Enteral Nutritional Support and Use of Diabetes-Specific Formulas for Patients With Diabetes

A systematic review and meta-analysis

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OBJECTIVE — The aim of this systematic review was to determine the benefits of nutritional support in patients with type 1 or type 2 diabetes.

RESEARCH DESIGN AND METHODS — Studies utilizing an enteral nutritional support intervention (oral supplements or tube feeding) were identified using electronic databases and bibliography searches. Comparisons of interest were nutritional support versus routine care and standard versus diabetes-specific formulas (containing high proportions of monounsaturated fatty acids, fructose, and fiber). Outcomes of interest were measures of glycemia and lipid status, medication requirements, nutritional status, quality of life, complications, and mortality. Meta-analyses were performed where possible.

RESULTS — A total of 23 studies (comprising 784 patients) of oral supplements (16 studies) and tube feeding (7 studies) were included in the review, and the majority compared diabetes-specific with standard formulas. Compared with standard formulas, diabetes-specific formulas significantly reduced postprandial rise in blood glucose (by 1.03 mmol/l [95% CI 0.58–1.47]; six randomized controlled trials [RCTs]), peak blood glucose concentration (by 1.59 mmol/l [86–2.32]; two RCTs), and glucose area under curve (by 7.96 mmol $\cdot l^{-1} \cdot min^{-1}$ [2.25–13.66]; four RCTs, i.e., by 35%) with no significant effect on HDL, total cholesterol, or triglyceride concentrations. In addition, individual studies reported a reduced requirement for insulin (26–71% lower) and fewer complications with diabetes-specific compared with standard nutritional formulas.

CONCLUSIONS — This systematic review shows that short- and long-term use of diabetes-specific formulas as oral supplements and tube feeds are associated with improved glycemic control compared with standard formulas. If such nutritional support is given long term, this may have implications for reducing chronic complications of diabetes, such as cardiovascular events.

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Abbreviations: AUC, area under the curve; CCT, controlled CT; CT, clinical trial; ETF, enteral tube feeding; MUFA, monounsaturated fatty acid; ONS, oral nutritional supplement; RCT, randomized controlled trial.

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

The impact of better glycemic control on long-term clinical outcome is well recognized in both type 1 (1) and type 2 (2) diabetes, where hyperglycemia may result in life-threatening complications and numerous comorbidities. In addition, many conditions, including accidental injury, stroke, and critical illness, show a worse outcome in the presence of hyperglycemia (3).

In the U.K., the costs associated with major hyperglycemic complications range from £872 (€1,256 or $1,607 for blindness in one eye) to £8,459 (€12,178 or $15,591 for amputation) per patient (4), and the U.S. has reported annual diabetes health care costs of $11,157 (€8,710) per patient (5). This large economic burden is unsurprising given that patients with diabetes are known to be admitted to the hospital more often than other patient groups, accounting for up to 25% of intensive care admissions (3,6). Many of these hospitalized patients will require nutritional support. In addition, an increasing number of patients receive long-term home enteral tube feeding (ETF), including those with diabetes (7).

Standard enteral (oral or tube) nutritional formulas are high in carbohydrate (mostly low–molecular weight sources), low in fat, and low in fiber. Standard formulas may compromise glycemic control in patients with diabetes, due to a rapid gastric emptying rate and rapid nutrient assimilation (8,9). For this reason, diabetes-specific formulas have been developed.

Diabetes-specific formulas contain a defined nutrient composition designed to enable better glycemic control. Such nutrients include fructose (10), fiber (11), monounsaturated fatty acids (MUFAs) (12), soy protein (13,14), and antioxidants (15). Although general guidelines exist regarding the composition of the diet for those with diabetes (16–18), there are no specific guidelines for patients with diabetes who are at risk of malnutrition, requiring nutritional support.

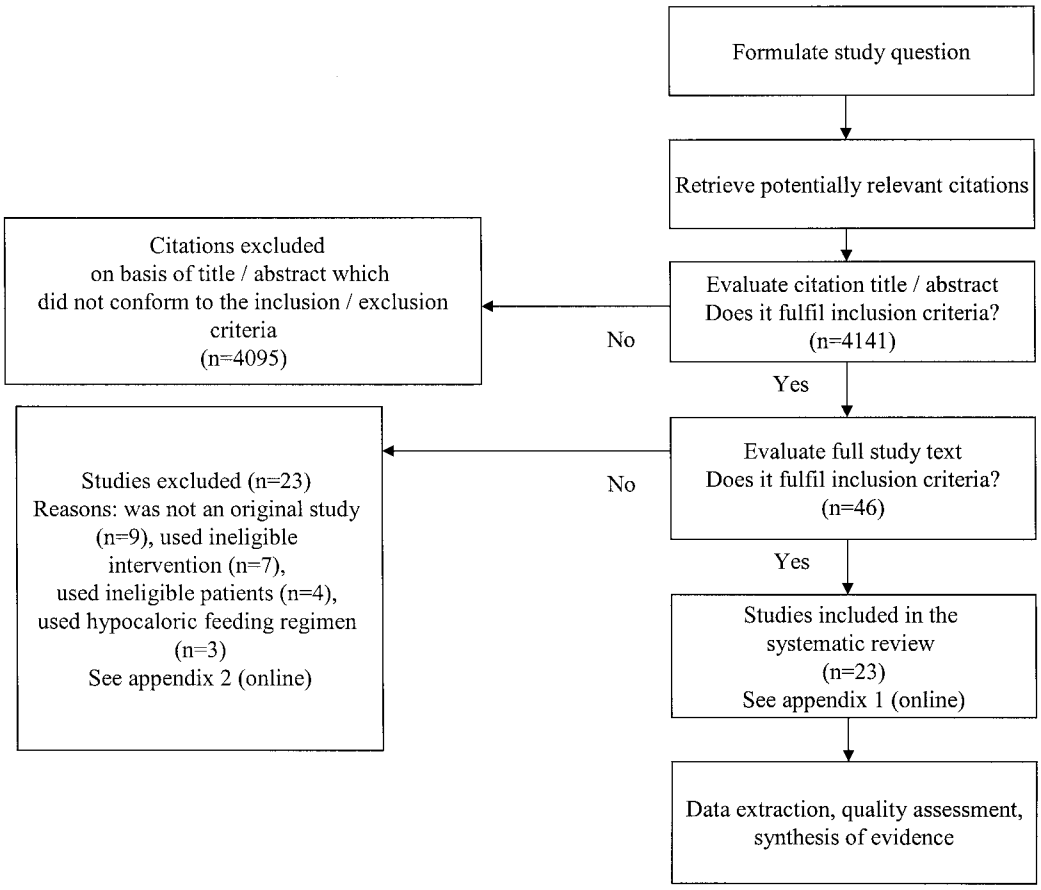

Fig. 1—*Summary of study methodology stages and process of the systematic review*

