Low–Glycemic Index Diets in the Management of Diabetes

A meta-analysis of randomized controlled trials

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OBJECTIVE — The use of diets with low glycemic index (GI) in the management of diabetes is controversial, with contrasting recommendations around the world. We performed a meta-analysis of randomized controlled trials to determine whether low-GI diets, compared with conventional or high-GI diets, improved overall glycemic control in individuals with diabetes, as assessed by reduced HbA_{1c} or fructosamine levels.

RESEARCH DESIGN AND METHODS — Literature searches identified 14 studies, comprising 356 subjects, that met strict inclusion criteria. All were randomized crossover or parallel experimental design of 12 days' to 12 months' duration (mean 10 weeks) with modification of at least two meals per day. Only 10 studies documented differences in postprandial glycemia on the two types of diet.

RESULTS — Low-GI diets reduced HbA_{1c} by 0.43% points (CI 0.72–0.13) over and above that produced by high-GI diets. Taking both HbA_{1c} and fructosamine data together and adjusting for baseline differences, glycated proteins were reduced 7.4% (8.8–6.0) more on the low-GI diet than on the high-GI diet. This result was stable and changed little if the data were unadjusted for baseline levels or excluded studies of short duration. Systematically taking out each study from the meta-analysis did not change the CIs.

CONCLUSIONS — Choosing low-GI foods in place of conventional or high-GI foods has a small but clinically useful effect on medium-term glycemic control in patients with diabetes. The incremental benefit is similar to that offered by pharmacological agents that also target postprandial hyperglycemia.

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Along with obesity, prevalence of diabetes is increasing in all parts of the world. With it comes an urgent need to identify the most cost-effective strategies of management. The benefits of improving glycemic, blood pressure, and lipid control on risk of complications are now confirmed (1,2). Whereas pharmacological therapies are clearly effective, the diabetes prevention trials in Finland and the U.S. remind us that nutrition and lifestyle approaches can be more effective in delaying onset of the disease (3,4). For those already diagnosed, however, the optimal diet remains controversial, particularly with regard to the glycemic index (GI) of foods (5).

Current dietary recommendations emphasize the quantity rather than the quality of carbohydrate, despite the fact that carbohydrate source and nature profoundly influence postprandial glycemia (6,7). Research on GI indicates that even when foods contain the same amount of carbohydrate (i.e., carbohydrate exchanges), there are up to fivefold differences in glycemic impact (8). In addition, several prospective observational studies have found that the overall GI and glycemic load (GI × g carbohydrate) of the diet, but not total carbohydrate content, are independently related to the risk of developing type 2 diabetes (9,10), cardiovascular disease (11), and some cancers (12,13). However, not all studies are in agreement, and further research is needed (14).

Although logic suggests that low-GI diets should improve glycemic control, the findings of randomized controlled trials have been mixed; some studies have shown statistically significant improvements (15,16) whereas other studies have not (17,18). As a result, the issue of the GI has been fraught with controversy and has polarized the opinions of leading experts (19,20). The American Diabetes Association acknowledges that use of low-GI foods may reduce postprandial hyperglycemia but asserts that there is not sufficient evidence of long-term benefit to recommend their use as a primary strategy (5). In contrast, the European Association for the Study of Diabetes recommends the substitution of low-GI foods for high-GI foods (21).

To help resolve this controversy and provide a more objective basis to guide dietary recommendations, we conducted a standard retrospective meta-analysis of randomized controlled trials comparing high- and low-GI diets in the management of type 1 and type 2 diabetes. The findings provide evidence that low-GI diets improve glycemic control over and above that obtained by

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Abbreviations: GI, glycemic index; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

See accompanying editorial, p. 2466.

Table 1—*Characteristics and outcomes of the studies included in the meta-analysis*

