

# Impact of Diet Composition on Blood Glucose Regulation

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*Nutritional management of blood glucose levels is a strategic target in the prevention and management of type 2 diabetes mellitus (T2DM). To implement such an approach, it is essential to understand the effect of food on glycemic regulation and on the underlying metabolic derangements. This comprehensive review summarizes the results from human dietary interventions exploring the impact of dietary components on blood glucose levels. Included are the major macronutrients; carbohydrate, protein and fat, micronutrient vitamins and minerals, nonnutrient phytochemicals and additional foods including low-calorie sweeteners, vinegar, and alcohol. Based on the evidence presented in this review, it is clear that dietary components have significant and clinically relevant effects on blood glucose modulation. An integrated approach that includes reducing excess body weight, increased physical activity along with a dietary regime to regulate blood glucose levels will not only be advantages in T2DM management, but will benefit the health of the population and limit the increasing worldwide incidence of T2DM.*

**Keywords** Postprandial glycemia, diabetes, human dietary intervention, insulin resistance, insulin sensitivity.

## INTRODUCTION

Around 366 million people worldwide have diabetes and this is projected to reach 552 million by 2030 (Whiting et al., 2011). Diabetes is a leading cause of death in developed countries and is predicted to become epidemic in newly industrialized nations. Additionally, poorly controlled diabetes is a major factor in several serious disorders including macrovascular disease, vision loss, renal failure, neuropathy, and amputations (Diabetes Control and Complications Trial

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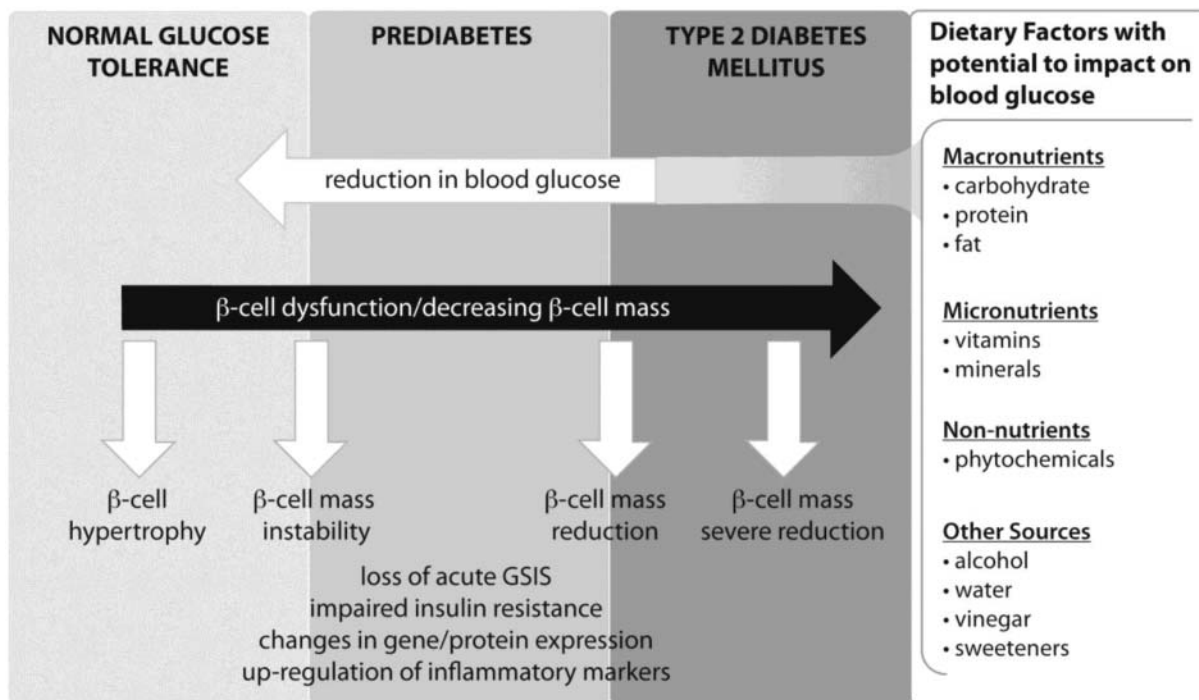
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Research Group, 1993; Ohkubo et al., 1995; Haffner et al., 1998; Niskanen et al., 1998; UK Prospective Diabetes Study Group, 1998; Huxley et al., 2006). Nutritional management of blood glucose dysregulation is a strategic target, as there is mechanistic evidence to suggest that elevated blood glucose levels contribute toward development of type 2 diabetes mellitus (T2DM) (Blaak et al., 2012). Moreover, high blood glucose levels, including values that are below the cutoff for the diagnosis of diabetes, have been shown to be associated with an increased risk of cardiovascular events. This relationship applies not only to fasting values but also to other markers of glucose homeostasis, which reflect blood glucose control in the postprandial period (after a glucose load or meal) or in a longer time frame, including both fasting and postprandial conditions over a prolonged period (glycated haemoglobin; HbA1c) (Heianza et al., 2011). Adoption of a nutritional approach could deliver a cost-effective T2DM prevention and management strategy, applicable across the population. However, to implement a successful strategy and provide clear guidance, it will be essential to understand the effect of food on the underlying metabolic derangements. Particular foods are implicated with increased or reduced incidence of T2DM and their macro-, micro-, and not-nutrient composition along with their energy content are all considered to be contributors to glucose homeostasis (Fig. 1). This comprehensive review will focus on the evidence from human dietary interventions, demonstrating that particular food components have significant and clinically relevant effects on blood glucose regulation.

### Search Strategy

A systematic and comprehensive review of the literature was undertaken using the highest quality data from the following bibliographic databases: MEDLINE (PubMed) and Web of Knowledge (or Science). These databases were searched for intervention trials investigating the effect of nutrients in postprandial hyperglycemia in T2DM patients or obese or control subjects with an explicit strategy for identifying data for extraction and summarizing the data. The search was conducted by combination (using Boolean operators) of the search terms of: “postprandial” + “specific macronutrient or other substance” and further refined by adding: “glucose” or “hyperglycemia” or “insulin sensitivity” or “insulin resistance.” Outputs were restricted to those completed studies only published in English. Terminology and quality of evidence was assigned according to guidelines from Oxford Centre for Evidence Based Medicine available at <http://www.cebm.net/?o=1116>. Strategy for identifying data for extraction and summarizing study findings are detailed in Tables 1–9 and include: Type of Study, Food source (including physical characteristics and delivery), Control, Population Group, Methodology, Study Duration, Primary and Secondary Outcomes, and References. In addition to inclusion of data regarding PPG, outputs considering impact of dietary components on blood glucose regulation were also included, as this was considered to be relevant. The search exclusion criteria were type 1 diabetes mellitus (T1DM), gestational diabetes, diabetes insipidus, infants and



**Figure 1** Potential for dietary factors to reduce blood glucose levels and impact on  $\beta$ -cell function and associated biomarkers. GSIS, glucose-stimulated insulin secretion.

**Table 1** Carbohydrates and carbohydrate foods and postprandial glycemic control in healthy or diabetic individuals

Reference	Design	Test products	Control	Study subjects	Duration	Glucose	Insulin
Larsen et al. 2000	Randomized crossover	Breakfast (CHO 50 g) Cooked polished rice: NP, TP, PP	WB	9 (6M/3F), T2DM, BMI = 26.6	3 h	iAUC: NP, TP, PP < control	iAUC: NP, TP, PP < control
Hallström et al. 2011	Randomized crossover	Breakfast(CHO 50 g) EAWB, EAWB-LA, WB	WB	14 (7F/7M), healthy, BMI = 22.2	3 h	iAUC (120 min): EAWB, EAWB-LA < WB	iAUC (120 min) ns
Granfeldt et al. 1995	Randomized crossover	Breakfast (CHO 50 g) raw rolled oats (muesli), boiled rolled oats (porridge), boiled intact oat, boiled intact wheat	WB	9 M, healthy, 65–70 years, BMI 26.1	3 h	iAUC (90 min): muesli, porridge ns; intact oat, wheat < control	iAUC (90 min): muesli, porridge ns; intact oat, wheat < control
Granfeldt et al. 2000	Randomized crossover	Breakfast (CHO 50 g) Oat flakes; thin roasted, thin roasted/steamed, thick raw, thick roasted, thick steamed Barley flakes: thin, thick steamed	WB	10 (5M/5F), healthy, BMI 21.0	3 h	iAUC (120 min): Oat - thick roasted steamed < control; thick raw < thin roasted/ steamed Barley - ns	iAUC 120 min Oat - thick steamed and thick roasted < control Barley - ns
Frid et al. 2005	Randomized crossover	Breakfast (CHO 50 g) WB: whey, lactose and lean ham Standardized Lunch (CHO 45 g) Mashed potatoes/ meatballs: whey, lactose and lean ham	WB with ham + lactose	14 (6M/8F), T2DM, BMI 26.2	4 h after breakfast 3 h after lunch	iAUC: Breakfast - ns Lunch - whey < control	iAUC: Breakfast - whey > control Lunch - whey > control
Nilsson et al. 2007	Randomized crossover	Breakfast (CHO 25 g) Glc Drink: whey (W), Lys, Thr (2AA), Leu, Ile and Val (3AA), Lys, Thr, Leu, Ile, Val (5AA)	Glc	12 (6M/6F) healthy, BMI = 22.4	2 h	iAUC 90 min W and AA5 < control	iAUC 90 min W and AA3 > control
Järvi et al. 1995	Randomized crossover	Breakfast (CHO 53–57 E%) 1 Durum: Low-GI pasta, High-GI 2 Cereal/Bean: Low-GI, High-GI	Glc	1: 10 (5M/5F), T2DM, BMI = 26.7 2: 10 (2M/8F) T2DM, BMI = 27.0	4 h	iAUC (120 min): pasta < bread; Cereal/Bean low-GI < high-GI	iAUC (120 min): pasta < bread; Cereal/Bean low-GI < high-GI
Robert and Ismail 2012	Randomized crossover	Breakfast Individual foods (CHO 25 g): rice, pancake, flatbread, noodles Mixed meals (CHO 28–32 g): coconut milk rice, pancake/ chicken curry, flat bread/dhal curry, fried noodles/chicken and prawn	Glc	10 (6M/4F), T2DM, BMI 28.1	3 h	iAUC: all foods < control; flatbread > rice, pancake pancake with chicken > pancake	iAUC (120 min): pasta < bread; Cereal/Bean low-GI < high-GI

(Continued on next page)

**Table 1** Carbohydrates and carbohydrate foods and postprandial glycemic control in healthy or diabetic individuals (*Continued*)