For example, although general guidelines suggest that a high intake of MUFAs/total fat may be disadvantageous for the well-nourished patient with diabetes, this may be advantageous for the treatment of a malnourished patient. Malnutrition is seen in several patient groups with diabetes, especially in the elderly (19,20) and those with complications such as renal failure or neurological dysfunctions. In these patients, an impaired nutritional status is associated with increased susceptibility to and recovery from infectious complications, the development of pressure sores (and their failure to heal), and general functional decline (21). Nutritional support using diabetes-specific formulas in these patient groups may prevent such complications.

There have been no systematic reviews or meta-analyses regarding the use of enteral nutritional support in patients with diabetes, although a few clinical reviews have been published (8,9,22). Therefore, a systematic review and meta-analysis was undertaken with the following aims: *1*) to examine the impact of enteral (oral or tube) nutritional support versus routine care on the nutritional status and clinical outcome of patients with diabetes and, more specifically, *2*) to investigate whether diabetes-specific enteral formulas are superior to standard enteral formulas by assessing the effects of these on glycemia, lipidemia, nutritional status, medication requirements, quality of life, complications, and mortality.

RESEARCH DESIGN AND METHODS

— The review was planned, conducted, and reported following published guidelines. These include those issued by the Cochrane Collaboration (23), the U.K. National Health Service Centre for Reviews and Dissemination (24,25), and the QUOROM guidelines (26). A flow chart (Fig. 1) illustrates the principle stages and processes undertaken.

Identification and retrieval of studies

Potentially relevant studies were identified by searching electronic databases. These included PubMed (27), accessed 10 August 2004; Cochrane (28), accessed 10 August 2004; Turning Research Into Practice (29), accessed 19 August 2004; Clinical Evidence (30), accessed 19 August 2004; National Electronic Library for Health Guidelines finder (31), accessed 19 August 2004; and National Service Frameworks (32), accessed 19 August 2004. The search terms included: diabetes mellitus, diabetic, monounsaturat*, mono-unsaturat*, MUFA, mono unsaturat*, soy, soya, fructose, fiber, fiber, nutrition*, nutrie*, enteral*, oral*, supplement*, sip, feed, formula*, liquid, tube, nasogastric, nasojejunal, nasoduodenal, gastrostomy, jejunostomy, clinical trial. Bibliographies of identified trials were checked and experts consulted for any additional studies.

Study selection criteria, data extraction, and outcome measures

Studies were deemed eligible for inclusion in the review if they conformed to predetermined inclusion and exclusion criteria. Subjects eligible for inclusion

were adults (aged >18 years) with type 1 or type 2 diabetes or stress diabetes caused by acute illness, of any nutritional status (well nourished, malnourished), and based in any setting (e.g., hospital, outpatient, home). Studies using hypocaloric feeding regimens in obese subjects with the intention of inducing weight loss were excluded. Eligible interventions were formulas given enterally, either orally (oral nutritional supplements [ONSs]]) or by tube (ETF) that contained at least two macronutrients as well as micronutrients. The intervention could provide either a portion of, or the complete daily requirement for energy and could be nutritionally complete or incomplete. Studies using concurrent parenteral nutrition or dietary advice were admissible, but those utilizing only parenteral nutrition or only dietary counseling were excluded. The comparisons of interest for both ONSs and ETF were nutritional support versus routine care, diabetes-specific formula versus standard formula, and a comparison of ETF versus parenteral nutrition. As the definition and composition of diabetes-specific formulas can be variable, for the purpose of this review formulas containing a high proportion (e.g., >60%) of fat, such as MUFAs and fructose and fiber, were designated "diabetes specific," and all other formulations were designated "standard formula." Where a study provided three or more eligible intervention arms, the two interventions used in the analysis were selected according to the compositions closest to a typical standard and a diabetes-specific feed.

Outcome measures sought were glycemia, lipidemia, nutritional status, medication requirements, quality of life, complications, and mortality. Where multiple measurements were provided (e.g., multiple blood samples taken postprandially), the last in each series was used. No other restrictions were placed on studies with regard to type of comparator (e.g., no nutritional support, dietary advice, parenteral nutrition), year of publication, language (providing an English translation of the report or its abstract was available), and source. Priority was given to randomized controlled trials (RCTs); however, nonrandomized controlled clinical trials (CCTs) and before-after clinical trials (CTs) were admissible. Observational study designs (e.g., cohort, case study) were excluded. Following the identification of potentially relevant studies based on titles and abstracts, full articles were obtained and evaluated by one researcher; a second assessor verified inclusion/exclusion decisions. A predetermined data extraction table was designed to capture study characteristics and outcome data and allow the assimilation of data from differing study designs.

Quality assessment

The quality of individual studies was assessed using two scales (33,34) by one researcher and verified by a second assessor. The first method was a six-point scale adapted from the Quality of Evidence Quality Assessment Scale (Agency for Health Care and Policy Research) (33), and the second method was that used by Jadad et al. (34), which was previously reported.

Synthesis of data and statistical methods

Following extraction of data, where appropriate and feasible, the results of comparable groups of trials were combined and meta-analysis undertaken on relevant outcome measures. The comparisons of interest were nutritional support versus routine care, diabetes-specific formula versus standard formula, and ETF versus parenteral nutrition. Subanalyses were planned for studies of different length follow-up (<1 day vs. >1day), and separate analyses were intended for diabetes type (type 1 versus type 2) and nutritional status (malnourished versus well nourished versus obese).

Hedges' unbiased estimator of the standardized mean difference for relevant treatment comparisons was calculated (35). The mean treatment difference was considered statistically significant if the 95% CI did not span the value zero. Forest plots were used to present each study's standardized difference and the meta-analysis estimate. Heterogeneity was investigated from the Q test of heterogeneity derived by the Mantel-Haenszel method (36). Due to the small number of studies included in the meta-analyses, it was deemed inappropriate to investigate publication bias through the use of funnel plots (37). A fixed-effects model was used to combine the treatment estimates, which assumes no heterogeneity between the study results. A meta-analysis estimate of the treatment effect size was calculated as a weighted sum of the effect size for each study, where the weight was calculated as the reciprocal of Hedges' estimated variance of the effect size for each individual study.