Study	Subjects (*n*)	Study design (GI of high versus low-GI diet)*	Duration on each diet (weeks)	Outcome HbA_{1c} or fructosamine†	Endpoint low GI	Endpoint high GI
Type 1 subjects						
Gilbertson et al. (16)	104	Parallel (79 vs. 77)	52	HbA_{1c}	8.0 (1)	8.6 (1.4)
Giacco et al. (15)	63	Parallel (90 vs. 70)	24	HbA_{1c}	8.6 (0.9)	9.1 (1.4)
Lafrance et al. (17)	9	Crossover (99 vs. 63)	1.9	Fructosamine	2.9 (0.6)	3.1 (0.3)
Fontvieille et al. (29)†	12	Crossover (90 vs. 53)	5	HbA_{1c}	8.3 (1.4)	8.3 (1.5)
				Fructosamine	3.41 (0.42)	3.88 (0.95)
Fontvieille et al. (44)	8	Crossover (84 vs. 65)	3	Fructosamine	2.17 (0.68)	2.77 (0.59)
Collier et al. (24)	7	Crossover (82 vs. 69)	6	HbA_{1c}	10 (1.2)	9.8 (1.5)
				GSA§	10.7 (5.8)	14.6 (5.0)
Type 2 subjects						
Fontvieille et al. (29)‡	6	Crossover (90 vs. 53)	5	HbA_{1c}	8.3 (1.4)	8.3 (1.5)
				Fructosamine	3.41 (0.42)	3.88 (0.95)
Komindr et al. (26)	10	Crossover (106 vs. 70)	4	HbA_{1c}	10.97 (1.55)	11.15 (2.02)
Luscombe et al. (18)	21	Crossover (88 vs. 60)	4	Fructosamine	3.22 (0.5)	3.28 (0.55)
Jarvi et al. (27)	20	Crossover (83 vs. 57)	3.5	HbA_{1c}	6.7 (1.3)	6.9 (1.3)
				Fructosamine	3.47 (0.72)	3.56 (0.75)
Frost et al. (25)	51	Parallel (82 vs. 77)	12	Fructosamine	3.2 (1.43)	3.6 (1.43)
Wolever et al. (28)	15	Crossover (87 vs. 60)	2	Fructosamine	3.17 (0.46)	3.28 (0.58)
Wolever et al. (32)	6	Crossover (86 vs. 58)	6	Fructosamine	4.56 (1.3)	5.12 (1.42)
Brand et al. (30)	16	Crossover (90 vs. 77)	12	HbA_{1c}	7.0 (1.2)	7.9 (2–0)
Jenkins et al. (31)	8	Crossover (91 vs. 67)	2	HbA_{1c}	7.6 (1.4)	7.8 (1.98)
				Fructosamine	2.98 (0.45)	2.95 (0.45)

Data are *n* or means (SD). *Mean GI on each diet using bread as the reference food (GI = 100). If glucose was used as the reference food, the value was multiplied by 100/70; †HbA_{1c} in % units and fructosamine in mmol/l; ‡Fontvielle et al. (30) presented combined results for 12 subjects with type 2 diabetes and 6 subjects with type 1 diabetes; §glycated albumin (GSA) in % units is an older measure of fructosamine.

conventional or high-GI diets. The incremental benefit is clinically significant and similar to that offered by newer pharmacological agents.

RESEARCH DESIGN AND METHODS

Identification and selection of studies

A detailed protocol was developed in advance. The question to be answered was whether low-GI diets, compared with conventional or high-GI diets, improved overall glycemic control in individuals with diabetes, as assessed by reduced HbA_{1c} or fructosamine levels. The low-GI diets were defined as those containing most carbohydrates from low-GI sources, such as beans, peas, lentils, pasta, pumpernickel bread, bulgur, parboiled rice, barley, and oats. High-GI diets were essentially standard diabetic diets and contained potato, wheat meal and white bread, and high-GI varieties of breakfast cereals and rice. Changes in HbA_{1c} or fructosamine levels, rather than fasting blood glucose level, were used as the outcome measures because both reflect overall glycemic control. HbA_{1c} reflects average glucose levels over the preceding 6–12 weeks and has been correlated with future risk of complications in both the Diabetes Control and Complications Trial (DCCT) (22) and U.K. Prospective Diabetes Study (UKPDS) (1). Fructosamine level reflects glycemic control over the preceding 2–4 weeks (23) and may provide a better measure of diabetes control than HbA_{1c} level in shorter trials.

The studies met the following strict inclusion criteria: published in full in English between 1981 and 2001, properly randomized cross-over or parallel experimental design, at least 12 days' duration, type 1 or type 2 diabetic patients as subjects, HbA_{1c} or fructosamine level as outcome measures of glycemic control, and modification of at least two meals per day (or >50% total carbohydrate) to constitute a high- or low-GI diet. Relevant studies were identified by Medline and internet searches using the key words "glyc(a)emic index" and "diabetes."