Reference	Design	Test products	Control	Study subjects	Duration	Glucose	Insulin
Wheeler et al. 1990	Randomized crossover Double-blind	Breakfast Glc (50 g), HSH5875 <sup>1</sup> , HSH6075 <sup>1</sup>	Glc	T2DM, <i>n</i> = 6, BMI 31.7; T1DM, <i>n</i> = 6, BMI 23.2 and nondiabetic (NGT) <i>n</i> = 6, BMI 24.4	5 h	iAUC (5 h): NGT < DM2 and DMI all meals; HSH-meals < Glc	iAUC (5 h): HSH-meals < Glc for NGT and DM2
d'Emden et al. 1987	Randomized crossover	Breakfast (CHO 50 g) Breads: white (WB), semolina (SB), white spaghetti (WS), whole meal, brown spaghetti (BS)		10 (3M/7F), T2DM, BMI 30.9	3 h	iAUC: WB, SB > WS, BS; WB vs. SB & WS vs. BS ns	iAUC: WB vs. SB, ns; WS < BS
Liljeberg et al. 1992	Randomized crossover	Breakfast (CHO 50 g) Breads: WK, RK, OK, BK, scalded BK (SBK), barley flour (BF)	WB	10 (5M/5F), healthy, BMI normal	3 h	iAUC: WK, RK, BK and SBK < control	iAUC: all kernel bread < control
Panlasigui and Thompson 2006	Randomized crossover	Breakfast (CHO 50 g) intact brown rice, milled brown rice	WB	10 (3M/7F), healthy; 9 (5M/4F), T2DM	3 h	iAUC: both groups milled > intact	
Haber et al. 1977	Randomized crossover	Breakfast (CHO 60 g) Apples: quartered/cored, Purée (fiber-disrupted), Juice (fiber-free)		10 (5M/5F), healthy	3 h	iAUC: ns	iAUC: juice > apples IIP: juice > purée > apples
Leclere et al. 1994	Randomized crossover	Breakfast (CHO 60 E%) Glc: HV-GG, LV-GG Pre-gelatinized Starch (S): HV, LV		6 (3M/3F), healthy	3 h	iAUC (90 min): SHV < SLV SLV < Glc-LV	iAUC (90 min): both HV < LV SLV < Glc-LV
Ellis et al. 1991	Randomized crossover	Breakfast (CHO 75 g) WB + GG flour: high (M150), medium (M90), low (M60) M <sub>w</sub> WB + granulated GG: coarse, medium, fine particle size	WB	17 (14M/3F), healthy, BMI 22.8	2 h		iAUC: control > all test bread products
Golay et al. 1995	Randomized crossover	Breakfast (CHO 52 E%) Standard Formula: soy/milk protein, sunflower/palm oil, maltodextrin/ sucrose; Diabetic Formula: milk protein, rape-seed oil, partially hydrolysed starch/ fructose Diabetic Formula: + hydrolyzed GG		6 (3M/3F), T2DM, BMI 30.4	4 h	iAUC: diabetic formula + guar < standard	iAUC: diabetic formula < standard

Pastors et al. 1991	Randomized crossover	Breakfast (CHO 53 E%) preceded by Placebo, Psyllium	Placebo	18 (6M/12F), T2DM	5 h	iAUC: ns	iAUC: Psyllium < Placebo
Rosen et al. 2009	Randomized crossover	Breakfast (CHO 40 g) white WP, ERB, ERP, WGRB, WGRB+LA, WGRP, bran RB	WB	12 (9M/3F), healthy, BMI = 23.1	3 h	iAUC (120 min): control > ERB, ERP, WGRB-LA, WGRP	iAUC (120 min): Control > ERB, ERP, WGRB, WGRB-lac,
Rosón et al. 2011	Randomized crossover	Breakfast (CHO 50 g) ERB, ERB-LA, WGRB, WGRB-LA, boiled RK, boiled WK	WB	10 (5M/5F), healthy, BMI = 22.6	4.5 h	IIP: control > ERB-LA, RK, WK, WGRB, WGRB-LA,	IIP: control > all test products

iAUC, integrated area under the curve; AUC, area under the curve; CHO, carbohydrate; DF, dietary fiber; NP, nonparboiled; TP, traditionally parboiled; PP, pressure parboiled; B, boiled, EA, elevated amylose; HV/LV, high/low viscosity; AA, amino acid; GG, guar gum; LA, lactic acid; WB, white bread, WP, wheat porridge; ERB, endosperm rye bread; ERP, endosperm rye porridge; WGRB, wholegrain rye bread; WGRP, wholegrain rye porridge; RK, rye kernel; WK, wheat kernel; OK, oat kernel; BK, barley kernel; T1DM, type 1 diabetes; T2DM, type 2 diabetes; Glc, glucose; IGP, Incremental Glucose Peak; IIP, Incremental Insulin Peak; HSH, hydrogenated starch hydrolysates; BMI, body mass index (given as mean in  $\text{kg m}^{-2}$ ), <sup>1</sup>HSH5875 (maltitol 60%, sorbitol 7% and reduced maltooligosaccharides 33%), HSH 6075 (reduced maltooligosaccharides 78%, sorbitol 14% and maltitol 8%).

**Table 2** Dietary fiber and postprandial glycemic control in diabetic individuals

Reference	Design	Fiber type / fiber source	Control	Study subjects	Duration	Glucose (Glc)	Insulin (Ins)
Maki et al. 2009	Randomised crossover DB	Breakfast (CHO 75 g) (HPMC 1, 2, 4 or 8 g)	Cellulose	39 (18M/21F), IGT, BMI $\geq 27$	2 h	iAUC: HPMC 4 and 8 g < control	iAUC: HPMC 2, 4 and 8 g < control
Kim et al. 2009	Randomized crossover	Breakfast (CHO ~ 62 g) $\beta$ -glucan (barley) 0, 2.5, 5, 7.5, 10 g		17 (F); NGT, increased risk for IR, BMI ~33.2	3 h	10 g < 0, 2.5, 5 g at peak 30 min; AUC, NS	10 g < 0, 2.5, 5, 7.5 g at 30, 60 min; AUC: 10 g < 0, 5 g (LR)
Jenkins et al. 2008	Randomized controlled SB	Breakfast (Biscuits, CHO 50 g) PolyGlycopleX (PGX) 70% glucomannan, 30% xanthan 10 g	Control (0 g)	9 (3M/6F), T2DM, BMI 28.8	3 h	PGX < control 30, 60, 90, 120, 150, 180 min	—
Nazare et al. 2009	Randomised crossover SB	Breakfast (CHO ~ 72 g) $\beta$ -glucan (oats) 5 g	Control (0 g)	12 (M), BMI 27.5, fast ing insulin 49	6 h	AUC (120–360 min): 5 g > 0 g	AUC: (120–360 min), 5 g > 0 g
Chearskul et al. 2007	Crossover controlled SB	Purified glucomannan 1 g with 200 mL water 30 min before 75 g oral Glc	White Rice Flour (1g)	20 (10M/10F), T2DM, BMI (M 25.1, F 27.4)	2 h	Glc increase, glucomannan < placebo 1 to 2 h	Ins: NS
Flammang et al. 2006	Randomised, crossover DB	Breakfast (crispy bar, CHO 50 g) GG 8.4 g	Control 1) DF 0 g 2) DF < 5 g	60 (41M/9F), T2DM, BMI 30.2,	4 h	30, 45, 60, 90, 120 min: GG < control; 240 min: GG > control (1 only); AUC: GG < control	30, 45, 60, 90, 120, 180 min GG < control Min: AUC : GG < Control
Tapola et al. 2005	Randomized controlled	Breakfast 1) OBF, CHO 12.5 g; DF 19.5 g ( $\beta$ -glucan 9.4 g); OBC CHO 12.5 g, DF 6.3 g ( $\beta$ -glucan 3.0 g); 2) CHO 6.1 g, DF 9.5 g ( $\beta$ -glucan 4.6 g)	Glc	12 (7M/5F), T2DM	2 h	1) OBF/OBC < gluc (15, 30, 45 min) OBF/OBC > Glc (90 min); AUC (0–60 min, 0–120 min): OBF < Glc; AUC (0–60 min): OBC < Glc; 2) OBF < Glc at 30, 45, 60 min; AUC (0–60 min, 0–120 min): OBF < Glc	
Rendell et al. 2005	Crossover DB	Breakfast prowash barley meal (CHO 20 g, DF 23 g, soluble 10 g); oatmeal (CHO 44 g, DF 7 g, soluble 3 g); LMR (CHO 35 g)	LMR	18 (12M/6F), T2DM, BMI 33	3 h	Prowash < oatmeal, replacer at 30, 60 min iAUC: prowash < oatmeal, replacer	Prowash < oatmeal, replacer at 30, 60 min iAUC: prowash < oatmeal, replacer
Jenkins et al. 2002	Randomized crossover Open-label	Breakfast (CHO 50 g) WB (DF 2.6 g); oat bran cereal (DF 10.3 g, 3.7 g $\beta$ -glucan); high $\beta$ -glucan cereal (14.9 g, 7.3 g $\beta$ -glucan); - high $\beta$ -glucan bar (DF 17.7 g, $\beta$ -glucan 6.2 g)	WB	16 (10M/6F), T2DM, BMI 29	3 h	high $\beta$ -glucan cereal, bar < WB, oat bran at 60, 90, 120 min; AUC, high $\beta$ -glucan cereal, bar < WB, oat bran	—

