

Appendix one. Studies included in the systematic review

Citation	Patients	Baseline status	Intervention	Regimen	Route	Length of nutritional intervention
<b>Nutritional support vs. routine care</b>						
<b>RCTs</b>						
Galkowski <i>et. al.</i> 1989 (57), RCT, 3 way latin square	5 elderly patients, type 2 diabetes	No information provided	<u>Diabetes-specific formula (17 En% protein, 33 En% CHO, 50 En% fat; fiber, fructose; exp. formula), n=5</u> Standard formula (17 En% protein, 53 En% CHO, 30 En% fat), n=5 <u>Mixed food (isocaloric equivalent food snack), n=5</u>	For 3 week period, the allocated snack was consumed on Mon, Weds, Fri afternoons (amount "equivalent to usual snack"). Effect on ac (supper) blood glucose concentration compared	oral	3 weeks
Sturmer <i>et. al.</i> 1994 (56), RCT, 3 way latin square	30 patients, type 2 diabetes (BMI 26.9 ± 2.7 kg/m <sup>2</sup> )	Diet alone (n=9), Glibenclamide+diet (n=10, morning dose 4.4mg), insulin+diet (n=11, morning dose 29IU). Mean baseline BMI=27 kg/m <sup>2</sup> , age=63 years, HbA1c=9%, fasting glucose=7.4mmol/L	<u>Diabetes-specific formula (15 En% protein (soy), 53 En% CHO, 32 En% fat (69% MUFA); 1.5g fiber/100ml (soy fiber), 3.5g fructose/100ml; Fresubin diabetes, Fresenius) n=20</u> Standard formula (15 En% protein, 53 En% CHO, 32 En% fat), n=30 <u>Mixed meal (typical breakfast), n=30</u>	Overnight fast, then medication, then test meal (400mL=360kcal). Multiple blood samples 0 (after medication)-240mins after meal	oral	single meal study

**Diabetes vs. standard formula studies, short-term (follow-up <24 hours)**

**RCTs**

del Carmen Crespillo <i>et. al.</i> 2003 (14), RCT 3 way latin square	11 patients with type 1 diabetes	Mean baseline BMI=24 kg/m <sup>2</sup> , age 30.4 years. All receiving stable doses of insulin (n=8, NPH+lispro insulin, n=1 NPH + regular, n=2 NPH alone. Mean dose at breakfast 15.3IU), all HbA1c in the range 5-7%	Diabetes-specific formula (17 En% protein (soy), 45 En% CHO, 38 En% fat (67% MUFA); 1.5g fiber/100ml (fiber mixture, mainly soluble), 1.9g fructose/100ml; Nutrison Diabetes/Diason, Nutricia), n=11	Each patient consumed 250mL (=250kcal) of each diet as a single meal after overnight fast on 3 separate days, separated by 1 week interval between each. Blood samples 0 (5-20 mins after medication, before meal) -150mins post meal	oral	single meal study
			Standard formula (16 En% protein, 49 En% CHO, 35 En% fat), n=11			
			Third intervention not considered (n=11)			
Fix <i>et. al.</i> 2004 (61), RCT, parallel groups	168 patients with type 2 diabetes	No information provided	Diabetes-specific formula (17 En% protein, 34 En% CHO, 49 En% fat (71% MUFA); 1.4g fiber/100ml (soy fiber), 1.8g fructose/100ml; Glucerna, Abbott), n=42	One dose challenge (amount not stated), blood samples 0-240mins	oral	single meal study
			Standard formula (14 En% protein, 64% CHO, 22% fat), n=42			

			Other interventions not considered (n=84)			
Golay <i>et al.</i> 1995 (62), RCT, double blind, 3 way latin square	6 patients, type 2 diabetes (BMI 30.4 ± 5.1kg/m <sup>2</sup> )	n=4 treated with sulphonylureas, n=2 diet alone, n=0 insulin. Mean baseline BMI=30 kg/m <sup>2</sup> , age=64 years, fasting glucose=7.4mmol/L	Diabetes-specific formula (16 En% protein, 52 En% CHO, 32 En% fat; 2.0g fiber/100ml (guar gum), 3.0g fructose/100ml, exp. formula), n=6 <hr/> Standard formula (14 En% protein, 52 En% CHO, 34 En% fat), n=6 <hr/> Third intervention not considered (n=6)	Test meal 60g CHO (454kcal) within 15mins, following overnight fast. Blood samples 0-4 hours.	oral	single meal study
Hofman <i>et al.</i> 2004 (66), RCT, double blind, 4 way latin square	10 patients with type 2 diabetes (BMI 28.1 ± 1.3kg/m <sup>2</sup> )	An unknown number were on oral hypoglycemics, but these were not taken prior to the test meal. Mean baseline BMI=28 kg/m <sup>2</sup> , baseline fasting glucose=8.9mmol/L, age=60 years.	Diabetes-specific formula (16 En% protein (50% soy), 35 En% CHO, 49 En% fat (70% MUFA); 2.5g fiber/100ml (fiber mixture, mainly soluble), 1.8g fructose/100ml; Diasip, Nutricia), n=10 <hr/> Standard formula (16 En% protein, 49 En% CHO, 35 En% fat), n=10 <hr/> Other interventions not considered (n=20)	Overnight fast then consumed 200mL (200kcal) within 2mins. Blood samples taken 0-120min	oral	single meal study
Peters and	11 patients	Insulin/dextrose from	Report of 3	Overnight fast, then	oral	single meal