These criteria resulted in inclusion of 14 studies (listed in Table 1) in the meta-analysis. All of these studies included the words "glyc(a)emic index" in the title and keywords. In four studies (15,16,24,25), the low-GI diet was specifically compared with standard dietary advice. In the case of Gilbertson et al. (16), this advice was measured carbohydrate exchanges. In Giacco et al. (15) and Collier et al. (24), the low-GI diet was higher in fiber than the high-GI diet. A total of 10 of the 14 studies documented a lower postprandial glucose profile on the low-GI diet versus the high-GI diet (15,17,24,26–32). In a study by Gilbertson et al. (16), low-GI dietary instruction was associated with fewer episodes of hyperglycemia. Two studies did not meet the inclusion criteria. Calle-Pascual et al. (33) was excluded because lunch was the only meal that was modified, and consequently <20% of the total carbohydrate was exchanged. The study by Jenkins et al. (34) included only healthy subjects.

The steps used to execute the meta-analysis were drawn from Petitti (35). A fixed-effects model was implemented rather than a random-effects one. A fixed-effects model assumes that the inference is

conditional on the studies actually performed, whereas a random-effects model assumes that the studies used in the analysis are a random sample of a hypothetical population of studies.

None of the studies gave standard deviations of individual low-GI to high-GI differences; however, Brand et al. (30) provided a graph from which raw data could be read. Therefore, the variance for each study was calculated under two assumptions: first, the two values for each person were independent; and second, the two values for each person were dependent with a correlation of 0.34, which was the value in Brand et al. (30). The studies were then weighted by the reciprocal of the variance. The overall effect estimate and 95% CIs were then computed using these weights. The hypothesis of homogeneity of effect was tested, and where it was rejected, a sensitivity analysis was conducted by removing individual studies one by one.

RESULTS — Altogether, 14 studies were included in the final analysis, comprising a total of 356 subjects (203 with type 1 diabetes and 153 with type 2 diabetes). The general characteristics and outcomes of the studies, including number of subjects, study design, mean GI, and duration of each dietary intervention, are shown in Table 1. The average GI of the high- and low-GI diets was 83 and 65, respectively, on the bread scale, but the difference between the two varied from study to study (mean difference 22 GI units, range 2–37). One study included 104 children with type 1 diabetes, making it one of the largest randomized dietary intervention studies to be conducted in this patient group (16). The biggest study in type 2 diabetic subjects had 50 subjects (25). Many studies, however, involved less than 25 subjects and were of short duration.

HbA_{1c}

In the eight studies in which HbA_{1c} level was determined, the analysis showed no evidence of heterogeneity among the studies. The mean difference in end point values between the low-GI and high-GI diets (i.e., low GI – high GI) was −0.40 absolute percentage points (95% CI −0.66 to −0.14), assuming dependence, or −0.43 (−0.72 to −0.13), assuming independence. If final HbA_{1c} values were adjusted for baseline values, the mean difference was reduced to −0.33 units (−0.59 to −0.07), assuming dependence, or −0.34 units (−0.64 to −0.05), assuming independence. Because zero fails to lie in the 95% CIs (assuming either independence or the same level of dependence), evidence of significant differences exists between end point HbA_{1c} values.