Tappy et al. 1996	Breakfast cereals (CHO 35 g) $\beta$ -glucan 4.0, 6.0, 8.4 g	Continental Breakfast	8, T2DM	Glc increase, 8.4, 6.0, 4.0 g $\beta$ -glucan < control AUC; linear inverse $\beta$ -glucan	Ins increase 8.4, 6.0, 4.0 g $\beta$ -glucan < control
Guévin et al. 1996	Breakfast (DF 10 g and 20 g) soluble:insoluble ratios 1:4 vs. 2:3		8, T2DM/hyper- 'triglyceridemic	4 h iAUC: 20 g < 10 g soluble insol ratio, NS	iAUC: 20 g < 10 g soluble insol ratio , NS
Gatenby et al. 1996	Breakfast (CHO 75 g) GG (low, med., high MWt) 7.6 g GG/meal	Control Meal	14, T2DM	Glc increase, GG < control	Ins increase, GG < control
Braaten et al. 1994	Porridge meals (Farina); isolated $\beta$ -glucan, oat gum; - native $\beta$ -glucan, oat bran; farina meal	Farina Meal	T2DM	oat bran, gum < control	oat bran, gum < control
Sels et al. 1992	Spaghetti meal (CHO 51%); - T. aestivum; T. durum wheat with/without 20 g% GG		6, T2DM	iAUC: GG vs. no GG, ns IGP lower at 60 and 90 min after GG T. aestivum	Ins profile, ns
Librenti et al. 1992	Breakfast soya fiber 7 g; purified cellulose 7 g - ingested before standard breakfast		8, T2DM	Glycemic profiles, soya < cellulose AUC; soya fiber < cellulose	Ins profile, ns
Pastors et al. 1991	Breakfast (CHO 73 g) psyllium 6.8 g (in 240 mL of water) vs. placebo before breakfast	Placebo	18 (6 M/12 F), T2DM, overweight/ obese	5 h psyllium < placebo up to 90 min; AUC, ns	psyllium < placebo up to 90 min; AUC, psyllium < placebo
Torsdottir et al. 1991	Breakfast (CHO 48%) meals with/ without sodium alginate 5.0 g (algae-isolate, 75% soluble)	Fiber-free meal	7(M), T2DM, BMI 25.6	alginate < fiber-free at 105 min	alginate < fiber-free at 15, 60, 90 min
Del Toma et al. 1988	low fiber (LF); high soluble fiber (HSF); high insoluble fiber (HIF)		10, T2DM	HSF < LF, HIF LF vs. HIF, NS	HSF < LF, HIF LF vs. HIF, NS
Del Toma et al. 1988	Lunch (CHO 45%) LF (6.7 g, sol. 2.0 g); HF (32.9 g, sol. 14.3 g)		13 (8 M/5F), T2DM, BMI 27	3 h HF < LF at 30, 45, 60, 90 min	HF vs. LF, NS
Tsai et al. 1987	Breakfast, (CHO 48.5%) noodles with/without soy 10 g	Fiber-free Meal	7 (3 M/4F), T2DM/ obese	4 h Soy < fiber-free at 180, 240 min	Soy vs. fiber-free, NS
McIvor et al. 1985	Breakfast high-CHO HF (HCF) bar consumed alone or with meals	Placebo Bar absorbable CHO and GG	20, T2DM	HCF < placebo (early PP period); bars with HCF < placebo (90 to 240 min)	

(Continued on next page)

**Table 2** Dietary fiber and postprandial glycemic control in diabetic individuals (*Continued*)

Reference	Design	Fiber type / fiber source	Control	Study subjects	Duration	Glucose (Glc)	Insulin (Ins)
Hagander et al. 1984		Breakfast HF and LF		8, T2DM	3 h	Glc increase/decrease, HF < LF; iAUC: HF < LF	
Jenkins et al. 1976	Randomized crossover	Test meals, CHO 106 g; control; control + GG 16 g, pectin 10 g		1) 8, T2DM (non-insulin-requiring) 2) 3, T2DM (insulin-dependent)		1) Glc decrease, GG + pectin > control from 30 to 90 min 2) Glc decrease, GG + pectin > control	1) Ins decrease, GG + pectin > control from 30 to 120 min
Weickert et al. 2005	Randomised crossover SB	Insoluble cereal fiber extracts from oat and wheat, and resistant starch, baked in white bread	WB	14F, healthy	24 h	Reduced AUC glucose in a second meal test in all interventions vs. control	ns difference between diets, trend to lower AUC insulin
Weickert et al. 2006	Randomised crossover SB	Insoluble cereal fiber extract from oat, baked in white bread	WB	17F, overweight /obese	72 h		Improved whole-body IS vs. control, EHC
Weickert et al. 2011a, 2011b (1)	Randomised crossover SB	HCF diet supported by twice daily supplements	Healthy (ADA) HP MF/ Protein + supplements	111, overweight / obese/ metabolic syndrome	18 wks		Improved whole-body IS vs. HP, EHC NS IS (HOMA-IR) Estimated IS (SI oral); iAUC C-peptide/insulin Increased IS using EHC
Robertson et al. 2003	Randomised crossover	RS	Waxy Maize	10, healthy	24 h		
Robertson et al. 2005	Randomised crossover	RS	Starch Rapidly digestible starch	10, healthy	4 wks		
Johnston et al. 2010	Randomised parallel SB	RS	Rapidly digestible starch	20, healthy	12 wks		Increased IS using EHC
Nilsson et al. 2008	Randomised crossover	Barley or kernel breakfast	WB	12, healthy	1 d	Improved iAUC glucose	Improved iAUC insulin
Pereira et al. 2002	Randomised crossover	Diet containing whole grains	Refined Grain Diet	11 overweight/obese hyper-insulinemic adults	6 wks		Improved whole-body IS vs. refined grain diet, EHC
Chandallia et al. 2000	Randomized crossover	HF diet (24 vs 50 g/d) oats, lima beans, sweet potatoes), no supplements	Healthy (ADA)	17 (16M/1F), T2DM, 45–70 y	6 wks	improved glycemic control (plasma glucose, urinary glucose, HbA1c) HbA1c reduced in low GI vs. HCF	decreased hyperinsulinemia (plasma insulin)
Jenkins et al. 2008	Randomized parallel	HCF diet (27–32 g/d vs. 25–27 g/d) whole grain bread, brown rice, whole wheat cereals	Low GI	210 (128M/82F), T2DM, 60 y, BMI 31	6 m		
Wolever et al. 2008	Randomized parallel	Low GI vs. low CHO (21 vs. 36 vs. 23 g/d) branbuds cereals, rye pumpernickel bread, beans	High GI	162, T2DM, 35–75 y, BMI 24–40	1 y	HbA1c NS DF PPG reduced (low GI diet)	



Sorensen and Johansen 2010	Randomized crossover	FOS dissolved in water 20 g/d (31–40 g/d from the diet)	12 (6M/6F), IRH, 41–75 y, BMI 20–29	2 wks	supplemental dietary fiber reduced glucose excursions in IRH	
de Natale et al. 2009	Randomized crossover	HCF diet (53 vs. 15 g/d) whole grain cereals legumes, veg.	18 (12M/6F), 59 y, T2DM, BMI 27	4 wks	PPG reduced	PP insulin response reduced
Schwab et al 2006	Randomized parallel	Sugar beet pectin + 16 g/d (24–30 g/d fiber from the diet)	66 (29M/37F), T2DM 10 IGT, IFG, 53 y, BMI 28	12 wks	ns fasting glucose	

DB, double blind; SB, single blind; HPMC, hydroxypropylmethylcellulose; EHC, euglycemic hyperinsulinemic clamp; IS, insulin sensitivity; HOMA-IR, homeostasis model assessment for insulin resistance; LMR, liquid meal replacer; IFG impaired fasting glucose; IGT, impaired glucose tolerance; IRH, idiopathic reactive hypoglycemia; NGT normal glucose tolerance; LR, linear response; OBF, oat bran flour; OBC, oat bran crisp; L(H)F, low (high) insoluble fiber; L(H)SF, low (high) soluble fiber; MF, moderate fiber; HP, high protein; iAUC, integrated area under the curve; AUC, area under the curve; CHO, carbohydrate; DF, dietary fiber; RS, resistant starch; GG, guar gum; WB, white bread; NS, no significant effect; T2DM, type 2 diabetes; Glc, glucose; IGP, Incremental Glucose Peak; IIP, Incremental Insulin Peak; BMI, body mass index ( $\text{kg m}^{-2}$ ), expressed as mean unless otherwise specified).

**Table 3** Non digestible carbohydrates with prebiotic properties on blood parameters related to glucose homeostasis

Reference	Design	Subjects	Source	Control	Duration	Outcome measures	Outcome
Lu et al. 2004	Randomized crossover	15 (9F/6M), T2DM, 60 ± 2 y, BMI 28.1 ± 0.9	Bread/Muffins with arabinoxylan (14%) 15.1 g/d arabinoxylan	arabinoxylan 0%	6 wks	fasting and 2h Glc, insulin, urinary Glc	decrease in fasting glycaemia, decrease in post-OGTT glycaemia&insulinemia
Garcia et al. 2006	Randomized crossover SB	11 (7F/4M), IGT, 60 y; BMI 31	WB supplemented with arabinoxylan (15 g) 15 g/d	WB	6 wks	fasting serum Glc, insulin	fasting serum glucose was significantly lower than placebo
Garcia et al. 2007	Randomized crossover SB	11 (7F/4M), IGT, 55.5 y, BMI 30.1	WB supplemented with arabinoxylan (15 g) 21 vs. 36 vs. 23 g/d	WB	6 wks	PPG and PPI	lower postprandial responses in serum glucose and insulin after a liquid meal challenge test in supplemented group
Parnell and Reimer 2009	Randomized crossover DB Placebo-controlled	48 overweight/obese, 20–70 y, BMI > 25	Supplement 21 g/d oligofructose	Maltodextran	12 wks	Serum Glc and insulin	decrease in body weight, decrease in caloric intake, increase GIP ns fasting glucose, insulin, GLP-1 PYY, leptin
Luo et al. 2000	Crossover DB	10 94F/6M) T2DM	Short-chain fructans 20 g/d with coffee, tea or yogurt	Sucrose 20 g/d	4 wks	fasting Glc, fasting insulin, ITT	<i>After MTT</i> decreased glycaemia, decreased insulin, increased AUC for PYY, ns AUC for GLP-1, ns GIP NS for caloric intake, body weight, glucose, insulin, hepatic glucose production, insulin-stimulated glucose metabolism decrease in fasting insulin, NS for fasting glycaemia
Daubioul et al. 2005	Randomized crossover DB	7M overweight with nonalcoholic steatohepatitis 37–66 y, BMI 29	Oligofructose 16 g/d with breakfast and dinner	Maltodextran	8 wks	fasting Glc, fasting insulin	

DB, double blind; SB, single blind; T2DM, type 2 diabetes; Glc, glucose; PPG postprandial glycaemia; PPI, postprandial insulinaemia; WB, white bread, NS, nonsignificant change. BMI, body mass index (kg m<sup>-2</sup>; expressed as mean unless otherwise specified).

