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PAPER SUMMARY: Diabetes-specific formulas high in monounsaturated fatty acids and metabolic outcomes in patients with diabetes or hyperglycaemia. A systematic review and meta-analysis.

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This is a **systematic review with meta-analysis: the strongest form of clinical evidence**. Reminder: a systematic review and meta-analysis brings together several clinical trials to look at the overall effect, in a larger population.

This study aimed to develop a systematic review and meta-analysis of the studies published comparing the metabolic and health benefits of a diabetes specific formula (DSF) high in monounsaturated fatty acids (MUFAs) and standard formulas (STDF) in adult patients with diabetes mellitus (DM) or hyperglycaemia. A literature search was conducted using different electronic databases and 18 studies involving 845 adult patients with type 1, type 2 diabetes or stress-induced hyperglycaemia contributed to the meta-analysis. Assessed outcomes included glycaemic control, lipid metabolism, insulin requirements, and gastrointestinal (GI) tolerance. In all studies, DSFs provided ≥20% of the total energy from MUFAs and ≥40% of the total energy from fat, however their compositions were not homogeneous.

Data from included studies were divided into postprandial response and medium- and long- term follow up (MLFU) studies. In six of the eight postprandial response studies, formula was administered orally and in two of the studies, formula was administered as a tube feed. All patients with DM were treated with oral antidiabetic drugs except in two studies in which some patients received insulin. None of the studies included patients with stress-induced hyperglycaemia in the postprandial data. All studies shared the same methodology, where patients consumed the nutritional formula instead of breakfast along with hypoglycaemic treatment, and then the postprandial glucose and insulin response was measured. Patients in the thirteen MLFU studies had different hyperglycaemic situations and in eleven of the thirteen MLFU studies, the route of administration was continuous tube feed. See table 1 for full characteristics of the studies included in the systematic review and meta-analysis.

OUTCOMES:

Postprandial data: Data showed statistically significant results in favour of the DSF group ($p = 0.001$) in postprandial glucose response outcomes, with a high effect size by standardised mean difference (SMD). However, significant heterogeneity was observed and this may hinder interpretation of the obtained effect size. Statistically significant results were also observed in incremental glucose response data which showed a combined SMD of -1.19 ($p < 0.001$) as well as when analysing the area under the curve of the plasma insulin (iAUC) ($p = 0.01$) without significant heterogeneity. All individual studies reported significant results favouring DSF use.

Data from medium-/long term follow up studies: A statistically significant and moderate effect size in favour of DSF use was shown in the mean blood glucose data without significant inter-study heterogeneity. An SMD of -0.63 was shown in the change from baseline between DSF and STDF arms for glycosylated haemoglobin (HbA1c) levels, resulting in a moderately favourable effect for the DSF arm, but with significant heterogeneity. For glycaemic variability, there was a high effect in favour of the DSF group, showing an SMD of -0.93. Mean blood high density lipoprotein (HDL) data reported a SMD of 0.42 which resulted in significantly higher moderate level of HDL associated with DFS use.

DISCUSSION:

This systematic review and meta-analysis provide evidence on the efficacy of DSF high in MUFAs use compared to STDF in patients with DM. Most analysed outcomes showed a significant and positive effect size in favour of DSF both in postprandial response and MLFU studies. This therefore supports recently published reviews reporting health benefits associated with the use of high MUFA DSFs in patients with DM.
The main strength of this meta-analysis was the high number of studies included, which may help to define the minimum amount of MUFAs that a DSF may contain to provide improved health outcomes in patients with DM.

The main limitation of this study was that it focused on the contribution of MUFAs and fats, without considering other important components of DSFs such as carbohydrates and fibres. Also, the high heterogeneity of the results meant differences presented were indirectly measured and prevented the ability to consider the effect size observed in all its intensity. Despite this, a positive level of significance in favour of the high MUFA DSFs was continuously shown.

Glycaemic response: Data consistently showed lower postprandial glycaemic response when using high MUFA DSFs when compared to STDFs.