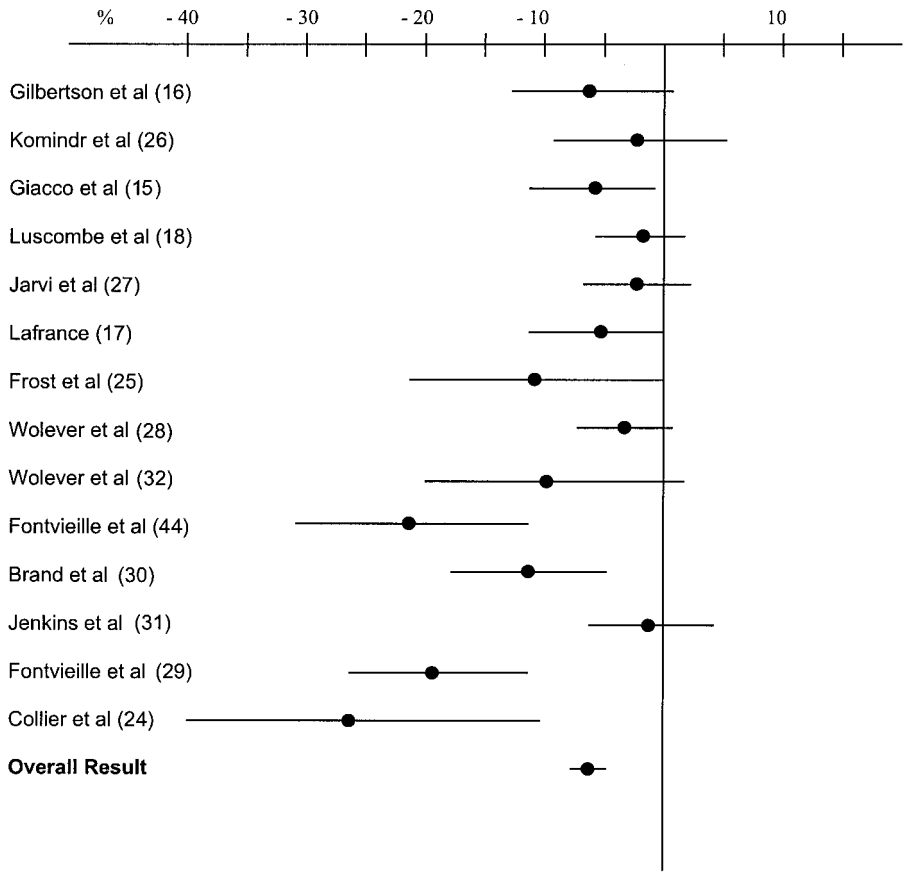

Figure 1—*A meta-analysis was performed using either the end point HbA_{1c} or fructosamine data in all 14 studies. Because these factors have different units of measurement, the difference between the two diets has been expressed in percentage terms. Points to the left of the vertical line indicate that the low-GI diet reduced values by x% over and above that seen with the high-GI diet. When final values were adjusted for differences at baseline, the mean difference was −7.4% (−8.8 to −6.0) in favor of the low-GI diet, assuming independence.*

Fructosamine

In the 10 studies that documented changes in fructosamine level, the mean difference (in favor of the low-GI diet) was −0.17 mmol/l (95% CI −0.30 to −0.04) using the dependent assumption and −0.18 mmol/l (−0.33 to −0.02) using the independent assumption. When we adjusted for baseline values, the differences were larger: −0.19 mmol/l (−0.32 to −0.06) dependent and −0.2 mmol/l (−0.35 to −0.04) independent. In each case, there was no problem with heterogeneity among the studies.

HbA_{1c} and fructosamine data combined

A meta-analysis was performed using either the HbA_{1c} or fructosamine data in all 14 studies. When both outcomes were reported, fructosamine was favored if the duration was ≤6 weeks. Because the units of measurement differ between these two indexes of glycemic control, the primary outcome was the mean difference between the two diets, expressed as a percentage of the final value on the high-GI diet [(low GI – high GI) × 100/high GI].

The mean difference was −6.8% in favor of the low-GI diet (95% CI −8.1 to −5.5) assuming dependence or −6.8% (−8.2 to −5.4) assuming independence. If final values were adjusted for differences at baseline, the difference was −7.3% (−8.6 to −6.0) in favor of the low-GI diet assuming dependence and −7.4% (−8.8 to −6.0) assuming independence. If the three shortest studies

were excluded (17,27,28), then the difference (baseline-adjusted) was even greater: −8.4% (−9.9 to −6.8) assuming dependence and −8.4% (−10.0%, −6.8%) assuming independence. Because zero does not lie within the 95% CIs, there are significant differences favoring the low-GI diet. The results of the full combined analysis are illustrated in Fig. 1.

Because there was evidence of heterogeneity in this combined analysis, a sensitivity analysis was performed. Systematically removing each study resulted in changes in the difference and the CIs; however, none of the CIs changed enough to include zero, and hence, no single study made a major impact on the overall conclusion.

Type 1 versus type 2 diabetes

Differences in outcomes between subjects with type 1 and type 2 diabetes were explored in the combined analysis. In the six studies of subjects with type 1 diabetes, the mean difference in favor of low-GI diets was −10.6% (−12.7 to −8.6) assuming dependence, and −10.2% (−12.4 to −8.1) assuming independence. In the nine studies that included subjects with type 2 diabetes, one of which (29) included both types of diabetes, the mean difference was −5.9% (−7.5 to −4.3) assuming dependence and −6.1% (−7.8 to −4.3) assuming independence. All differences were adjusted for baseline values.