**Table 4** Dietary fatty acids and postprandial glycemic control

Reference	Design	Subjects	Source	Daily Intake	Duration	Outcome measures	Outcome
Scalfi et al. 1991	Randomized crossover	6 Lean: 28 ± 1.5 y, BMI 23.1 ± 0.7; 6 Obese: BMI 35.1 ± 3.7, 47.1 y, Italy	FA length: MCT oil C6:0 2%, C8:0 56%, C10:0 40%, and C12 2% est. with glycerol LCT = corn oil	Test Meal: 15% protein, 58 g; 55% CHO, 194 g; and 30% fat, 38g	6 h	iAUC, indirect calorimetric for RMR, glucose oxidase method and immunoassay for insulin	resting metabolic rate decreased when LCT were replaced by MCT; incremental Glc AUC lower in lean but not obese subjects after MCT. NS for chain length on insulin or free fatty acids
Zambon et al. 1992	Randomized crossover	10M, T2DM; 64±2 y; BMI 28.6±1, USA	n-3 capsules	8 g/d	8 wks	iAUC plasma Glc and insulin	decreased IR to meal with fish oils in presence of glyburide compared to drug alone. NS for HDL and triglycerides
Lerman-Garber et al. 1994	Randomized crossover	12F, T2DM, Mexico	Avocados high source of MUFA	n/a	4 wks	blood samples pre- and post	glycemic control was similar with both diets. MUFA diet was associated with a greater decrement in plasma triglycerides (20 vs. 7% in the high CHO diet).
Rivellese et al. 1996	Placebo DB parallel	16, T2DM, 35–75 y, BMI 24–40, Italy	Fish oil supplements EPA/DHA	2.7 g/d for 2 m then 1.7 g/d for 4 m	6 m	euglycemic hyperinsulinemic clamp	NS for fish oil on insulin stimulated Glc uptake. reduction in TG but not Glc after intervention.
Christiansen et al. 1997	Randomized crossover	16 (7 post-menopausal F/9M), free-living obese T2DM, 55 ± 3y BMI 33.5±1.2, Denmark	Saturated FA diet, cis-MUFA diet, trans-MUFA diet	20 g/d (31–40 g/d from the diet)	6 wks	incremental serum insulin, fasting and 2h plasma Glc, insulin and C-peptide	decreased serum insulin and C-peptide following cis-MUFA (NS for control) compared with trans-MUFA and saturated FA diets. NS for fasting levels of serum lipids (total cholesterol, TG, phospholipid, and nonesterified fatty acids) or lipoproteins of HDL, VLDL, LDL and apolipoprotein B
McCargar et al. 1998	Randomized prospective	32 T2DM Canada	CHO and Fat Ensure with Fat or Glucerna	n/a	4 wks	PPG	PP rise in blood Glc was lower on MUFA diet. NS for fasting plasma Glc, fructosamine, TG and cholesterol levels
Madigan et al. 2000	Randomized crossover	11M T2DM, HbA1c 5.7 ± 0.8%, 56.0 ± 2.5 y, Ireland	isocaloric diet, high MUFA (olive) or PUFA (sunflower). Meal: High-fat breakfast, 50 g Glc load (30 min). WB fried in oil 1,100 kcal, 55% fat	30 mL/daily	8 h	Fasting Glc and Insulin	plasma cholesterol, LDL, chylomicron Apo B48 & Apo B100, PP chylomicron, VLDL Apo B48 & B100 higher on the linoleic acid diet. Fasting Glc/ insulin higher after PUFA compared to MUFA.
Piers et al. 2003	Randomized crossover	8M, obese/ overweight	Total E from SFA, MUFA & PUFA 24, 13 and 3% on SFA diet; 11, 22 and 7% on MUFA diet. In selected foods.	4 wks	5 h	Fasting Glc and Insulin	lower weight -2.1 ± 0.3 kg & fat mass -2.6 ± 0.6 kg on MUFA vs. SFA rich diet. Blood Glc -0.04 + 0.6 mM (SFA) & -0.15 + 0.53mM (MUFA); insulin +0.2 + 3.68 (SFA) & -0.66 + 2.44 (MUFA)
					8 h	iAUC	

**Table 4** Dietary fatty acids and postprandial glycemic control (*Continued*)

Reference	Design	Subjects	Source	Daily Intake	Duration	Outcome measures	Outcome
Thomsen et al. 2003	Randomized crossover	12, T2DM, overweight, 64 ± 4 y, BMI 27.9 ± 5.3, HbA1c 6.9 ± 0.8%, Denmark	Control: Soup CHO 50 g, Control + 100 g butter, Control + 80 g olive oil				iAUC: lower for olive oil vs. control, NS for fat-induced insulin, plasma TG and chylomicron TG highest after butter, HDL decreased after butter but NS after olive oil. GLP-1 responses highest after olive oil
Brady et al. 2004	Randomised parallel DB	29, T2DM, 48 ± 2 y; BMI = 26 Fasting Glc = 5.3 mM, Asian UK	Moderate (olive oil) or high (corn oil) n-6 PUFA oils. Test breakfast : energy (3904 kJ), fat (49 g) CHO (109 g) protein (18 g)	6 wk daily supplement of n-3 LC-PUFA fish oil (4.0 g); EPA + DHA (2.5 g) in combination	8 h	iAUC	NS for fasting or PP plasma triacylglycerol or apo B48 for moderate and high intervention groups after fish-oil treatment. Over entire study period: reduction in fasting plasma TG (20%). AUC and iAUC: reduction in PP TG
Manning et al. 2004	Randomized crossover	18, T2DM (2-60 m) nonsmokers, 61 ± 10 y, BMI 28.5 ± 4.4 fGlc 6.8 ± 1.7 mmol/l, HbA <sub>1c</sub> 6.5 ± 0.6%, Canada	meals of starch +/- SFA or MUFA		6 h	FBG mM, insulin pM	NS for PPG and PPI after fatty meals, CHO increased PPG and PPI, FFA and TG increased in fat diets at 4h and 6h. IL-6 decreased after 1h and TNF- $\alpha$ decreased after 4 and 6h in all diets
West et al. 2005	Randomized crossover DB	18, T2DM (duration 4.4 ± 1.6 y), HbA1c 7.2%, 55.1 ± 2 y, fGlc = 7.69 ± 0.35 mM, fI = 12 ± 1.5 uU/ml, BMI 29.2, US	Test meal: n-3 PUFA, prepared in 473 mL skimmed milk, flavourings designed to mask the characteristic aroma and flavors of the oils	50 g fat from three blends of unsaturated fatty acids	4 h		correlation between PP change in flow-mediated dilation and PP increase (absolute change) in TG for MUFA alone were as follows: r = -0.50, p < 0.05 for the MUFA meal; r = 0.49, p = 0.052 for the EPA/DHA meal; and r = 0.49, p = 0.046 for the ALA meal. NS for meal composition on Glc levels
Lefevre et al. 2005	Crossover	Overweight, FABP Ala54 homozygous or Thr54-carriers, US	Breakfast: provided 40% of their daily energy requirement and containing 50% of energy as fat		8 h	PPG	NS for PPG between diets but Thr54 allele increased PPG, fractional TG synthesis rates were higher after trans fats in Thr54 carriers only
Paniagua et al. 2007	Prospective crossover	overweight, family history of obesity and T2DM, BMI > 25 Kg/m <sup>2</sup> , WC (M/F) > 102/ 88, HbA1c < 6.5%, IR after OGTT, Spain	Breakfast: isocaloric : virgin olive oil compared high CHO or high in saturated fat (SAT)		Single meal effect	FBG, Homa-IR, iAUC for insulin and Glc	MUFA decreased fGlc and increased IS, PPI and PPG, iAUC decreased with MUFA vs. isocaloric CHO rich breakfast, GLP-1 increased with MUFA and SAT; HDL cholesterol increased with MUFA (fasting and PP), fasting proinsulin and stimulated proinsulin NS for MUFA diet
Devaraj et al. 2008	Randomized crossover	11 metabolic syndrome, US	Breakfast: AHA vs. SFA. Control: breakfast E 914, protein 14.1%, CHO 36%, fat 50%		2h & 8 h		Glc levels significantly increased compared to pre-meal after both meals i.e. NS

Li et al. 2008

Author	Study Design	Population	Intervention	Comparison	Duration	Measurements	Results
De Natale et al. 2009	Controlled parallel DB	127, T2DM 40–65 y, China	25 g/day oil for 120 d	diacylglycerol (DG) compared to triacylglycerol (TG)	6 h	fasting measurements taken at days 0, 60, 120, No PP study	reduced body weight, BMI, waist circumference, HOMA-IR, serum insulin and leptin levels in DAG vs. TG vs. baseline, serum Glc improved in patients with higher Glc at baseline in the DG, NS for liver/kidney function and FA in serum phospholipids Increased Glc following fiber vs. MUFA diets at 2h & 3 h, increased lipids, triacylglycerols following fiber vs. MUFA diets, NS for cholesterol, plasma Glc & insulin higher 6 h after thigh CHO/high fiber meal vs. high MUFA meal Decreased PPG and PPPI on MUFA or low fat vs. control/western diet, NS for fasting insulin, pancreatic polypeptide, peptide YY, glucagon-like peptide-1 and glucagon-like peptide-2 lowered after weight loss diet
Sloth et al. 2009	Randomized	131, 8-week weight loss diet, Denmark	For 4 wks	isoenergetic diet, low CHO and high MUFA vs. high CHO, High fiber	6 m	mM, glycemic variability and IAUC	
Li et al. 2011	Randomized crossover	20 (9M, 11F) T2DM, China 58 years, BMI = 26kg/m <sup>2</sup>	NCEP step II diet with or without 60 g almonds	High MUFA, low GI MUFA, moderate - fat (35–45 E%) high in MUFA with low GI, low fat (20–30 E%), control (35 E%)	12 wks	fI, fBG, IR	almond diet had lower levels of fasting Glc, insulin and homeostasis model assessment of insulin resistance index, respectively, decreased total cholesterol, LDL, LDL/HDL
Lopez et al. 2011	Crossover		14.9% SFA, 81.0% MUFA, 4.1% PUFA (olive oil); 65.3% SFA, 31.3% MUFA, and 3.4% PUFA (butter)	MUFA vs. SFA vs. no fat in enriched meals. Test meal no fat isocaloric meal	8 h	PPi	high-fat meals significantly increased TG, nonesterified fatty acids, and insulin and PP indexes of $\beta$ cell function. However, PP indexes of IS decreased and were attenuated with MUFA relative to SFA
Jans et al. 2012	Randomized crossover SB	10M obese (IR), Holland	2.6MJ high fat mixed meal	PUFA vs. MUFA vs. SFA, 3 high-fat mixed meals (2.6 MJ), which were high in SFAs, MUFA, or PUFA	6 h	Fasting and PP skeletal muscle FA, skeletal muscle biopsy, AUC	AUC (Glc and insulin): significantly higher for SFA vs. PUFA, TG-derived FAs lower in the PP phase after PUFA meal c.f. other meals, fractional synthetic rate of the TG, DG, and phospholipid pool was higher after the MUFA meal vs. SFA
Kelley et al. 2012	Placebo-controlled parallel	14–17M hypertriglyceridemic	3 g/d vs. 0 g/d supplement	DHA without EPA vs. control	90 d	Fasting plasma Glc and insulin, PPG,	increased fasting plasma Glc with DHA. NS for indices of fasting IR, PPI and PPG. AUC: NS

**Table 4** Dietary fatty acids and postprandial glycemic control (*Continued*)

Reference	Design	Subjects	Source	Daily Intake	Duration	Outcome measures	Outcome
						PPI, AUC Matsuda index	increased Glc in placebo (2.7%). NS for both groups. DHA decreased several lipocentric markers of IR, including circulating non-esterified fatty acids, small, dense LDL particles and TG/HDL ratio, NS for placebo

DB, double blind; NS, no significant effect; IR, insulin response; T2DM, type 2 diabetes; AUC, area under the curve; CHO, carbohydrate; F, female; M, male; FA, fatty acid; PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid; Glc, glucose; fGlc, fasting glucose; WC, waist circumference; IR, insulin resistance; IS, insulin sensitivity; TG, triglycerides; HDL, high-density lipoprotein; VLDL very low-density lipoprotein; LDL, low-density lipoprotein; PPG postprandial glycemia; RMR, resting metabolic rate; PPI, postprandial insulinemia; BMI, body mass index (kg m<sup>-2</sup>; expressed as mean unless otherwise specified).