Davidson 1992 (70), RCT, CCT, CCT	with type 1 diabetes (BMI 25.1 ± 0.8kg/m <sup>2</sup> )	BIOSTATOR, no other medication known to affect glucose metabolism. Mean baseline BMI=25 kg/m <sup>2</sup> , age=32 years.	different studies comparing diabetes- specific formulae and standard formulae	attached to BIOSTATOR, brought to steady state over several hours (blood glucose of 8.4mmol/L). Ingested 20mL formula every 15 mins for 4 hours (total 320mL). Blood samples 0-4 hours.		study
Peters <i>et al.</i> 1989 (71), RCT, crossover	10 patients with type 1 diabetes (range BMI 21-29kg/m <sup>2</sup> )	Insulin/dextrose from BIOSTATOR. 1 patient on hypertensives. No long or intermediate acting insulin for previous 24hours. Range baseline BMI= 21-29 kg/m <sup>2</sup> , age=23-57 years. Mean baseline HbA1c, serum albumin, respectively: 9.6%, 40g/L (diabetes formula group) vs. 9%, 38g/L (standard group)	<u>Diabetes-specific formula (17 En% protein, , 33 En% CHO, 50 En% fat (71% MUFA); 1.4g fiber/100ml (soy fiber), 1.8g fructose/100ml; exp. formula), n=10</u> Standard formula (17 En% protein, 53 En% CHO, 30 En% fat), n=10	Each patient had both formulae on 2 separate days separated by 2 weeks. Overnight fast, attached to BIOSTATOR, brought to steady state (blood glucose 8.4mM). Ingested 20mL (20kcal) formula every 15 mins for 240mins.	oral	single meal study
Printz <i>et al.</i> 1997 (72), RCT, 3 way latin square	10 patients with type 2 diabetes (BMI 26.2 ± 3.6kg/m <sup>2</sup> )	All patients taking glibenclamide (3.5- 10.5mg/day). Mean baseline BMI=26 kg/m <sup>2</sup> , age=56 years, fasting glucose=133mg/dL, HbA1c=8.4%.	<u>Diabetes-specific formula (15 En% protein (soy), 53 En% CHO, 32 En% fat (69% MUFA); 1.5g fiber/100ml (soy fiber), 3.5g fructose/100ml; Fresubin diabetes, Fresenius), n=10</u> Standard formula (16 En% protein, 49 En% CHO, 35 En% fat ), n=10 <u>Third intervention not considered (n=10)</u>	Each patient consumed test diets as a single meal (500mL) after overnight fast, each on a separate day, separated by 10 days. Multiple postprandial blood samples taken, after medication, 0-180mins after meal	oral	single meal study

Sanz <i>et. al.</i> 1994 (59), RCT, parallel groups	80 patients with type 2 diabetes	Patients were taking insulin or oral agents; no further details provided.	Diabetes-specific formula (17 En% protein, 33 En% CHO, 50 En% fat (71% MUFA); 1.4g fiber/100ml (soy fiber), 1.8g fructose/100ml; Glucerna, Abbott), n=not stated ?40 Standard formula (15 En% protein, 54 En% CHO, 31 En% fat), n=not stated ?40	250cc eaten after medication. Blood samples 0-120 mins	oral	single meal study
Sanz-Paris <i>et. al.</i> 1998 (58), RCT, parallel groups	52 patients with type 2 diabetes (BMI 29.2 ± 2.7kg/m <sup>2</sup> )	Diabetes-specific group had n=7 treated by a sulfonylurea compared to n=5 in standard group. Both groups comprised n=20 treated with NPH insulin. Mean baseline BMI=29 kg/m <sup>2</sup> , age=65 years, HbA1c=6.5%, triacylglycerols=151mg/dL	Diabetes-specific formula (17 En% protein, 33 En% CHO, 50 En% fat (71% MUFA); 1.4g fiber/100ml (soy fiber), 1.8g fructose/100ml; Glucerna, Abbott), n=27 Standard formula (15 En% protein, 54 En% CHO, 31 En% fat (30% MUFA), n=25	Single meal (250ml = 250kcal) after a 12 hour fast. Blood samples taken 0 (before medication) - 120mins	oral	single meal study
Sturmer <i>et. al.</i> 1994 (56)	See above					