The selection of data for analysis was conducted as follows: change from baseline data were used, except if one or more studies in the meta-analysis failed to report baseline data, in which case postintervention data were used. The correlation between baseline and postintervention data for measures of glycemia and lipidemia was assumed to be zero ($r = 0$), which results in the most conservative method of analysis. The sensitivity of this assumption was tested by additionally conducting the analyses using $r = 0.5$. All statistical analyses were conducted using SAS version 8.2 (SAS Institute, Cary, NC). All data are presented as means ± SD, unless otherwise stated.

RESULTS

Overall search findings

A total of 4,141 studies were identified by the search strategy, of which 23 complied with the inclusion criteria and were included in the review (Fig. 1). Study details are provided in appendix 1 (online appendix [available at http://care.diabetesjournals.org]), and reasons for study exclusion are provided in appendix 2 (online appendix).

Of the 23 studies included in the review, 19 were RCTs (11,14,38–54) scoring the highest grade of one, according to the Quality of Evidence Scale (33). However, the methodology of individual RCTs was often poorly described (with regard to methods of randomization, blinding, and recording number of drop-outs), with only three studies (45,47,48) scoring the top grade of five on the Jadad scale (34). The remaining RCTs scored four (46,49), three (38,54), two (11,14,39–44,50,52), or one (51,53). The review also included three CCTs (55–57), scoring two on the Quality of Evidence Scale (33) and one CT (58) scoring four.

Most trials consisted of patients with type 2 diabetes ($n = 16$), with fewer studies of patients with type 1 diabetes ($n = 4$). A minority of studies did not specify the type of diabetes ($n = 1$), included patients with type 1 or type 2 diabetes and/or stress diabetes caused by acute illness ($n = 1$), or included only patients with stress diabetes caused by acute illness ($n = 1$).

Table 1—*Data used in the meta-analyses*

Variable	Citation	Timing of samples	Intervention	*n*	Baseline	Postintervention	Change from baseline
Postprandial rise in glucose	Peters et al., 1989	baseline (fasted) = 0 mins, postintervention = postprandial 240 mins after meal start	Standard formula	10	NR	NR	1,900 ± 320 mg · l^{-1} · 4 h^{-1}*
			Diabetes-specific formula	10	NR	NR	−20 ± 330 mg · l^{-1} · 4 h^{-1}*
	Sanz-Paris et al., 1998 (insulin)	baseline = 0 mins (fasted), postintervention = postprandial 120 mins after meal start	Standard formula	20	1,750 ± 480 mg/l*	2,560 ± 540 mg/l*	NR†
			Diabetes-specific formula	20	1,940 ± 560 mg/l*	2,160 ± 720 mg/l*	NR†
	Sanz-Paris et al., 1998 (sulphonyurea)		Standard formula	5	1,510 ± 200 mg/l*	1,900 ± 460 mg/l*	NR†
			Diabetes-specific formula	7	1,580 ± 290 mg/l*	2,030 ± 480 mg/l*	NR†
	del Carmen Crespillo et al., 2003	baseline = 0 mins (fasted), postintervention = postprandial 150 mins after meal start	Standard formula	11	NR	NR	184 ± 133 mg/l
			Diabetes-specific formula	11	NR	NR	−8 ± 99 mg/l
	Craig et al., 1998	Baseline = fasted, postintervention = postprandial, both after 3 months intervention	Standard formula	13	6.9 ± 0.6 mmol/l*	10.4 ± 1 mmol/l*	NR†
			Diabetes-specific formula	14	7.3 ± 0.4 mmol/l*	9 ± 1.3 mmol/l*	NR†
	McCargar et al., 1998	Baseline = fasted (premeal), postintervention = 2 h postprandial after 28 days intervention	Standard formula	16	NR	NR	1.6 ± 0.4 mmol/l*
			Diabetes-specific formula	16	NR	NR	1.1 ± 0.2 mmol/l*
	Mesejo et al., 2003	Baseline = on admission (study start), postintervention = postprandial after 14 days intervention	Standard formula	24	2,103 ± 630 mg/l	2,228 ± 471.2 mg/l	NR†
			Diabetes-specific formula	26	1,909 ± 450 mg/l	1,768 ± 440.1 mg/l	NR†
Peak blood glucose	Hofman et al., 2004	Baseline = 0 mins (fasted), postintervention = 6 h after meal start	Standard formula	12	NR	NR	4 ± 1.4 mmol/l
			Diabetes-specific formula	12	NR	NR	2.5 ± 1 mmol/l
	Hofman et al., 2004	Baseline = 0 mins (fasted), postintervention = 120 mins after meal start	Standard formula	10	NR	NR	4 ± 0.4 mmol/l*
			Diabetes-specific formula	10	NR	NR	2.3 ± 0.4 mmol/l*
Blood glucose AUC	Golay et al., 1995	IAUC (mmol/Lxh), 4 h	Standard formula	6	NR	NR	15.9 ± 2.3 mmol · l^{-1} · h^{-1}*
			Diabetes-specific formula	6	NR	NR	8.9 ± 1.8 mmol · l^{-1} · h^{-1}*
	Printz et al., 1997	AUC (mmol/l*min), over basal (0–180 mins)	Standard formula	10	NR	NR	893 ± 77 mmol · l^{-1} · h^{-1}*
			Diabetes-specific formula	10	NR	NR	620 ± 64 mmol · l^{-1} · h^{-1}*
	Hofman et al., 2004	iAUC (mmol/Lx min), 6 h	Standard formula	12	NR	NR	945 ± 474 mmol · l^{-1} · min^{-1}
			Diabetes-specific formula	12	NR	NR	584 ± 322 mmol · l^{-1} · h^{-1}
	Hofman et al., 2004	AUC (mmol/l/120mins) above baseline level	Standard formula	10	NR	NR	307 ± 29 mmol · l^{-1} · 120 $mins^{-1}$*
			Diabetes-specific formula	10	NR	NR	168 ± 31 mmol · l^{-1} · 120 $mins^{-1}$*
Fasting blood glucose	Craig et al., 1998	baseline = study start, postintervention = after 3 months intervention, all fasted	Standard formula	13	6.9 ± 0.6 mmol/l*	8.3 ± 1.7 mmol/l*	NR†
			Diabetes-specific formula	14	7.3 ± 0.4 mmol/l*	6.7 ± 0.7 mmol/l*	NR†
	McCargar et al., 1998	baseline = study start, postintervention = after 28 days intervention, all fasted	Standard formula	16	8.73 ± 0.46 mmol/l*	7.97 ± 0.53 mmol/l*	NR†
			Diabetes-specific formula	16	9.16 ± 0.59 mmol/l*	7.54 ± 0.37 mmol/l*	NR†