**Table 5** Dietary vitamins and minerals and postprandial control

Reference	Design	Subjects	Source	Daily intake	Duration	Outcome measures	Outcome
Neri et al. 2005	Controlled SB	46, T2DM, 41±3 y, BMI 24±2, USA	Vitamin E, vitamin C and N-acetyl cysteine	8 g/d	8 wks	iAUC plasma Glc and insulin	Only measured at baseline
Frauchiger et al. 2004	Randomized crossover SB	13M, healthy, nonsmoking, 23.8–25.6y, BMI 22–23	Test meals (75g CHO) WB with added chromium	Placebo vs. 400 µg vs. 800 µg	8 h	Glc tolerance test, AUC plasma insulin	30%–36% reduction in capillary Glc AUC with 400 µg Cr in 10 responders
Anderson et al. 1997	Randomized crossover DB	180 (M/F), T2DM	Normal diet supplemented with chromium picolinate	Placebo vs. 200 µg/d vs. 1000 µg/d	4 m	HbA <sub>1c</sub> fasting Glc and insulin; 2 h Glc and insulin	HbA <sub>1c</sub> , fasting, 2 h Glc and insulin significantly reduced in patients supplemented with Cr for 4 months
Cheng et al. 1999	Follow-up survey	833, T2DM	Supplementation (500 µg/d) with chromium picolinate	500 µg/d	10 m	fasting and PPG	fasting Glc and PPG improved in >90% of subjects, and similar improvements occurred after 1–10 months. Fasting Glc level and PPG lowered in 1 month and remained significantly lower in the following 9 months.

DB, double blind; SB, single blind; Cr, chromium; NS, no significant effect; IR, insulin response; WB, white bread; T2DM, type 2 diabetes; Glc, glucose; HDL, high-density lipoprotein; PPG postprandial glycemia; BMI, body mass index ( $\text{kg m}^{-2}$ ; expressed as mean unless otherwise specified).

pediatric studies, although reference has been made to these studies for discussive purposes.

### ***Impact of Macronutrients on Blood Glucose Levels***

#### ***Dietary Carbohydrates and Glycemic Control***

By promoting subclinical inflammation, chronic hyperglycemia is a major contributor to endothelial damage, providing a link between diabetes and cardiovascular disease (Ceriello, 2004). It has been suggested that oscillatory postprandial glycemic fluctuations are particularly detrimental in relation to interleukin 6 expression, indicating that foods which release their carbohydrates at a slow rate to the blood are to be preferred. Available intervention studies regarding the impact of dietary Glycemic Index (GI), or Glycemic Load ( $\text{GL} = \text{GI} \times \text{the amount of carbohydrates per portion}$ ) on glycemic control in subjects with diabetes was compiled in an extensive Cochrane review in 2009 (Thomas and Elliott, 2009). Data from 11 intervention studies lasting four weeks or longer were included and subjected to meta-analysis. The overall conclusion was that low GI diets improved diabetic control and reduced HbA<sub>1c</sub> to an extent that was comparable to that seen following medication in newly diagnosed T2DM subjects. It was also put forward that a low GI diet may improve whole body peripheral insulin sensitivity (Rizkalla et al., 2004), and reduce the number of hypoglycemic events (Gilbertson et al., 2001). Of interest in this context is that hypoglycemia may be an additional risk factor for cardiovascular

disease in children with type 1 diabetes, independently of HbA<sub>1c</sub> (Pena et al., 2012). Consequently, carbohydrate foods that promote low but sustained blood glucose levels may be considered advantageous with regard to metabolic control of diabetes and possibly reduce risk of future cardiovascular events.

One potential point for criticism of the GI concept is that the glycemic impact of foods may be markedly affected by certain meal components. This has been shown in healthy subjects when adding, e.g., certain proteins or lipids to mixed meals (Wolever and Bolognesi, 1996). Consequently, adding whey and/or certain amino acids to a meal may substantially reduce the glycemic excursion in healthy and T2DM subjects (Frid et al., 2005; Nilsson et al., 2007; Gunnerud et al., 2012a, 2012b). However, for foods and meals rich in carbohydrates it appears as if the GI of mixed meals can be predicted from the component foods in healthy subjects indicating that for carbohydrate-rich meals the effects of additive components of GI are minor. This has also been demonstrated in T2DM subjects (Järvi et al., 1995; Robert and Ismail, 2012). The authors concluded that generally, the single foods were ranked similarly to the mixed meals, supporting the utility of the GI concept also for mixed meals in T2DM subjects (Robert and Ismail, 2012).

The GI of foods is influenced by the type and amount of dietary fiber (DF). In a study by Järvi and coworkers (Järvi et al., 1999), a four-week intervention was performed in T2DM subjects comparing a high versus low GI diet, using a cross-over design. The differences in GI of the diets were achieved by manipulating the food structure, thus essentially maintaining the same food composition- including that of the

**Table 6** Effect of phytochemical rich sources (cocoa, plant extracts) on postprandial glycaemia

Reference	Design	Subjects	Source	Daily intake	Duration	Outcome measures	Outcome
Grassi et al. 2008	Randomized crossover DB	19 (11M/8F), IGT (no diabetes), 44.8±8.0 y, BMI < 30	Dark chocolate bar (epicatechin, catechin, procyanidin) Control: WC	100 g/d	15 d	OGTT, AUC, lipids, CRP, endothelial function	decreased HOMA, increased QUICKI, PPG ( $p < 0.0001$ )
Grassi et al. 2005	Randomized crossover DB	15 (7M/8F), healthy, 44.8±8.0 y	Dark chocolate bar (epicatechin, catechin, procyanidin) Control: WC	100 g/d	15 d	OGTT, AUC, lipids, CRP, endothelial function	decreased HOMA, increased QUICKI, PPG ( $p < 0.0001$ )
Muniyappa et al. 2008	Randomized crossover DB	20 (7M/13F), 13 White, 7 African Americans, mild-moderate hyper-tension 21–65 y	Flavanol-rich cocoa drink (epicatechin, catechin, procyanidin)	300 mL/d contains ~900 mg flavanols/d	2 wks	Glc clamp, metabolites, endothelial function, BP	NS for IR
Kar et al. 2009	Randomized crossover DB	32 (16M/16F), T2DM, 61.8±6.36 y, BMI 31.2±5.92	Grape seed extract (flavonoids, other phenolics)	600 mg/d	4 wks	HOMA-IR, fructosamine endothelial function, CRP	decreased fructosamine, NS for HOMA-IR
Serraclara et al. 1998	Randomized crossover DB	10 (6M/4F), IDMM, 22–38 y, BMI 20.8±3.0	Fig supplement (flavonoids, other phenolics) Control: non-sweet commercial tea control	53 vs. 15 g/d	1 m	2h PP lipids	decreased plasma Glc
Lehtonen et al. 2010	Randomized parallel	10, healthy, 20–34 y, BMI 19.8–26.9	Sea buckthorn extract in yogurt (flavanol glycosides)		6 h	OGTT, AUC	decreased plasma Glc/insulin
Torronen et al. 2010	Randomized crossover	12 (2M/10F), Healthy, 25–69 y, BMI 25.4 ± 2.9	Berry puree (flavonoid, other phenolics) Control: carbohydrate drink	150 g	3 h	1.5, 30 min plasma Glc	decreased plasma Glc
Goni et al. 2000	Crossover	12F, healthy, 22.08 ± 1.44 y, BMI 2.19 ± 2.78	Nori alga with WB	3 g	2 h	OGTT, AUC	Increase in PPG
Mankey et al. 2011	Randomized crossover SB	9 (3M/6F), healthy, 26.2 ± 3 y, BMI 22.4 ± 2.5	High-fat meal supplemented with cinnamon or placebo	3 g	360 min	OGTT, AUC Arterial stiffness, BP	NS for PPG

DB, double blind; SB, single blind; WC, white chocolate; NS, no significant effect; IR, insulin response; WB, white bread; T2DM, type 2 diabetes; Glc, glucose; HDL, high-density lipoprotein; PPG postprandial glycaemia; IGT, impaired glucose tolerance; BMI, body mass index ( $\text{kg m}^{-2}$ ); expressed as mean unless otherwise specified) iAUC, integrated area under the curve; AUC, area under the curve; CHO, carbohydrate; DF, dietary fiber; OGTT, oral glucose tolerance test; HOMA-IR, homeostasis model assessment for insulin resistance; CRP c-reactive protein.