Hofman <i>et al.</i> 2004 (65), RCT, double blind, 3 way latin square	12 patients with diabetes (type unspecified)	No information provided	Diabetes-specific formula (17 En% protein (soy), 45 En% CHO, 38 En% fat (67% MUFA); 1.5g fiber/100ml (fiber mixture, mainly soluble), 1.9g fructose/100ml, Nutrison Diabetes/Diason, Nutricia), n=12	Continuous feed (125mL/h) for 6 hours following overnight fast, route not stated. Blood samples 0-6 hours.	tube	single meal study
			Standard formula (49 En% CHO), n=12			
			Third intervention not considered (n=12)			

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**Non RCTs**

Harley <i>et al.</i> 1989 (64), CCT, design unclear	10 obese patients with type 2 diabetes	Mean baseline HbA1c 9.5%. No further information provided	Diabetes-specific formula (17 En% protein, 33 En% CHO, 50 En% fat; fiber, fructose; exp. formula), n=10	48 hour fast, then 20kcal every 15mins for 4 hours (simulated tube feeding)	oral	single meal study
			Standard formula (17 En% protein, 53 En% CHO, 30 En% fat), n=10			

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**Diabetes vs. standard formula studies, long-term (follow up > 6 days)**

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**RCTs**

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<p>Craig <i>et. al.</i> 1998 (60), RCT, double blind, 2 centre, parallel groups</p>	<p>27 elderly patients with type 2 diabetes</p>	<p>61% patients in diabetes-formula group and 44% patients in standard group were on insulin at baseline. Mean baseline HbA1c, fasting glucose, respectively: 6.9%, 7.3mmol/L (diabetes-formula group) vs. 6.9%, 6.9mmol/L (standard group). No baseline BMI provided. Mean age 81 years.</p>	<p>Diabetes-specific formula (17 En% protein, 33 En% CHO, 50 En% fat (71% MUFA); 1.4g fiber/100ml (soy fiber), 1.8g fructose/100ml; <b>Glucerna, Abbott</b>), n=14</p> <hr/> <p>Standard formula (17 En% protein, 53 En% CHO, 30 En% fat), n=13</p>	<p>Diets were administered <i>solus</i> via enteral access device, continuously or intermittently, to provide the total energy requirement of each patient</p>	<p>tube</p>	<p>3 months</p>
<p>Galkowski <i>et. al.</i> 1989 (57) McCargar <i>et. al.</i> 1998 (68), RCT, 2 centre, parallel groups</p>	<p>See above 32 patients with type 2 diabetes (BMI 28.4/28.7 ± 1.1/1.1kg/m<sup>2</sup>)</p>	<p>Not taking insulin. 23/32 on oral medication at baseline (groups balanced). Mean baseline BMI, age, fasting glucose, respectively: 28.4, 55 years, 9.16mmol/L (diabetes formula group) vs. 28.7, 59 years, 8.73mmol/L (standard group)</p>	<p>Diabetes-specific formula (17 En % protein, 33 En% CHO, 50 En% fat (71% MUFA); 1.4g fiber/100ml (soy fiber), 1.8g fructose/100ml; <b>Glucerna, Abbott</b>), n=16</p> <hr/> <p>Standard formula (15 En% protein, 55 En% CHO, 31 En% fat), n=16</p>	<p>Diets prescribed as main source of energy (&gt;80%). Measurements conducted for every meal 2 days each week (by patients), and by laboratory (days 1, 8 29)</p>	<p>oral</p>	<p>28 days</p>

Mayr <i>et. al.</i> 2004 (67), RCT, double blind, multi centre, parallel groups	78 patients with type 2 diabetes (BMI 25.6/26.5 kg/m <sup>2</sup> )	Patients received insulin during study. Median baseline BMI, age, fasting glucose, HbA1c, respectively: 25.6, 71 years, 143mg/dL, 7.7% (diabetes formula group) vs.26.5, 72 years, 158mg/dL, 7.4% (standard formula group)	Diabetes-specific formula (18 En% protein, 37 En% CHO, 45 En% fat (71% MUFA); 2.0g fiber/100ml (fiber mixture), 1.6g fructose/100ml; Diben, Fresenius), n=39 <hr/> Standard formula (isoenergetic, isonitrogenous, composition not provided), n=39	Administered at rate of 27kcal/kgBW/day (max 2025kcal/day). Route not described	tube	84 days
Mesejo <i>et. al.</i> 2003 (69), RCT, single blind, 2 centre, parallel groups	50 critically ill patients with diabetes (type 1 or 2) and/or stress diabetes caused by acute illness (BMI 24.7/25.7 ± 2.57/2.41 kg/m <sup>2</sup> )	Continuous insulin infusion. Diabetes-formula group: mean baseline BMI=25 kg/m <sup>2</sup> , age=65 years, HbA1c=6.8%, plasma glucose=190.9mg/dL, creatinine height index=52.8% Standard formula group: mean baseline BMI=26 kg/m <sup>2</sup> , age=65 years, HbA1c=6.8%, plasma glucose=210.3mg/dL, creatinine height index=50.2%.	Diabetes-specific formula (20 En% protein, 40 En% CHO, 40 En% fat (36% MUFA); 1.5g fiber/100ml (guar gum), 3.2g fructose/100ml; Novasource Diabet Plus, Novartis), n=26 <hr/> Standard formula (22 En% protein, 49 En% CHO, 29 En% fat), n=24	Administered when possible by nasogastric tube, changing to transpyloric tube if intolerant. Continuous infusion, 24h/day, at rate of Harris Benedict with stress factor of 1.2. 50% administered day 1, 100% day 2 onwards	tube	14 days