Blood glucose management: Mean blood glucose level was found to be significantly lower in the high MUFA DSF group in most of the MLFU studies included and a significantly decreased change from baseline was also observed in fasting blood glucose with DSFs. HbA1c levels were improved after high MUFA DSF use in the pooled analysis, but this effect was not consistent in all the studies which may have been due to the inadequate intervention duration.

Lipid metabolism: The relevance of the plasma lipid changes must be analysed in a longer-term period.

Insulin requirements: Daily insulin dose required to maintain the glucose target level was found to be lower with DSFs and these results are of high clinical relevance as frailty is a common comorbidity in patients with DM and treatment simplicity is always advisable.

GI tolerance: GI adverse events data did not show any significant differences between treatments.

CONCLUSIONS:

This meta-analysis provides evidence that DSFs containing ≥20% energy from MUFAs or ≥40% energy from fat have beneficial effects on glucose control and metabolic risk factors among individuals with DM or stress-induced hyperglycaemia compared with STDFs.

Table 1: Characteristics of the studies included in the systematic review and meta-analysis (*n*=18)

	Study design	Arms	Duration of intervention	Route of administration	DSF composition			STDF composition			Difference in % of energy from	
					Fat (% TE)	MUFA (% TE)	Carbohydrate type	Fat (% TE)	MUFA (% TE)	Carbohydrate type	Fat	MUFA
Lansink 2017[1]	Crossover, RCT	2	Postprandial	Nasogastric tube	46.4	27.6	**Nutrison Advanced Diason Energy HP *(Nutricia)*** Isomaltulose	34.4	19.4	**Nutrison Energy Multi Fibre (*Nutricia)*** Sugars, polysaccharides	12	8.2
Alish 2010[2]	Parallel, RCT	2	Postprandial	Oral	45	27.7	**Glucerna 1.2 *(Abbott Nutrition)*** Maltodextrin, isomaltulose, sucromalt, fibersol, fructooligosaccharides, soy and oat fibre, glycerine	29	10.4	Corn, maltodextrin, corn syrup solids, short chain, fructooligosaccharides, soy and oat fibre	16	17.3
Sanz Paris 1998[3]	Parallel, RCT	2	Postprandial	Oral	50	35.7	**Glucerna 1.0 *(Abbott Nutrition)*** Fructose, corn maltodextrin, soy fibre	31	8.6	**Precitene Diabet. *(Laboratorios Novartis)***	19	27.1
Sanz Paris 1998[3]	Parallel, RCT	2	Postprandial	Oral	50	35.7	**Glucerna 1.0 *(Abbott Nutrition)*** Fructose, corn maltodextrin, soy fibre	31	8.6	**Precitene Diabet. *(Laboratorios Novartis)***	19	27.1
Vanschoon-beek 2009[4]	Crossover, RCT	2	Postprandial	Oral	50	34.8	**Glucerna *(Abbott Nutrition)*** Fructose, maltodextrin, fructooligosaccharides	30	12.6	**Isosource Fibre *(Nestle Health Science)*** Polysaccharides, fibre	20	22.2
Voss 2008[5]	Crossover, RCT		Postprandial	Oral	49	32	Fibersol, fructose, maltitol, short chain fructooligosaccharides	29	15	Corn maltodextrin, fibre	20	17
Yokoyama 2008[6]	Crossover, RCT	2	Postprandial	Oral	49.3	34.3	**Glucerna *(Abbott Nutrition)*** Maltodextrin, fructose, soy fibre	30.8	8.5	**Enrich-SF** Maltodextrin, sucrose, soluble fibre	18.5	25.8