**Table 7** Effect of ginseng on postprandial glycaemia

Reference	Design	Subjects	Source	Daily intake	Duration	Outcome measures	Outcome
Stevenpiper et al. 2003a	Randomized controlled crossover	11 (8M/3F), 29 ± 3 y, BMI 28.5 ± 2.1; 11 (6M/5F), 27 ± 3 y, BMI 26.9 ± 1.4	Asian Ginseng	1) 0, 1, 2, 3 g; 2) 0, 3, 6, 9 g	120 min	OGTT	decreases in PPG American c.f. Asian
Stevenpiper et al. 2003b	Randomized, crossover SB	12 (6M/6F), 31 ± 3 y, BMI 28 ± 2	American Ginseng	6 g	120 min	OGTT, iAUC	NS for AG on iAUC Glc
Stevenpiper et al. 2004	Randomized, multiple-crossover DB	12 (6M/6F), healthy, 34 ± 3 y, BMI 25.8 ± 1.2, Canadian	American, American-wild, Asian, Asian-red, Siberian, Vietnamese- wild, Sanchi and Japanese-rhizome, Ginsengs (alkaloids, ginsenosides)	3 g	120 min	OGTT	American Ginseng and Vietnamese Ginseng decreased 90 min PPG; Asian Ginseng increased peak-PPG and AUC-PG; American-wild Ginseng increased 120 min PPG and Siberian Ginseng increased 90 min PPG, 120-min-PG, and AUC- PG.
Stevenpiper et al. 2006	Randomized crossover DB	7 (3M/4F), healthy, 32 ± 4 y, BMI 24 ± 2; 12 (9M/3F), healthy, 29 ± 3 y, BMI 22.5 ± 1	Korean Ginseng (ginsenosides, alkaloids)	0 g (placebo) and 6 g KRG- rootlets, -body, and -H <sub>2</sub> O extract	120 min	OGTT, AUC	decrease in PPG
Dascalu et al. 2007	Randomized crossover placebo controlled	12 (5M/7F), healthy, 26.5 ± 2 y, BMI 23.96 ± 3.41, Canadian	American ginseng (5 farms), whole, dried and ground root	9 g, 40 min before 75 g OGTT, placebo 500 mL water	2 h	OGTT	1 mM reduction peak Glc, 28% reduction iAUC, 24% reduction iAUC insulin. NS for 2 batches
Reay et al. 2006	Balanced-crossover DB placebo-controlled,	1) 30 healthy, BMI 22.6 ± 5.46, 2) 27 healthy, BMI 1.89 ± 4.46, UK	Asian Panax Ginseng Extract (G115)	1) placebo, 200 or 400 mg 2) placebo, 200 mg placebo and Glc (25 g) and 200 mg 30 mins before and Glc (25 g)	2h	OGTT	1) decreased Glc at 60, 90, 120 mins 2) decreased Glc at 60 min for ginseng vs placebo. Higher Glc for ginseng and glucose compared to glucose alone.

(Continued on next page)

Table 7 Effect of ginseng on postprandial glycemia (Continued)

Reference	Design	Subjects	Source	Daily intake	Duration	Outcome measures	Outcome
Reay et al. 2009	Cross-over DB placebo-controlled,	1) 24 healthy, BMI 33.3 ± 10.4 (2/18) healthy, BMI 41.5 ± 9.7, UK	1) Asian Panax Ginseng Extract (G115); 2) Asian Panax ginseng extract Cheong Kwan Jang	200 mg/d	57 d	HbA1c, plasma insulin, blood Glc	NS for HbA1c
Sotamiemi et al. 1995	DB placebo-controlled	36 T2DM, 60 ± 6 y, 59 ± 7 y, 57 ± 9 y, Finland	Ginseng	100 mg or 200 mg	8 wks	Fasting blood Glc, HbA1c	100 mg decreased fasting Glc 8.3 to 7.7 ( $p < 0.05$ ), 200 mg reduced HbA1c from 6.5 to 6.0 ( $p < 0.05$ ). NS for Glc, insulin, C-peptide over OGGT (75 g) Reduction in HbA1c
Vuksan et al. 2000	Randomized crossover placebo controlled	10 (6M/4F), nondiabetic 41 ± 13 y, BMI 24.8 ± 3.5	American Ginseng, ground root, encapsulated (500 mg)	0, 3, 6 or 9 g	120 min	OGTT, AUC	All AG doses reduced AUC and IIG (3g, 26.6%; 6g, 29.3%; 9g, 38.5%). AG taken at different times did not influence PPG
Vuksan et al. 2000	Randomized crossover placebo controlled	10 (6M/4F), T2DM, 63 ± 2 y, BMI 27.7 ± 1.5, Canadian	American Ginseng, ground root (500 mg)	0, 3, 6, or 9 g	120 min	OGTT, AUC	3, 6 or 9 g significantly reduced iAUC (19.7, 15.3 and 15.9%). NS for time of administration
Vuksan et al. 2000	Randomised crossover placebo controlled	1) 9 T2DM, 62 ± 7 y, BMI 29 ± 5.2) 10 healthy, 34 ± 7 y, BMI 25.6 ± 3	American ginseng	3 g	120 min	OGTT	1) reduction (19%) in iAUC 40 minutes before the Glc challenge, reduction (22%, $p < 0.05$ ) when given glucose; 2) reduction (18%) in iAUC 40 minutes before the Glc challenge, NS when given together. decreased PPG
Vuksan et al. 2001	Randomized crossover DB	10 (6M/4F), IDMM, 63 ± 2 y, BMI 27.7 ± 1.5	American Ginseng, Ontario-grown ground root encapsulated	0, 3, 6, or 9 g	120 min	OGTT	Decreased PPG (final 45 min) 1, 2, or 3 g ginseng c.f. placebo; decreased AUC (final hour) when administered 40 min c.f. 20, 10, or 0 min before the challenge decrease in PPG
Vuksan et al. 2001	Randomized crossover SB placebo controlled,	12 healthy, 42 ± 7 y, BMI 24.1 ± 1.1, Canadian	American Ginseng, dried and ground root encapsulated (500 mg)	0, 1, 2, or 3 g	120 min	OGTT	Decreased PPG (final 45 min) 1, 2, or 3 g ginseng c.f. placebo; decreased AUC (final hour) when administered 40 min c.f. 20, 10, or 0 min before the challenge decrease in PPG
Vuksan et al. 2006	Randomized crossover SB	19 (11M/8F), well-controlled T2DM, 64 ± 2 y, BMI 28.9 ± 1.4	Korean Red Ginseng, root with meal (ginsenosides alkaloids)	2 g/meal = 6 g/day	12 wks	OGTT, AUC	decrease in PPG
De Souza et al. 2011	Randomized crossover	13 (6M/7F), healthy,			120 min	OGTT, AUC	27% decrease in glycaemic response

Heacock et al. 2008	Randomized crossover	28 ± 10 y, BMI 24.1 ± 3  39 (15M/24F), healthy, 25.7 ± 0.9 y, BMI 23.7 ± 0.4	Korean Red Ginseng with standard meal (ginsenosides alkaloids) Beverage 480 mL (14 g fat, 82 g, CHO 20 g protein) with <i>S. oblonga</i> extract (salacinol/kotalanol) Control Beverage (C) 480 mL (14 g fat, 82 g CHO, 20 g protein), C plus phenylalanine and leucine (3.5 g, A); C plus <i>S. oblonga</i> extract (1000 mg, S), Control plus S and AA <i>S. oblonga</i> extract	3 g of KRG-body, rootlets or placebo 0, 500, 700, or 1000 mg of <i>S. oblonga</i> extract	2 h	Finger prick	decrease in PPG/PPI
Collene et al. 2005	Randomized crossover	43 (20M/23F), healthy, 23.5 ± 0.6 y, BMI 23.9 ± 0.4, 29 Caucasian, 1 African American, 8 Asian, 1 Latino	Control Beverage (C) 480 mL (14 g fat, 82 g CHO, 20 g protein), C plus phenylalanine and leucine (3.5 g, A); C plus <i>S. oblonga</i> extract (1000 mg, S), Control plus S and AA <i>S. oblonga</i> extract	1000 mg of <i>S. oblonga</i> extract	3 h	OGTT, AUC	decrease in PPG
Williams et al. 2007	Randomized crossover DB	66 (53M/13F), T2DM, 61.3 ± 1.2 y, BMI 28.8 ± 0.4, 1 American India/Alaskan, 7 African American, 58 Caucasian	<i>S. oblonga</i> extract	240 mg and 480 mg	3 h	OGTT, AUC	decrease in PPG/PPI

DB, double blind; SB, single blind; IDMM, insulin-dependent diabetes mellitus NS, no significant effect; IR, insulin response; WB, white bread; T2DM, type 2 diabetes; Glc, glucose; HDL, high-density lipoprotein; PPG postprandial glycaemia; IGT, impaired glucose tolerance; BMI, body mass index ( $\text{kg m}^{-2}$ ); expressed as mean unless otherwise specified) iAUC, integrated area under the curve; AUC, area under the curve; CHO, carbohydrate; DF, dietary fiber; OGTT, oral glucose tolerance test; HOMA-IR, homeostasis model assessment for insulin resistance; CRP c-reactive protein.

**Table 8** Effect of phytochemical rich sources (nuts and beverages) on postprandial glycaemia

Reference	Design	Subjects	Source	Daily intake	Duration	Outcome measures	Outcome
Josse et al. 2007		9 (7M/2F), healthy, 27.8 ± 6.9 y BMI 22.9 ± 3.6	50 g CHO from white bread +/- almonds phenolics, flavonoids, sterols	30, 60, 90 g almonds	120 min	OGTT, AUC	decreased PPG, lower serum cholesterol
Cohen and Johnston 2011	Randomized crossover	1) 13 (2M/11F), healthy, 53.3 ± 3 y; 2) 7 (4M/3F), T2DM, 66.3 ± 3 y	test meal (bagel, juice, and butter) with or without almonds phenolics, flavonoids, sterols	28 g/d	120 min	OGTT, AUC	decreased PPG compared to T2DM; NS for iAUC insulin or 30 min GLP-1
Cohen and Johnston 2011	Randomized parallel, pilot	13 T2DM, 66 ± 3.3 years, BMI 32.6 ± 2.3 Control BMI 36.7 ± 3.6	Almonds Control: cheese sticks	1 oz, 5 d/week	acute	HbA1c on fasting venous blood	HbA1c: -4% vs. +1%, <i>p</i> = 0.045 to T2DM
Kendall et al. 2011a, 2011b	Randomized crossover	10, healthy, 48.3 ± 6.4 years, BMI: 28 ± 4.8	Pistachio consumed with/without WB (50 g CHO)	28, 56 or 84 g	120 min		lower relative glycaemic response vs. WB
Mori et al. 2011	Randomized crossover	14 IGT, 18-60y	75 g CHO matched breakfast (orange juice and cream of wheat) containing vehicle, whole almonds, almond butter, defatted almond flour or almond oil phenolics, flavonoids, sterols	42.5 g	acute	OGTT, AUC	decreased PPG
Jenkins et al. 2006	Crossover	15 healthy, 26.3 ± 8.6 years, BMI 23.4 ± 3.4	WB (50 g CHO), WB and 60 g almonds, parboiled rice and mashed potatoes, these last 2 were balanced for fat (butter), protein (cheese)	60 g	240 min	iAUC	insulin iAUC lower for almond and rice compared to potato.
Kendall et al. 2011a, 2011b	Randomized crossover	14 healthy, 36 ± 4 y, BMI: 21.8 + 0.6) 10 T2DM 68 ± 2 years, BMI: 26.5 ± 0.5	WB (50 g CHO) with or without 30, 60, 90 g mixed nuts	30, 60, 90 g	120 mins		1) 30, 60, 90 g reduced the GR by 11.2 + 11.6%, 29.7 + 12.2 and 53.5 + 8.5%; 2) 30, 60, 90 reduced the GR by 6.6 + 8.8%, 16.6 + 9.3 and 30.8 + 7.6