HDL	Craig et al., 1998	baseline = study start, postintervention = after 3 months intervention, all fasted	Standard formula	13	0.98 ± 0.05 mmol/l*	0.83 ± 0.05 mmol/l*		NR†
			Diabetes-specific formula	14	1.01 ± 0.05 mmol/l*	0.98 ± 0.05 mmol/l*		NR†
	McCargar et al., 1998	baseline = study start, postintervention = after 28 days intervention, probably fasted	Standard formula	16	1.37 ± 0.19 mmol/l*	1.08 ± 0.07 mmol/l*		NR†
			Diabetes-specific formula	16	1.5 ± 0.16 mmol/l*	1.2 ± 0.1 mmol/l*		NR†
Triglycerides	Peters et al., 1989	baseline = 0 mins (fasted), postintervention = 240 mins after meal start (postprandial)	Standard formula	10	0.54 ± 0.1 g/l*	0.75 ± 0.14 g/l*		NR†
			Diabetes-specific formula	10	0.54 ± 0.17 g/l*	1 ± 0.22 g/l*		NR†
	del Carmen Crespillo et al., 2003	baseline = 0 mins (fasted), postintervention = 150 mins after meal start (postprandial)	Standard formula	11	NR	NR		26 ± 42 mg/l
			Diabetes-specific formula	11	NR	NR		9 ± 88 mg/l
	Craig et al., 1998	baseline = study start, postintervention = after 3 months intervention, all fasted: measured as triacylglycerol.	Standard formula	13	0.9 ± 0.07 g/l†	1.06 ± 0.12 g/l†		NR†
			Diabetes-specific formula	14	0.97 ± 0.13 g/l†	0.91 ± 0.17 g/l†		NR†
	McCargar et al., 1998	baseline = study start, postintervention = after 28 days intervention, probably fasted	Standard formula	16	1.81 ± 0.27 mmol/l*	1.86 ± 0.28 mmol/l*		NR†
			Diabetes-specific formula	16	1.46 ± 0.29 mmol/l*	1.33 ± 0.24 mmol/l*		NR†
Change in total Cholesterol	Craig et al., 1998	baseline = study start, postintervention = after 3 months intervention, all fasted	Standard formula	13	4.21 ± 0.18 mmol/l*	3.96 ± 0.23 mmol/l*		NR†
			Diabetes-specific formula	14	4.16 ± 0.31 mmol/l*	3.95 ± 0.31 mmol/l*		NR†
	McCargar et al., 1998	Baseline = study start, postintervention = after 28 days intervention, probably fasted	Standard formula	16	5.06 ± 0.21 mmol/l*	4.58 ± 0.27 mmol/l*		NR†
			Diabetes-specific formula	16	5.24 ± 0.19 mmol/l*	5.05 ± 0.28 mmol/l*		NR†

Data are means ± SD or *SE. †Change from baseline data calculated by subtracting baseline from postintervention value and SD of the difference calculated by standard formulas SD(post-pre) = $\sqrt{}$[Var(post) + Var(pre) − Cov(pre,post)]. NR, not recorded.

Nutritional support versus routine care

There were no long-term studies of ONSs or ETF compared with routine care in patients with diabetes. Two shorter RCTs (39,41) compared nutritional support versus routine care. Both of these studies also provided data for the diabetes-specific versus standard formula comparison (below).

Diabetes-specific formula versus standard formula

Most studies (14,38–56) compared diabetes-specific formulas with standard formulas. Eighteen of these were RCTs (14,38–54) and two were CCTs (55,56). Most (14,40–44,46–48,51–53,55) were short-term single-meal studies with <24 h follow-up; only seven were longer-term studies (38,39,45,49,50,54,56) with follow-up of 6 days to 3 months. In all but one (47) of the short-term studies, an ONS was used (14,40–44,46,48,51–53,55). In contrast, all but two (38,39) of the longer-term studies used ETF (45,49,50,54,56).

Other studies

Two studies, including one RCT (11) and one CCT (57), compared different formulas. One was a single-meal study comparing three high-fat formulas (57), and in the other study, two standard formulas were given as a sole source of nutrition for 5 days (11). One additional CT (58) involved the follow-up of elderly patients with diabetes receiving a diabetes-specific formula via tube for 42 days.

No trials comparing tube feeding with parenteral nutrition were identified, and there were insufficient data for separate analyses according to diabetes type (type 1 versus type 2) and nutritional status (malnourished versus well nourished versus obese).

Outcomes

Table 1 provides details of absolute data used in meta-analyses.

Nutritional support versus routine care

Glycemia and lipidemia. In one short-term RCT (41), a diabetes-specific formula given as an ONS produced significantly smaller rises in postprandial glucose and insulin concentrations and glucose area under the curve (AUC) compared with both routine care and a stan-

dard formula. A further RCT reported that the use of diabetes-specific ONSs as an afternoon snack resulted in similar postprandial blood glucose concentrations (1,950 mg/l) to an isocaloric food snack (1,960 mg/l) after a standard test meal (supper), which in both cases was significantly lower than that produced by a standard formula (2,430 mg/l) (39). No changes in HbA_{1c} (A1C) or in lipid profiles (undefined in the study report) were found in this short-term study.

Other outcomes

No studies investigated the impact of ONSs or ETF versus routine care on other clinically relevant outcomes in diabetic patients, including changes in nutritional status, requirement for medication, quality of life, complication rates, or mortality.