Mc Cargar 1998[7]	Parallel, RCT	2	Postprandial and 28 days	Oral; 80% rec in EN	50	32	**Glucerna 1.0 *(Abbott Nutrition)*** Fructose, corn maltodextrin, soy fibre	30.5	7.9	**Ensure *(Abbott Nutrition)*** Hydrolysed corn starch, sucrose	19.5	24.1
Vaisman 2009[8]	Parallel, RCT	2	Postprandial and 12 weeks	Nasogastric tube	38	26.1	**Nutrison Advanced Diason *(Nutricia)*** Polysaccharides, fructose, fibre	30	18.9	Corn maltodextrin, corn syrup solids, and soy fibre	8	7.2
Egi 2010[9]	Crossover, RCT	2	16 h	Jejunostomy	29.7	21.5	**Inslow *(Meiji Dairy Products)*** Dextrin, isomaltulose	25.2	12.6	Dextrin, glucose, fructose	4.5	8.9
Van Steel 2018[10]	Parallel, RCT	2	72 h	Nasogastric tube	45	29.4	**Glucerna 1.5 kcal *(Abbott Nutrition)*** Maltodextrin, fibersol, oat fibre, soy fibre, fructooligosaccharides, isomaltulose, sucromalt, glycerine	34.8	22.8	**Fresubin Energy Fibre *(Fresenius Kabi)*** Maltodextrin, sucrose, wheat dextrin, insulin	10.2	7.2
Alish 2010[1]	Crossover, RCT	2	5 days	Percutaneous endoscopic gastrostomy	45	27.7	**Glucerna 1.2 *(Abbott Nutrition)*** Maltodextrin, isomaltulose, sucromalt, fibersol, fructooligosaccharides, soy and oat fibre, glycerine	29	10.4	Corn maltodextrin, corn syrup solids, short chain fructooligosaccharides and soy and oat fibre	16	17.3
Leon 2005[11]	Parallel, RCT	2	13 days	Nasogastric tube	50	34.2	**Glucerna 1.0 *(Abbott Nutrition)*** Soy polysaccharide (fibre), Corn maltodextrin, fructose	31	9.4	**Precitene Diabet *(Novasource)*** Fructose and Starch and fibre	19	24.8
Mesejo 2003[12]	Parallel, RCT	2	14 days	Nasogastric tube	40	23.16	**Novasource Diabet Plus. *(Nestle Health Sciences)*** Starch and fructose and fibre	29	11.4	Sucrose and Maltodextrin without fibre	11	11.7
Celaya 1992[13]	Parallel, RCT	2	14 days	Nasogastric tube	50	35.7	**Glucerna 1.0 *(Abbott Nutrition)*** Maltodextrin, fructose, soy fibre	24	14.5	Maltodextrin, sucrose	26	21.2
Mesejo 2015[14]	Parallel, RCT	3	28 days	Nasogastric tube	49	32.2	**Glucerna Select *(Abbott Nutrition)*** Modified maltodextrin, Fructose and Maltitol	30	12.9	**Isosource Protein Fibra *(Nestle Health Science)*** Standard maltodextrin and Sucrose	19	19.3
Mesejo 2015[14]	Parallel, RCT	3	28 days	Nasogastric tube	40	20	**Diaba HP *(Vegenat Nutrition)*** Modified maltodextrin (low dextrose equivalent and type IV resistant)	30	12.9	**Isosource Protein Fibra *(Nestle Health Science)*** Standard maltodextrin and Sucrose	10	7.1
Pohl 2009[15]	Parallel, RCT	2	70 days	Nasogastric tube	45	32.2	**Diben *(Fresenius Kabi)*** Starch, fructose, maltodextrins	30	17	Maltodextrins	15	15.2
Craig 1998[16]	Parallel, RCT	2	84 days	Nasogastric tube	50	35.7	**Glucerna *(Abbott Nutrition)*** Maltodextrin, soy polysaccharide (fibre), fructose	30	14.5	**Jevity *(Abbott Nutrition)*** Maltodextrin, soy polysaccharide	20	21.2
Magnoni 2008[17]	Parallel, RCT	2	84 days	Oral	49	34.2	**Diasip *(Nutricia)*** Fructose, polysaccharides, fibre	30	17.1	Sugars, polysaccharides without fibre	19	17.1
Pohl 2005[18]	Parallel, RCT	2	84 days	Nasogastric tube, percutaneous endoscopic gastrostomy	45	32.2	**Diben *(Fresenius Kabi)*** Starch, fructose, maltodextrins	30	17	Maltodextrins	15	15.2

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