Brown et al. 2009	Randomized crossover	46M, obese/Overweight, 40-65 y	Green Tea, purified extract, > 97% epigallocatechingallate	Lactose	8 wks	OGTT, AUC HOMO, fasting Glc/insulin	no change in insulin sensitivity/secretion or Glc tolerance
Josic et al. 2010	Randomized crossover	14(7M/7F), healthy, 27 ± 3, BMI 22.3 ± 3.4	Green Tea, beverage + breakfast, flavan-3-ols	Water + breakfast	120 mins	OGTT	no Glc/insulin lowering, increased satiety
Bryans et al. 2007	Randomized crossover	16(4M/8F), healthy, 35.5 ± 1.5 y, BMI 23.8 ± 0.7	Black tea, beverage, flavan-3-ols, theaflavins	Water, caffeine, Glc	120 mins	OGTT	late phase plasma Glc response/elevated insulin
Johnston et al. 2003	Randomized crossover	9, healthy, 26 ± 3.2 y, BMI < 25	Coffee, beverage (caffeinated/decaffeinated chlorogenic acid caffeine)	Water	3 h	OGTT	increased Glc/insulin; delayed GI glucose absorption
Nagao et al. 2009	Controlled DB	1) 23(15M/8F), T2DM (no ins.), 64.9 ± 1.6 y, BMI 25.6 ± 0.8 2) 20(10M/10F) 62.8 ± 2.2 y, BMI 24.0 ± 0.9	Green tea, (catechin rich) beverage, flavan-3-ols	Low-catechin beverage	12 wks	plasma glucose, insulin HbA1c	Increased insulin, waist circumference, & adiponectin

DB, double blind; SB, single blind; IDMM, insulin-dependent diabetes mellitus, NS, no significant effect; IR, insulin response; WB, white bread; T2DM, type 2 diabetes; Glc, glucose; HDL, high-density lipoprotein; PPG postprandial glycaemia; IGT, impaired glucose tolerance; BMI, body mass index ( $\text{kg m}^{-2}$ ); expressed as mean unless otherwise specified) iAUC, integrated area under the curve; AUC, area under the curve; CHO, carbohydrate; DF, dietary fiber; OGTT, oral glucose tolerance test; HOMA-IR, homeostasis model assessment for insulin resistance; CRP c-reactive protein.

**Table 9** Effect of miscellaneous food sources (water and low-calorie sweeteners) on postprandial glycaemia

Reference	Design	Subjects	Source	Daily intake	Duration	Outcome measures	Outcome
Torsdottir et al. 1989	Randomized crossover controlled	7, healthy, 23–31 y, BMI: 21.0–29.4; 20, T2DM well controlled: 46–67 y, BMI 21.5–31.8, Poorly controlled 44–71 y, BMI 19.2–27.6	Water, test meal: boiled potatoes, beef, fried in margarine (415 kcal, 55 EN% CHO, 2.8 fiber) with or without water	300 mL	180 min	iAUC	iAUC increase in Glc, 68% for healthy, 40% for well controlled DM2, NS for poorly controlled DM2, time to glucose peak: NS in HV, 58 (water) min vs. 69 in well controlled DM2, NS in poorly controlled DM2
Nehrling et al. 1985	Randomized placebo-controlled parallel DB	32 T1DB, 31 T2DB, mean 18–65 y	Aspartame, with meal	0.9 g × 3 for 18 wks		Fasting Glc/insulin, PPG and HbA1c	NS for fasting Glc, 2h PPG or HbA1c
Okuno et al. 1986	Crossover	7, healthy, 46.7 y	Aspartame or Glc 100 g	Single dose 500 mg	180 min		Small, but significant decrease in Glc (mean in healthy 7 mg/dl, 14–28 mg in 3 subgroups of DM). NS for insulin or glucagon
Okuno et al. 1998	Not blinded, not randomized	9 T2DM (hospitalized), mean 57 y, mean duration of diabetes 5 y	Aspartame, in jelly cake given as dessert, No control Group	125 mg for 2 wks	180 min	OGTT	NS for OGGT after 2 weeks, total cholesterol, HDL or triglycerides
Grotz et al. 2003	Randomized double blind Placebo-controlled	128, T2DM	Sucralose	667 mg/d for 13 wks		Fasting Glc HbA1c serum C-peptide levels	NS fasting Glc, HbA1c or serum C-peptide levels
Mezitis et al. 1996	Double blind crossover	13, T1DM; 13, T2DM	Sucralose	Single dose 1000 mg		IAUC	NS for IAUC or serum C-peptide levels
Raben et al. 2011	Randomized placebo-controlled parallel	33, healthy, 20–50y; BMI 25–30, 12 sucrose group, 11 sweeteners group	Foods and drinks Containing Sucrose (~2g/kg BW) or artificial sweeteners in the diet	10 weeks		Fasting Glc/insulin, IAUC PPG and HbA1c	NS for fasting Glc, 2h PPG or HbA1c

DB, double blind; NS, no significant effect; T2DM, type 2 diabetes; T1DM, type 1 diabetes; Glc, glucose; HDL, high-density lipoprotein; PPG postprandial glycaemia; BMI, body mass index ( $\text{kg m}^{-2}$ ); expressed as mean unless otherwise specified) iAUC, integrated area under the curve; OGTT, oral glucose tolerance test.

DF, but with different rates of digestion and absorption of the available carbohydrates. It was concluded, that the low GI diet with slow release carbohydrates lowered the glucose and insulin responses throughout the day and improved the lipid profile and capacity for fibrinolysis, suggesting a therapeutic potential of such a diet in diabetes.

The impact of carbohydrate foods on blood glucose levels is affected by a range of food factors, e.g., the type of carbohydrate, the food form, type and amount of DF, and the presence of certain food components capable of interfering with the digestive and/or absorptive mechanisms. As for the roles of sugars on glycemic regulation in diabetic subjects, Wheeler and Pi-Sunyer published a review in 2008, which is still valid (Wheeler and Pi-Sunyer, 2008). One of their messages was that adding an amount of sugar up to 10% of total energy to the diet did not negatively influence glycemic regulation as measured by HbA1c. Another message put forward by the same authors was that high-fructose corn syrup should be considered as sucrose rather than fructose when included in the diabetic diet, since it most often consist of equal amounts of glucose and fructose (Wheeler and Pi-Sunyer, 2008). Regarding the effects of fructose on glycemic control in diabetes, Cozma et al., recently published a meta-analysis (Cozma et al., 2012). Their aggregated analyses of short-term controlled feeding trials revealed that isocaloric fructose replacement of other carbohydrates (mainly starch and/or sucrose) resulted in clinically significant improvements in glycemic control, without significant effects on insulin, when including both type 1 and type 2 diabetic individuals. In stratified analysis, however, the reduction in glycated albumin and/or haemoglobin was only significant in people with type 1 diabetes. There are certainly trends toward positive outcomes on glycemia regulation also for individuals with T2DM, but larger and longer trials of higher quality are warranted to establish such associations (Cozma et al., 2012). However, it should be taken into account that a higher intake of sucrose or fructose should not be recommended to people with diabetes or other conditions of impaired blood glucose regulation, in view of a potential detrimental impact on body weight, insulin sensitivity, and blood lipids (Johnson et al., 2009; Stanhope et al., 2009).

#### *Effect of Carbohydrate Structure and Properties*

Chemical composition as well as the degree of gelatinization may play a role for glycemic responses to starchy foods. Most of the knowledge concerning the differences in PPG to carbohydrates and carbohydrate foods stem from studies in healthy subjects. Information regarding the GI features of carbohydrate foods is available in the international GI tables (Atkinson et al., 2008), where studies in diabetic subjects are presented.

*Amylose-amylopectin ratio in starch:* In a study of parboiled rice of a high-amylose (27%) variety, it was suggested that a combination of the high-amylose rice and formation of

stable amylose-lipid complexes of the complex II type were responsible for substantial lowering of GI (Larsen et al., 2000). Furthermore, the results indicated that the severity of processing during parboiling may be an important tool to reduce the GI of rice. In bread products, the use of wheat (Hallstrom, Sestili et al., 2011), barley (Liljeberg, Åkerberg et al., 1996), and corn (Granfeldt, Drews et al., 1995) varieties with elevated amylose contents have been reported to have increased contents of resistant starch (RS). In addition to the formation of an enzyme-resistant starch fraction in bread with elevated amylose content, a slowly digestible starch fraction appears to be formed, as judged from decreased PPG in healthy subjects. When combining the use of cereal varieties with elevated amylose contents with baking at pumpnickel conditions (low temperature-long time), the formation of RS is promoted even more (Hallström et al., 2011). Some suggested mechanisms behind the increased RS-formation are: a compact structure that results in restricted starch swelling and gelatinization, formation of amylose-lipid, or amylose-protein complexes, or encapsulation of gelatinized starch between layers of RS.

*Native versus gelatinized starch:* Processing by heat is common in the manufacturing of cereal products. During heat treatment the starch is more or less completely gelatinized. However, although the degree of gelatinization may be rather low, the rate of amylolysis and thus the glycemic response appear to increase rapidly. This has been shown for, e.g., oat flakes in healthy subjects (Granfeldt, Hagander et al., 1995; Granfeldt, Eliasson et al., 2000). A possibility to lower the glycemic response to starchy food is by using native starches, rather than gelatinized or partly gelatinized forms. The use of uncooked corn starch to prevent nocturnal hypoglycemia in diabetic children is one example of how glycemic features of a food product can be optimized by a conscious choice of ingredients. Thus, in a study by Kaufman and Devgan (1996), the frequency of nocturnal and before breakfast hypoglycemic episodes was significantly reduced in type 1 diabetic subjects after having uncooked corn starch included in an evening snack, compared with their normal snack without such starch.

*Chemically modified starch:* Hydrogenated starch hydrolysates (HSH) are used as bulking and nonreducing sweetening agents in for example, candy and gums. When comparing the glycemic response to glucose and two varieties of HSH in both insulin- and noninsulin dependent diabetic subjects as well as healthy individuals, the glycemia was significantly reduced after the HSH-meals (Wheeler et al., 1990). Furthermore, when combining all the subjects, a difference in glycemic responses between the two HSH-varieties could be detected, pointing in favor of the HSH with shorter hydrogenated saccharide chains (HSH, 5875).