Diabetes-specific formula versus standard formula

Glycemia (postprandial rise in glucose, peak glucose, glucose AUC, insulin AUC, A1C, and fasting glucose). Figure 2, a meta-analysis of six RCTs (14,38,44,45,51,54), demonstrated that diabetes-specific formulas result in significantly lower postprandial rise in blood glucose concentrations (by 1.03 mmol/l [95% CI 0.58–1.47]) compared with standard formulas (effect size −0.52 [−0.81 to −0.24]) (Fig. 2 and Table 1). Both the short-term (effect size −0.71 [−1.14 to −0.27]) and longer-term (effect size −0.38 [−0.76 to 0.0]) studies supported this overall effect (Fig. 2). Exclusion of one RCT (54) in hyperglycemic critically ill patients from the analysis did not alter the result (effect size −0.57 [−0.91 to −0.24]). These meta-analyses assumed zero correlation ($r = 0$) between baseline and postintervention results, but when this assumption was relaxed ($r = 0.5$), all meta-analyses remained significant (overall effect size −0.59 [−0.87 to −0.3]). Four RCTs provided incomplete (39,46) or graphically presented (41,47) data that could not be included in the meta-analysis. However, all four studies suggested a lower postprandial rise in glucose concentrations with diabetes-specific formulas versus standard formulas; these were statistically significant in two studies (41,46).

A meta-analysis of two RCTs (47,48) demonstrated that diabetes-specific formulas result in significantly lower peak blood glucose concentrations (by 1.59 mmol/l [95% CI 0.86–2.32]) than standard formulas (effect size −1.28 [−1.94 to −0.63], assuming $r = 0$) (Fig. 3 and Table 1).

A meta-analysis of four RCTs (46–48,40) demonstrated that diabetes-specific formulas result in significantly smaller (31–45% lower) glucose AUC than standard formulas (effect size −1.19 [95% CI −1.69 to −0.7], assuming $r = 0$) (Fig. 4 and Table 1). Six further RCTs (14,41,42,50,52,53) reported smaller glucose AUC with diabetes-specific or low-carbohydrate versus standard formulas. In three of these (61,73,74), the difference was reported to be statistically significant, while the remaining three studies (14,56,59) did not report any statistical analysis. However, these were not meta-analyzable due to incomplete data being reported (41,52,53) or incompatible data presentation (14,50) or study design (42).

Three RCTs (42,46,52) reported significantly smaller insulin AUC following diabetes-specific or low-carbohydrate compared with standard formulas. The results of two other RCTs (40,50) were less conclusive. The data were not sufficiently comparable to permit meta-analysis of this outcome measure.

Three long-term RCTs involving ONSs (38) and ETF (45,49) reported favorable effects of diabetes-specific formulas on A1C or fructosamine concentrations. One of these studies (49) demonstrated statistical significance, reporting a reduction from baseline of A1C by −0.8% in the diabetes-specific group and no change from baseline in the standard group. The other two studies (38,45) showed reductions of A1C by 0.6% and of fructosamine by 3%, respectively, whereas increases were noted in the group receiving standard food. Two shorter studies (39,58) reported no changes in A1C with diabetes-specific formulas given orally or by tube. The data were not sufficiently comparable to permit meta-analysis of this outcome measure.

A meta-analysis was conducted to examine the effect of diabetes-specific versus standard formulas on fasting blood glucose concentrations, following a combination of data from two RCTs involving ONSs (38) and ETF (45). Although in both studies fasting blood glucose concentrations were reduced by the use of diabetes-specific formulas, there was no significant difference compared with the standard formula when r was assumed to be zero (effect size −0.35 [95% CI −0.86 to 0.17]). Another RCT (49) showed that diabetes-specific ETF was associated with a significantly greater reduction in fasting blood glucose (−28.6 g/l) than standard formulas (−1.4 g/l) compared with baseline. This study was not meta-analyzable because it provided no measure of variability. In contrast, in a further RCT, where an ONS was given as the sole source of nutrition for 6 days, no differences were found between standard and diabetes-specific formulas, although no numerical data were reported (50).

Lipidemia (total cholesterol, HDL, and triglycerides)

A meta-analysis was conducted to examine the effect of diabetes-specific versus standard formulas on total serum cholesterol concentrations. Following combination of the data from two RCTs involving ONSs (38) and ETF (45), no significant effect on cholesterol was found (effect size 0.13 [95% CI −0.38 to 0.64], assumed $r = 0$; effect size 0.18 [−0.33 to 0.69], assumed $r = 0.5$, respectively). Three other longer-term RCTs (two ETF and one ONS) and one short-term RCT (ONS), which did not provide suitable data for meta-analysis, also reported no significant difference in total cholesterol of those fed diabetes-specific and standard formulas (49,54).

There was inadequate information to address the effects on LDL in the meta-analysis. Four RCTs (38,45,49,54) reported no significant differences in LDL/VLDL in patients receiving diabetes-specific and standard formulas.

Meta-analysis of two RCTs involving ONSs (38) and ETF (45) found no significant effect of diabetes-specific versus standard formula on HDL (effect size 0.2 [95% CI −0.31 to 0.72], $r = 0$; effect size 0.28 [−0.24 to 0.8], $r = 0.5$), although in both studies the diabetes-specific formulas showed higher HDL concentrations than the standard formulas (Table 1). Other long-term RCTs (49,54) reported no significant difference in HDL concentration following diabetes-specific versus standard formulas, although they provided no suitable data for meta-analysis.

A meta-analysis was conducted to investigate the effect of diabetes-specific versus standard formulas on blood triglyceride concentrations. Although in the