Wang <i>et al.</i> 2003 (74), RCT, multi centre, parallel groups	120 patients with type 2 diabetes	No information provided	Diabetes-specific formula (15 En% protein (soy), 53 En% CHO, 32 En% fat (69% MUFA); 1.5g fiber/100ml (soy fiber), 3.5g fructose/100ml; Fresubin diabetes, Fresenius) , n=not stated ?60	Feeds administered bolus for 6 days. 30kcal/kgBW/d. 100mL/h, for 14-16hours/day. Route not described	tube	6 days
			Standard formula (isoenergetic, isonitrogenous; composition not provided), n=not stated ?60			

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#### Non RCTs

Grahm <i>et al.</i> 1989 (63), CCT, parallel groups	20 critically ill patients with stress diabetes caused by acute illness	Mean baseline serum albumin = 37 (diabetes formula group) vs. 35 (standard formula group) g/L. No further information provided.	Diabetes-specific formula (17 En% protein, 33 En% CHO, 50 En% fat; fiber, fructose; exp. formula), n=10	Support begun immediately via continuous pump infusion. "small bowel feeding tube". Metabolic cart used to determine caloric requirements	tube	7 days
			Standard formula (17 En% protein, 74 En% CHO, 9 En% fat), n=10			

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#### Other studies

##### RCTs

Druetzler <i>et al.</i> 1985 (11), RCT, crossover	10 patients with type 2 diabetes	No information provided	Standard formula (composition not provided), n=10 Standard formula + soy polysaccharide: composition not provided), n=10	Subjects consumed each formula as sole source of nutrition for 5 days. 9 day washout between crossover phases	oral	5 days
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<i>Thomas et al. 1988 (73), RCT, 4 way latin square</i>	12 patients with type 2 diabetes (BMI 28.5 ± 3.13kg/m <sup>2</sup> )	Oral hypoglycemic agent (n=6) or diet alone (n=6). Mean baseline BMI=29 kg/m <sup>2</sup> , age=56 years	<p>Low carbohydrate formula with fiber (17 En% protein, 28 En% CHO, 55 En% fat; exp. formula), n=12</p> <hr/> <p>Standard formula (17 En% protein, 54 En% CHO, 29 En% fat), n=12</p> <hr/> <p>Other interventions not considered (n=24)</p>	Each patient consumed each diet as a single meal (333mL = approx 500kcal) after overnight fast. Blood samples -15 (?before medication) to +180mins	oral	single meal study
<b>Non RCTs</b>						
<i>Abbruzzese 1993 (76), CT, single group, before / after</i>	8 elderly patients with type 2 diabetes	No information provided. Previously fed various standard formulae (high carbohydrate)	Diabetes-specific formula (17 En% protein, 33 En% CHO, 50 En% fat (71% MUFA); 1.4g fiber/100ml (soy fiber), 1.8g fructose/100ml; Glucerna, Abbott), n=8	Continuous total enteral nutrition - no further details.	tube	42 days
<i>Peters and Davidson 1996 (75), CCT, single blind, 3 way latin square</i>	12 patients with type 1 diabetes	Insulin/dextrose from BIOSTATOR. No further information provided	<p>Formula X (12 En% protein, 40 En% CHO, 48 En% fat), n=12</p> <hr/> <p>Formula Y (11 En% protein, 29 En% CHO, 60 En% fat), n=12</p> <hr/> <p>Formula Z (11 En% protein, 20 En% CHO, 69 En% fat), n=12</p>	Each patient had each formula on 3 separate days separated by 1 week. Overnight fast, then attached to BIOSTATOR, brought to steady state over several hours (blood glucose of 8.4mmol/L). Ingested 30mL formula every 15 mins for 4 hours (total 480mL). Blood samples 0-4 hours.	oral	single meal study