CONCLUSIONS — Many of the studies included in the meta-analysis involved only small numbers of subjects and were of short duration. Nonetheless, the findings suggest that there are clinically useful benefits of using low-GI diets in the management of diabetes, over and above those produced by conventional or high-GI diets. After an average duration of 10 weeks, subjects with type 1 and type 2 diabetes who were following low-GI diets had HbA_{1c} levels ~0.4% points (CI 0.1–0.7) lower than those ingesting a high-GI diet. Over a shorter period (~4 weeks), fructosamine levels were 0.2 mmol/l lower (0.04–0.35). A total of 14 randomized controlled trials comprising 356 subjects (203 with type 1 diabetes and 153 with type 2 diabetes) enrolled for periods ranging from 12 days to 12 months were included in the meta-analysis. Only those trials that assessed HbA_{1c} or fructosamine level as outcome measures and modified at least two meals per day (or >50% total carbohydrate) were considered. A total of 10 of the 14 studies documented differences in the postprandial glucose profile between the two types of diet.

It is not likely that the meta-analysis has overestimated the effect of a low-GI diet. The mean incremental benefit in HbA_{1c} units of ~0.4 was smaller than that observed in the largest and longest randomized controlled trial, the study by Gilbertson et al. (16), in which the difference was 0.6 HbA_{1c} units. Studies of more than 8 weeks' duration have a greater chance of demonstrating the full effect of an intervention on HbA_{1c} level, whereas the meta-analysis included several short studies. In those instances, fructosamine level provides a better estimate of overall glycemic control. Taking HbA_{1c} level in the longer studies (>6 weeks) and fructosamine level in the shorter studies (≤6 weeks), the combined meta-analysis suggests that low-GI diets will reduce glycated proteins by an additional 7 or 8% over and above that seen with high-GI diets. This equates to an incremental benefit of 0.6 HbA_{1c} units if the end point HbA_{1c} level is 8.0%. The UKPDS found that in patients with type 2 diabetes, a 1% point reduction in mean HbA_{1c} level resulted in a reduction of 21% in any diabetes-related end point, 21% for diabetes-related death, 14% for myocardial infarction, and 37% for microvascular complications (36). Because the relationship was continuous, any reduction in HbA_{1c} level, no matter how small, improves prognosis.

The high-GI diets in the meta-analysis were, on the whole, representative of standard diabetic diets. Their average GI of 83 (using the bread scale) is comparable to the mean GI of 82 in the EURODIAB study of ~2,800 people with type 1 diabetes (37) and the mean GI of 85 in individuals with type 2 diabetes (38). In some cases, the low-GI diets were designed to maximize differences in GI between the two diets, but there was a wide range, varying from as little as 2 to 15 GI units in one-half of the studies (Table 1).

Although most studies proved differences in postprandial glycemia on profile days, dietary compliance is still debatable because the subjects were all free-living individuals. Investigators often provided the key carbohydrate foods for each diet, but in only one case were all foods provided (27). Dietary records were also used to verify nutrient composition and calculate the average GI. In the study by Gilbertson et al. (16), the prescribed diets differed in GI but the children's food diaries did not reveal a significant difference at 12 months. The high prevalence of under-reporting suggested that their dietary data were unreliable. Self-blood glucose monitoring revealed more frequent hyperglycemia among children on the exchange diet and their end point HbA_{1c} levels were 0.6% points higher than in those given low-GI advice.

The findings of the meta-analysis are also consistent with large-scale observational studies. The EURODIAB study of >2,800 people with type 1 diabetes in 31 clinics throughout Europe reported that the GI of the diet was positively and independently related to HbA_{1c} level (37). Compared with the highest GI quartile, adjusted HbA_{1c} level in the lowest GI quartile was 11% lower in patients from southern Europe and 6% lower in patients from the remaining parts of Europe. This implies that self-selected low-GI diets, not simply those used in a research setting, are associated with better metabolic control.