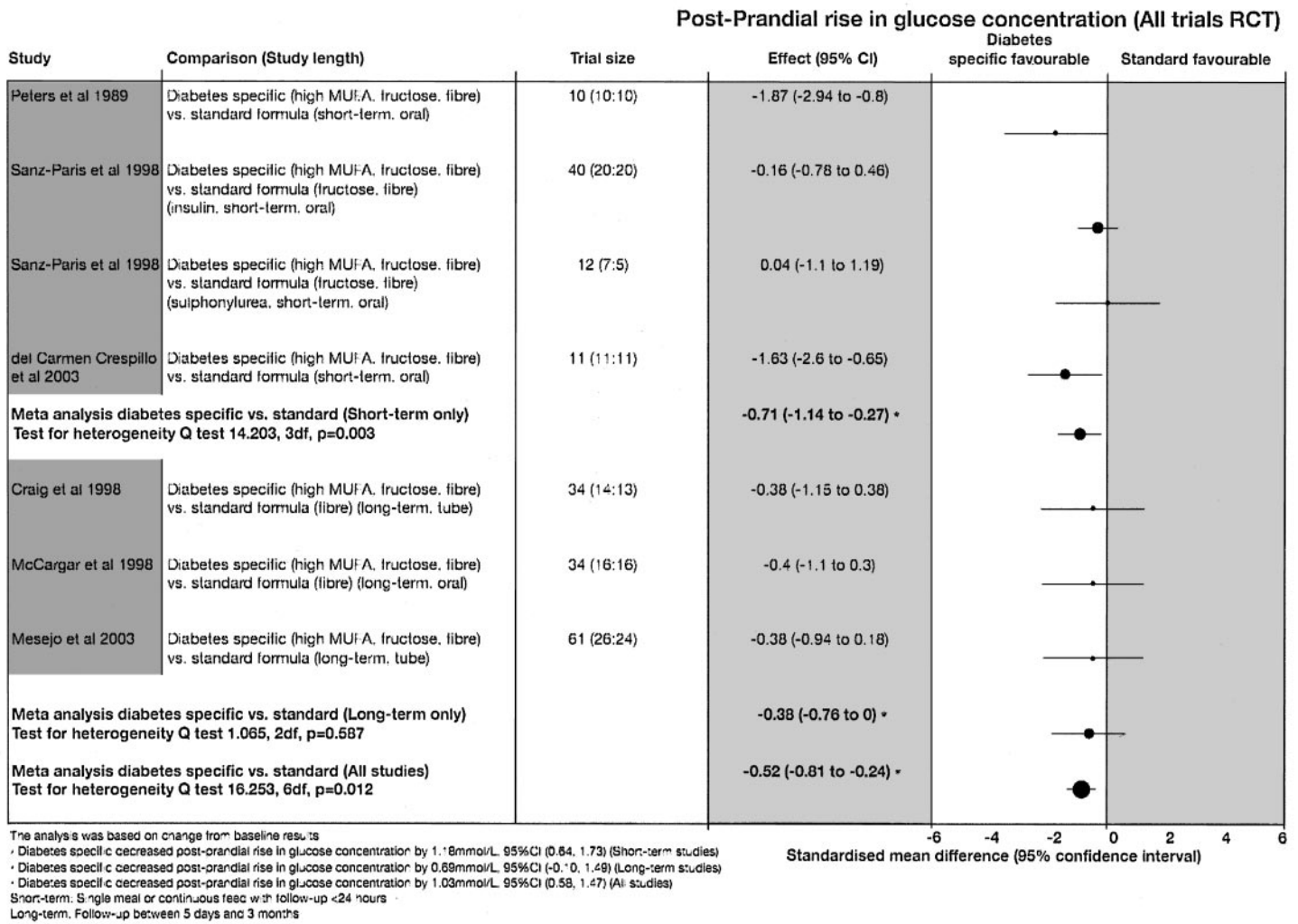

Fig. 2—*The effect of diabetes-specific versus standard formulas on the postprandial rise in blood glucose concentration: a meta-analysis of five RCTs (14,38,44,45,51,54).*

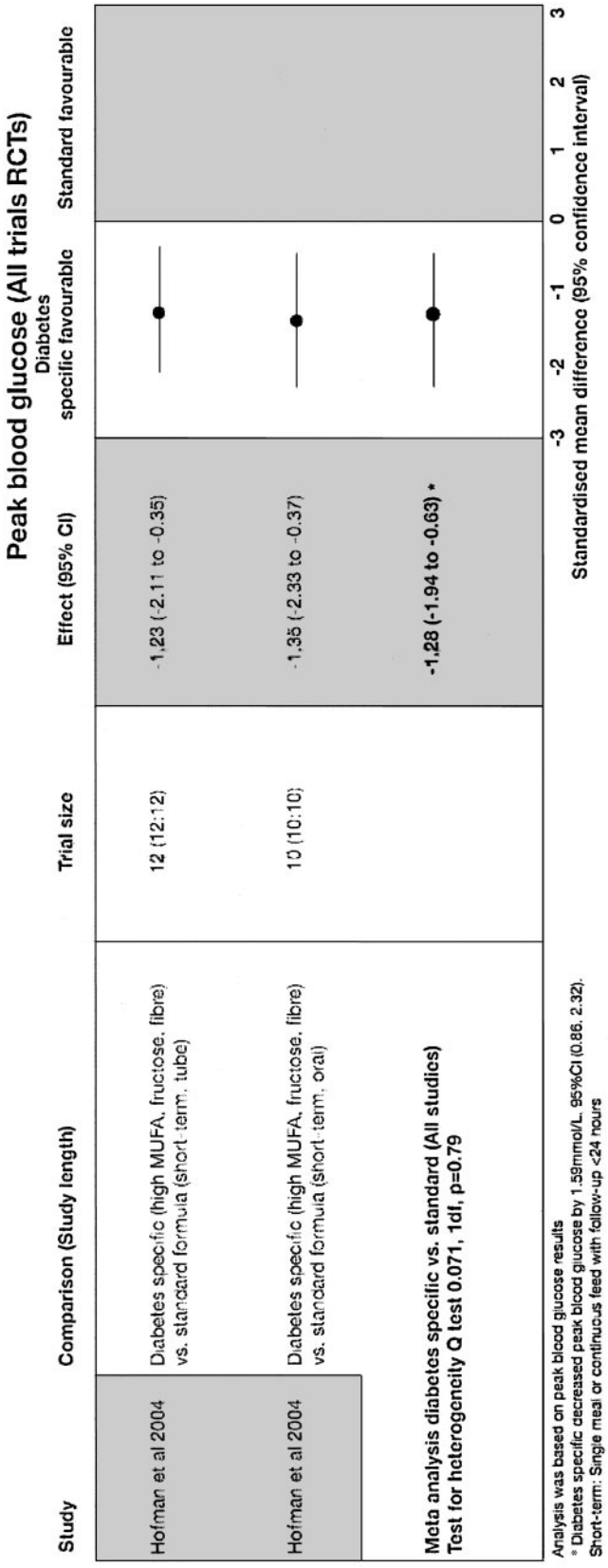

Fig. 3—*The effect of diabetes-specific versus standard formulas on peak blood glucose concentration in short-term studies: a meta-analysis of two RCTs (47,48).*

majority of the studies the diabetes-specific formulas showed lower triglyceride concentrations than the standard formulas, the combined data from four RCTs (14,38,44,45) indicated no significant effect (effect size −0.11 [95%CI −0.5 to 0.28], $r = 0$; effect size −0.13 [−0.53 to 0.26], $r = 0.5$) (Table 1). Furthermore, two other long-term RCTs (49,54) reported no significant effect of diabetes-specific versus standard formulas on triglycerides, whereas the findings of a short-term RCT were unclear (48). None of these studies provided any detailed data.

