TC concentrations of healthy subjects improved significantly on low-GI diets[18,24] while the studies of Frost *et al*.[29,31] found no change in patients with CHD (Fig. 4). The results of Frost *et al*.[29,31] could be attributed to the short intervention period of only 3 weeks.

In all the studies low-GI intervention diets improved TC to a greater or lesser extent. No significant improvements were observed in the 2 studies conducted on CHD patients, while a significant reduction was observed in the 2 studies performed on healthy subjects. From these findings it can be concluded that by lowering the GI by 19 ± 8 units over a time period of 8 ± 6 weeks, a significant decrease of 0.3 mmol/l can be expected in the TC concentrations of type 2 diabetic subjects.

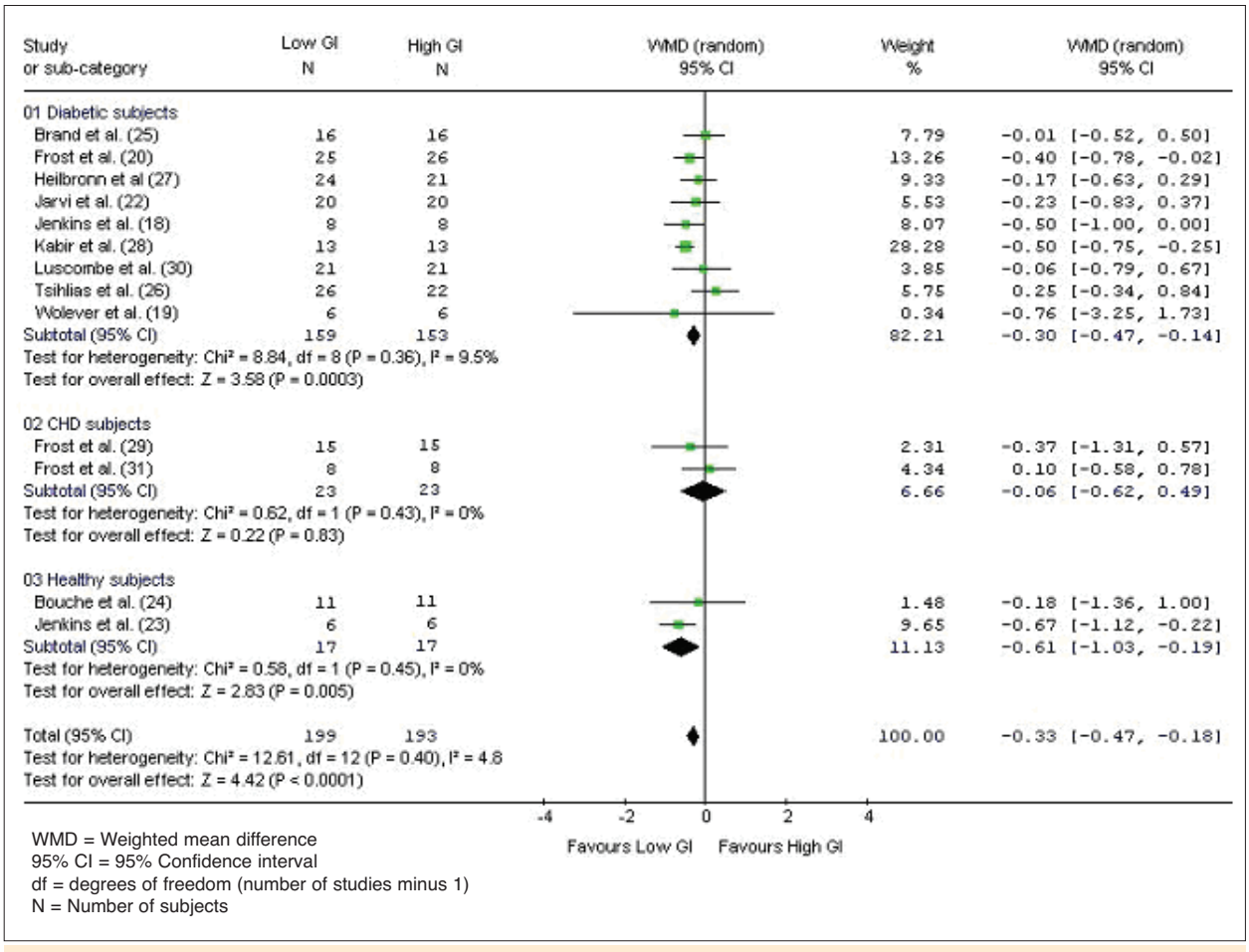

Fig. 4. Net changes in total cholesterol.

The mechanisms by which low-GI diets may reduce TC concentrations remain unclear. Speculatively, these mechanisms involve lower insulin-stimulated HMG-CoA reductase activity as a result of a reduced rate of carbohydrate absorption, impaired bile acid and cholesterol reabsorption from the ileum owing to the high fibre content of low-GI foods and inhibition of hepatic cholesterol synthesis by short-chain fatty acids such as propionate.[40]

Judging the evidence

When making decisions about clinical interventions Guyatt *et al.*[5] order the different types of primary study as follows: (*i*) systematic reviews and meta-analysis; (*ii*) well-designed randomised controlled trials with definite results (i.e. CIs that do not overlap the threshold clinically significant effect); (*iii*) randomised controlled trials with non-definitive results (i.e. a point estimate that suggests a clinically significant effect but with CIs overlapping the threshold for this effect); (*iv*) cohort studies; (*v*) case-control studies; (*vi*) cross-sectional surveys; and (*vii*) case reports.

Considering the evidence obtained, it seems that this review conforms to the first 2 criteria presented. This proves that there is convincing evidence to recommend the use of low-GI diets to improve markers for carbohydrate and lipid metabolism profiles. One could, therefore, expect significant improvements in fructosamine of –0.1 mmol/l with a GI reduction of 24 ± 9 units, and HbA_{1c} will improve by –0.27% with a reduction of 21 ± 7 GI units. For lipid metabolism, low-GI diets will significantly decrease LDLC concentrations by –0.24 mmol/l with a reduction of 21 ± 10 units and TC by –0.33 mmol/l with a GI reduction of 20 ± 9 units. Therefore, it is strongly recommended that the GI concept be implemented in a healthy diet, and dieticians should be encouraged to use the GI in practice, especially with regard to diets of patients with diabetes and other lifestyle diseases where hyperlipidaemia and poor glycaemic control are present.

Recommendations

Considering the information obtained from this review, the following recommendations are proposed. In the first place, epidemiological evidence showed improvements in HDLC concentrations when low-GI diets were consumed over long-term periods, while the meta-analysis of RCTs showed no effect over periods from 2 weeks to 6 months. It is therefore recommended that more long-term (> 6 months) intervention studies be performed to assess the effects of low-GI diets on

HDLC concentrations. It is also important to recruit highly motivated participants to ensure optimal compliance over such a long period.

Secondly, the possible relationship between low-GI diets and other non-communicable diseases should be investigated more thoroughly focusing on low-GI (< 55) versus high-GI (> 70) foods. There are indications that low-GI diets may benefit the prevention of obesity,[24,47,48,54] colon cancer and breast cancer[49-51] and a meta-analysis analysing the effect of low-GI diets on these diseases is suggested. Additionally a meta-analysis on epidemiological data regarding the glycaemic load and its effect on TG should be performed. Finally, the use of the GI concept in sports performance should be exploited fully. A systematic review of GI and sports performance is on our priority list.

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