The incremental improvement in glycemic control afforded by a low-GI diet can be compared with that achieved with other medical interventions. Diets high in monounsaturated fat have been found to produce desirable effects on the lipid profile but not HbA_{1c} or fructosamine level (39). New insulin preparations such as insulin lispro and insulin aspart, which specifically target postprandial glycemia, produce small improvements in comparison to soluble human insulin, typically a decrease of 0.1–0.2 HbA_{1c} units (40,41). Acarbose therapy, which also targets postprandial glycemia, produced a decrease of 0.5% points in the UKPDS (42). The end point difference between the metformin group and the conventional group in the UKPDS was 0.6 HbA_{1c} units (43).

One of the potential effects of low-GI diets is to reduce insulin secretion in patients with type 2 diabetes and to reduce daily insulin requirements in patients type 1 diabetes. Wolever et al. (38) observed a 30% reduction in urinary C-peptide levels in subjects with type 2 diabetes on a low-GI diet, indicating reduced endogenous insulin demand. However, in the five of the six studies per-

formed in subjects with type 1 diabetes, the differences in HbA_{1c} or fructosamine level were not related to differences in insulin dose at the end of the study period or to changes in insulin dose over time. In only one study were daily insulin needs reduced (by ~6%) on the low-GI diet (44). In separate studies of patients on continuous subcutaneous insulin infusion, the GI was found to be helpful in the prediction of prandial insulin requirements (45), but in subjects on basal-bolus regimens, the GI did not affect premeal insulin requirements (46).

The strength and limitations of this meta-analysis should be considered. A rigorous appraisal of the evidence was undertaken according to strict principles: a prospective protocol, comparable definitions of outcomes, quality control of data, and a total sample large enough to provide reliable results. The trials were randomized, but the adequacy of randomization can only be verified by checking the data of individual patients. Published trials often do not include outcomes of withdrawals after randomization. Results of negative trials may not have been published (publication bias), and a meta-analysis of small trials with nominally significant *P* values will tend to overestimate the difference between the two diets. However, controversy surrounding the GI may mean that negative studies are more, not less, likely to be published. The present analysis included several large studies involving ~50–100 patients, in which the effect of intervention was greater than that determined by the meta-analysis.

Any difference in glycated proteins between two diets may be confounded by differences in energy intake or weight loss. In most studies, body weight, calories, protein, fat, and carbohydrate and fiber intake were generally held constant. In two studies (15,24), the low-GI diet was found to contain substantially more fiber, and it is not possible to separate the effects of the fiber per se from that of the low-GI foods. However, the mechanisms by which viscous fiber exerts its beneficial effects on glycemic control may be similar to those of low-GI foods, by slowing the rate of carbohydrate absorption. Indeed, the classic studies that demonstrated the beneficial effects of high-carbohydrate diets on glycemic control were so high in fiber that they were probably de facto low-GI diets (47,48). Alternative strategies that slow absorption of carbohydrate from meals, including use of acarbose therapy (42) and supplements of viscous fiber (49), also produce improvements in glycemic control.

Limitations of the meta-analysis include the small number of subjects in many of the studies, their relatively short duration, and the doubt surrounding dietary compliance that compromises any free-living study. These factors tend to reduce rather than increase the chance of a significant finding. Finally, because the meta-analysis is retrospective, it is subject to the limitations of any form of retrospective research.

Taking these limitations into account, the meta-analysis provides objective evidence that targeting postprandial hyperglycemia via choice of low-GI foods has a small but clinically useful effect on medium-term glycemic control in diabetes. Nutrition and lifestyle approaches to diabetes prevention and treatment should be given at least as much attention as drug therapies. Low-GI dietary advice seems to improve glycemic control to the same or greater extent as newer pharmacological agents, such as the short-acting insulin analogs. This gives patients a choice as well as reduces the size of the health care budget. Only large long-term randomized, controlled trials will determine whether low-GI diets decrease the risk of complications as well. The wider implementation of a low-GI diet will depend on the continuing identification of low-GI foods. This requires GI testing of local products according to standardized in vivo methodology (50) to expand the list of low-GI foods so that dietary variety and palatability are not compromised.

ADDENDUM — Since the completion of the meta-analysis, Heilbronn et al. (51) published a study of 45 subjects with type 2 diabetes. Inclusion of their data does not change the CIs: in the combined analysis, the mean difference becomes −7.20% (−8.56 to −5.85); in the HbA_{1c} analysis, the difference is −0.34 (−0.61 to −0.07).

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