Requirement for medication

Three RCTs (45,49,54) and one CCT (56) in patients with type 2 diabetes reported reduced insulin requirements in those receiving diabetes-specific formulas versus standard formulas; two RCTs demonstrated statistical significance. In one RCT (49), patients fed diabetes-specific ETF had significantly reduced insulin requirements (from 38.7 units/day at study start to 32.7 units/day) compared with those who received a standard formula (44 units/day throughout study); a difference of 26% between the two groups. In the RCT (54) of critically ill hyperglycemic patients, those receiving a diabetes-specific ETF had a significantly lower total insulin requirement compared with those receiving standard formula (median 8.73 vs. 30.2 IU/day, respectively; a difference of 71%), requirement per gram carbohydrate ingested (median 0.07 vs. 0.18 IU/day), and requirement per gram carbohydrate ingested per kilogram body weight (median 0.98 vs. 2.13 IU/day). In a further RCT (45), 25% of the patients receiving standard formulas needed to start with regular insulin treatment, compared with none in the group receiving diabetes-specific ETF. Nevertheless, these four studies provided insufficient comparable data to allow meta-analysis of the effect of diabetes-specific versus standard formulas on the requirement for hypoglycemic medication.

Complications

Two RCTs (45,54) of ETF reported this outcome, and neither showed a significant difference in overall complication rates between diabetes-specific and standard formulas. However, post hoc χ^2 analysis of the data from one of these trials (45) demonstrated a tendency for a lower

incidence of urinary tract infections, pneumonia, and episodes of fever in the diabetes-specific versus standard group. The higher rate of skin infections in the diabetes-specific group was influenced by higher rates at baseline. The data were not sufficiently comparable to permit meta-analysis of this outcome measure.

Mortality

Only one RCT of ETF in critically ill patients (54) reported data on mortality. No significant differences between patients receiving diabetes-specific and standard formulas were found in the 2-week study period.

Other outcomes

No studies reported assessments of quality of life or other functional measures. One RCT in critically ill patients (69) reported dietary intake. No significant differences in total dietary energy and nitrogen intakes were found between those given diabetes-specific versus standard formulas. One RCT (68) reported anthropometric data. In this study, ONSs provided 80% of total energy intake, and no significant differences in body weight, BMI, total body fat, or waist-to-hip ratio between those fed diabetes-specific versus standard formulas were found.

CONCLUSIONS — This systematic review (19 RCTs, 3 CCTs, and 1 CT) shows that the use of diabetes-specific compared with standard formulas, given as ONSs or ETF, consistently results in significantly lower postprandial rise in blood glucose, peak blood glucose concentrations, and glucose AUC in patients with diabetes (Figs. 2–4). This was achieved without evidence of hypoglycemia; this suggests that glycemic control may be facilitated by the use of diabetes-specific enteral formulas compared with standard formulas in patients with diabetes.

Compared with standard formulas, diabetes-specific formulas are typically higher in fat (40–50% of energy, with a large contribution from MUFAs, e.g., >60% of fat), with a lower carbohydrate content (~35–40% of energy) and up to 15% of energy from fructose. These nutrients could facilitate glycemic management by delaying gastric emptying (fat and fiber), delaying the intestinal absorption of carbohydrate (fiber), and producing smaller glycemic responses (fructose).

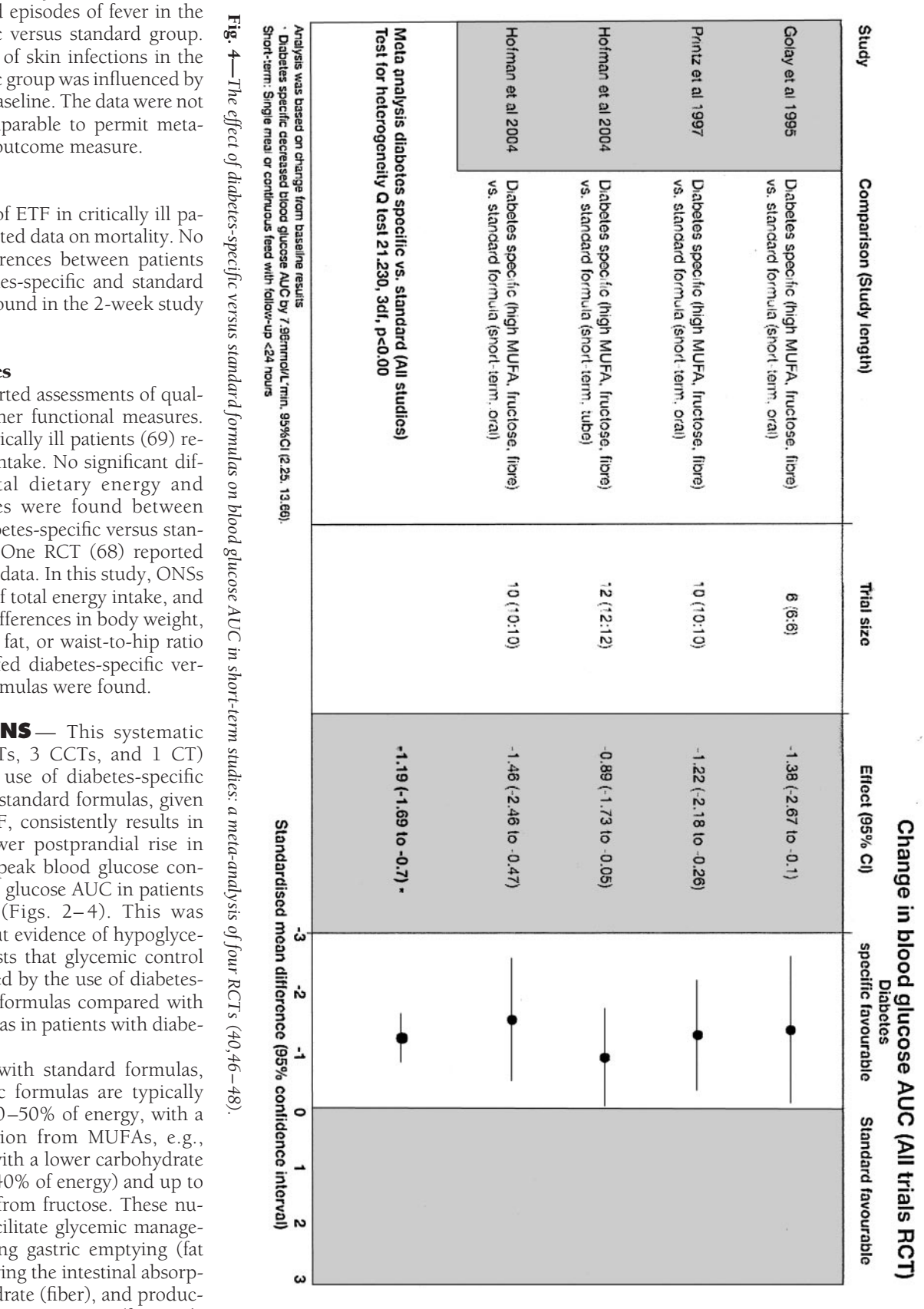

Fig. 4—*The effect of diabetes-specific versus standard formulas on blood glucose AUC in short-term studies: a meta-analysis of four RCTs (40,46–48).*

A high proportion of MUFAs may also have beneficial effects on lipid profiles, but no significant effects were noted in our review. Due to the multinutrient nature of the formulation, it is difficult to assess which components of the diabetes-specific formulas were responsible for the effects observed.

The impact of improved glycemic control on long-term clinical outcomes is well recognized in both type 1 (1) and type 2 (2) diabetes. The current meta-analyses found that postprandial rise in glucose concentration was lower by 1.03 mmol/l (95% CI 0.58–1.47), and the peak glucose concentration was reduced by 1.59 mmol/l (0.86–2.32), following diabetes-specific compared with standard formulas (Figs. 2 and 4). Recent studies have demonstrated a strong correlation between postprandial glucose regulation and cardiovascular complications in patients with diabetes (1,2,59–62), impaired glucose tolerance (63,64), and all-cause mortality, whereas no such correlation was demonstrated for fasting glucose control (62). Furthermore, a large epidemiological study (65) has demonstrated that postprandial hyperglycemia is a better predictor of cardiovascular disease than fasting glucose. This suggests that by improving glycemic control, the long-term use of diabetes-specific versus standard enteral formulas may reduce cardiovascular complications in patients with diabetes, although this was not assessed by the studies reviewed.

Patients with diabetes who are likely to receive specific nutritional support on a longer term may include nursing home patients, frail patients with infectious complications, patients with slow-healing ulcers or a history of falls and associated fractures, and those in the pre- and post-operative period who are assessed to have poor nutritional status. Improved glycemic control may also be important in acute care (e.g., stroke, intensive care), where hyperglycemia is associated with a worse outcome (3).

Intensive insulin therapy in critically ill patients to maintain a glucose concentration of 4.4–6.1 mmol/l (compared with 10.0–11.1 mmol/l in the control group) improved mortality, blood stream infections, requirement for transfusion, and critical illness polyneuropathy (66). The improved outcome was mainly due to the lower blood glucose concentration (67,68) rather than insulin therapy (69), with mechanisms likely to include osmotic effects and those involving generation of free radicals and the immune system. In the study of critically ill patients (54) included in this analysis, the diabetes-specific formula reduced both insulin dosage and circulating glucose concentrations; there were no significant differences in morbidity or mortality; however, the sample size and study length may have been too small to detect significance.

In some studies, (one RCT and one CCT), diabetes-specific formulas reduced the quantity of hypoglycemic medication and in some cases prevented the need for insulin injections (45,56). Next to potential health economic savings, these reduced medication requirements may help attenuate fluctuations in blood glucose concentrations and improve the quality of life of these patients.

There are few long-term studies examining clinical outcomes. One study of ETF (45) found that the diabetes-specific formula was associated with a trend toward reduced incidence of pneumonia, fever, and urinary tract infection relative to the standard formula, which may have clinical relevance for hyperglycemic patients who are at increased risk of infections. Further common comorbidities in patients with diabetes include cardiovascular disease and hyperlipidemia. Although diabetes-specific feeds had a higher fat content than standard feeds, this review suggests that diabetes-specific formulas had no detrimental effect on total cholesterol, HDL, or triglycerides. There was inadequate information to address the effects on LDL in a meta-analysis.

For ETF studies, as details on the route of administration or tube positioning and the choice between continuous or bolus feeding regimens were insufficiently reported, it was impossible to evaluate how far the administration of the feeds might have influenced the metabolic effects. A further consideration is the amount of feed administered, since patients receiving ONSs may obtain only ~25% of daily energy from this source compared with up to 100% in tube-fed patients.

National organizations (16,17) generally recommend low-fat (25–35% of energy) and high-carbohydrate diets (45–60%), rich in complex carbohydrates for those with diabetes. The situation for MUFAs is less clear, with the American Diabetes Association reporting that there is lack of evidence that MUFAs exert long-term effects on glucose control or other metabolic parameters (16). In addition, formulas that have a particularly high proportion of fructose should probably be given with some caution to critically ill patients, who are at risk of lactic acidosis. However, dietary therapy, including the use of ONSs and ETF, given under medical supervision, can be individualized to include more liberal use of fat (such as MUFAs) (70). This may be particularly important in the treatment of the malnourished patient, where an increased dietary energy density may be important (71). Ultimately, there is a need to be guided by the desired clinical outcome for the individual patient (45).

Due to the absence of RCT data comparing the effects of nutritional support with routine care in patients with diabetes, this review primarily focused on the effects of diabetes-specific versus standard formula on metabolic control. Some of them were short-term studies in well-nourished individuals, although a number of studies were in patients in need of nutritional support (39,45,49,54,56,58). Many of the studies, however, scored poorly in methodology, but in some cases it may be difficult or unethical to undertake double-blinded placebo-controlled trials with some nutritional support interventions (e.g., tube feeding; oral supplement versus regular meal), and this may account for lower RCT quality scores. There was insufficient data available to address the efficacy of nutritional support, including diabetes-specific formulas, according to diabetes type (type 1 or type 2) or nutritional status.

There is clearly a need for further research in the form of well-designed, adequately powered trials that aim to determine the role of enteral nutritional support and diabetes-specific formulas on the management, clinical outcome, and quality of life of malnourished patients with diabetes. Furthermore, it would be useful to establish the optimal composition of nutritional feeds designed to assist metabolic control, improve immune function, and achieve satisfactory nutritional status.

This systematic review shows that the use of diabetes-specific oral and tube formulas (containing high proportions of MUFAs, fructose, and fiber) are associ-

ated with improved glycemic control compared with standard formulas. In the long term, this may aid the management and outcome of patients with diabetes. In particular, cardiovascular complications may be reduced, although research specifically designed to examine these outcomes is warranted.

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