*Intact botanical structure or physical form:* As mentioned above, studies in T2DM subjects have clearly indicated the importance of food structure on PPG (Järvi et al., 1995). In an earlier study (d'Emden et al., 1987) the glycemic responses to equi-carbohydrate portions of bread made from either white

wheat or semolina, respectively, or spaghetti made from white and whole grain wheat, respectively, were tested in a group of noninsulin dependent diabetic subjects. No differences were found in glycemic response between either forms of bread, or either type of spaghetti, but both bread products showed higher glucose responses than the spaghetti meals. Thus, it was concluded that the physical form of the food was a major factor influencing the glycemic response. Similarly, maintaining the botanical structure of cereal kernels (Liljeberg et al., 1992) as well as rice (Panlasigui and Thompson, 2006) intact has been shown to reduce PPG. The importance of botanical structure has recently been investigated in two semiacute studies in healthy subjects (Nilsson et al., 2008a; Nilsson et al., 2008b). Interestingly, it was revealed that the semiacute benefits of barley kernels on daylong glycemia was lost when the kernels were milled into flour and consumed as porridge (Nilsson et al., 2008a). On the other hand, by mimicking the content of DF and RS in barley kernel bread, a flour-based bread product improved glucose tolerance in an overnight perspective study (10 h), compared with a white wheat bread (Nilsson et al., 2008b). The benefits observed on semiacute glucose tolerance are mediated by mechanisms emanating from colonic fermentation of the indigestible carbohydrate fraction.

In an earlier attempt to investigate the potential of depletion and disruption of dietary fiber, Haber et al. (1977) compared the postprandial blood glucose levels in healthy subjects after intake of apples, fiber-disrupted apple purée and fiber-free apple juice. The results showed that plasma glucose rose to the same extent after all three meals, but there was a substantial difference in the rebound fall with the apple juice causing a marked hypoglycemia between approximately 60–120 min after the meal. The postprandial glucose response after intact apples did not fall below the fasting level at any time point. In addition to its detrimental effect on glucose regulation, the disruption and removal of fiber also favored faster and easier ingestion, which may promote over-eating of such products.

*Course of glycemia:* After reviewing the literature regarding effects of available carbohydrates on blood glucose levels in diabetic patients it is concluded that there are surprisingly few studies focusing on carbohydrate foods. However, as reported in the International tables of glycemic index (Atkinson et al., 2008), there is a high correlation between GI-values derived from studies performed in healthy and diabetic subjects, respectively. Therefore, much of the information on the glycemic response of different foods gained in healthy people may be relevant also to predict the impact of these foods on blood glucose levels in diabetic patients. Another important aspect to consider when discussing acute and semiacute glycemia is to acknowledge not only the GI-value of a food product but the course of glycemia. In 2009, the concept of glycemic profile (GP) was introduced and is defined as the duration of the incremental postprandial blood glucose response divided by the blood glucose incremental peak ( $\text{min mM}^{-1}$ ) (Rosen et al., 2009). Rye products generally produced high GI-values

despite low insulin indices. When examining the course of glycemia after rye products, there was a sustained blood glucose increment beyond the 120 min used for GI-calculations, resulting in a higher than expected GI-value. It has been suggested that GP is more strongly correlated with insulin response (both insulin index and insulin incremental peak) compared with GI (Rosen et al., 2009; Rosen, Östman et al., 2011). Taking into account also the avoidance of hypoglycemia after high-GP food, this GP measure describing the course of glycemia may also be interesting to apply to PPG and glycemic regulation in diabetic subjects.

#### *Dietary Fiber and Glycemic Control*

Dietary fiber has traditionally been defined as edible plant polysaccharides and lignin naturally occurring in foods, and which are resistant to hydrolysis by human digestive enzymes (Trowell et al., 1976). Later definitions of fiber in nutrition have also included isolated fibers from food raw materials or edible synthetic carbohydrates that are resistant to digestion and absorption in the human small intestine but are partly or completely fermentable in the colon, and display beneficial physiological effects, i.e., improved bowel function, blood cholesterol, and blood glucose attenuation (Raninen et al., 2011). These beneficial effects, i.e., improvements in metabolic and disease control, are essentially based on the dominant attributes of different fiber types when passing through the gastrointestinal tract.

*Types of dietary fiber:* Dietary fiber is chemically a heterogeneous group of compounds with variable molecular size and different physicochemical properties, such as water solubility, viscosity, cation exchange properties, organic acid absorption and water-holding capacity (Eastwood and Morris, 1992; Guillon and Champ, 2000). Several classifications for fiber have been established (Slavin et al., 2009; Raninen et al., 2011) in which the traditional one is based on water solubility dividing fiber into soluble (pectins, gums, mucilages) and insoluble (cellulose, hemicelluloses, lignin) fiber types. Although solubility per se is an essential determinant of the physiological responses, viscosity and fermentability are likely to play a more pronounced role in the physiological benefits in humans.

Major dietary sources of DF are whole grain cereals, legumes, vegetables, and fruits, which include a wide variety of different types of fiber. The strongest and most consistent effects on reduced risk of developing T2DM are observed with diets high in insoluble and often only moderately fermentable cereal fiber, whereas fruits and vegetables, which are more important sources for soluble/fermentable fiber, do not show any protective effect on this outcome in meta-analyses of prospective cohort studies (Weickert et al., 2006; de Munter et al., 2007; Schulze et al., 2007).

However, most commonly used fiber supplements are primarily soluble fiber types, such as guar gum, glucomannan, xanthan gum, psyllium, pectin, alginate,  $\beta$ -glucan concentrates,



and various fiber combinations (Vuksan et al., 2009; Papathanasopoulos and Camilleri, 2010). To date, it has not been investigated in long-term controlled human interventions whether these agents influence the risk of developing T2DM. Due to the diversity of DF in natural fiber sources it is generally recommended to adhere to these food sources to improve daily DF intake, thereby also assuring the additional nutritional qualities of a healthy diet. Even so, it is usually challenging to meet the recommended DF intake. Therefore, fiber supplements can play an important role in increasing DF intake but also in managing daily glucose levels both in healthy individuals and individuals with impaired glucose metabolism. However, although the potential health benefits of different types of DF are known, there is still no clear consensus about the ideal composition and proportion for the consumption of the major sources of DF.

*Amount of fiber:* In addition to the type of DF, the amount of DF plays a marked role in acute glycemic and insulinemic responses. For example, findings from studies using  $\beta$ -glucan have shown that 4 g of soluble  $\beta$ -glucan appear to be a threshold for a significant reduction in postprandial glucose and insulin responses in healthy individuals (Granfeldt et al., 2008; Juvonen et al., 2011), whereas in T2DM subjects somewhat lower amounts may be sufficient (Tapola et al., 2005). However, the amount of fiber does not appear to explain the lower postprandial insulin response observed after a meal containing rye bread as compared to white wheat bread (Juntunen et al., 2003). Furthermore, the food matrix, i.e., liquid or solid food forms in which fiber is consumed and macronutrient content in mixed meals can markedly affect postprandial glucose and insulin responses, as described elsewhere in the text.

*Postprandial trials on fiber foods and supplements:* Recently, an obvious reappearance in the research interest on the role of DF in the regulation of glycemic and insulinemic responses in individuals with T2DM has emerged. Until now, a large number of postprandial studies involving different fiber types, either in the form of unprocessed foods or as isolated DF supplements, have been carried out in people with T2DM (Table 1 & 2). Additionally, data are derived from a few longer-term dietary interventions in which either modified total diets or individual fiber products were served to individuals with T2DM for periods from two weeks up to one year (Table 2).

The randomized short-term trials clearly indicate that especially soluble fibers with viscous properties (e.g., glucomannan, guar gum, psyllium,  $\beta$ -glucan) exert acute improvements in glucose and insulin responses in individuals with T2DM (Table 1). Guar gum (GG), an example of such a water-soluble nonstarch polysaccharide, has shown both glucose and insulin lowering properties (Ellis et al., 1991; Golay et al., 1995), and psyllium fiber administered to NIDDM patients immediately before breakfast and dinner lowered postprandial glucose by 14% at breakfast and 20% at dinner compared to placebo. A second meal effect was observed at lunch (served 5 h after breakfast), where glucose was 31%

lower compared with placebo. Psyllium's ability to reduce glycemia was not affected by the patients mode of therapy (diet-treated or on oral hypoglycemic agents) (Pastors et al., 1991).

In the majority of these postprandial studies, relatively high doses of single DF types have been used to produce significant postprandial reduction especially in glucose but also in insulin responses when compared with no or low-fiber test products (Tappy et al., 1996; Östman et al., 2006; Kim et al., 2009). The significant effects of DF on postprandial glucose are not necessarily accompanied with similar insulin responses which may partly result from the DF type or amount used in these studies. Insoluble cereal fiber is nonviscous/gel-forming and, therefore, does not directly influence GI. However, cereal fiber has been shown to improve whole-body insulin sensitivity, an effect that can be observed as short as 24 h after intake, i.e., second meal effect (Weickert et al., 2005; Nilsson et al., 2008c, 2008d, 2008e, 2008f). Since many low-GI foods are also rich in insoluble cereal fiber interpretation of the results is often not straight forward (Weickert and Pfeiffer, 2009). It is also worth to note that the food matrix in which the fiber is incorporated may actually modulate the postprandial responses (Brennan, 2005) so that the effect of the added fiber may be partly masked (Sels et al., 1992). These examples highlight the difficulties when trying to investigate the metabolic effects of single components of complex foods (Weickert, 2012).

*Semiacute effects:* The presence of intrinsic DF in certain cereal products has been shown to influence PPG in healthy humans at a subsequent meal, through a mechanism involving gut fermentation (Nilsson et al., 2008a, 2008b). Consequently, provision of evening meals based on barley kernel bread significantly lowered blood glucose excursions at a subsequent standardized breakfast compared with an evening meal with white bread. Also, markers of inflammation and insulin resistance were lowered, and the incretin hormone GLP-1 increased at breakfast (Nilsson et al., 2008a). In the case of barley, similar benefits on over-night glucose tolerance could be mimicked by adding a similar amount and ratio of barley DF and RS to white wheat bread. In contrast, a flour-based whole grain barley evening meal failed to induce benefits the subsequent morning (Nilsson et al., 2008c), indicating a role of the combined barley DF and RS in case of the kernel-based barley meal. Additionally, ingestion of boiled cereal kernels from rye and barley in the morning, not only reduced the acute PPG, compared with white bread, but additionally improved PPG at two subsequent standardized meals in healthy subjects. It is clear that cereal products rich in intrinsic DF may improve day-long PPG (Nilsson et al., 2008b). It is put forward that whereas the benefits of certain kernel-based products in the 10 h perspective is related to gut fermentation; benefits from breakfast to lunch are probably mediated by the latent features of the breakfast meal. In contrast to barley, most rye meals are characterized by improved PPG, including both flour-based and kernel-based products (Rosen et al., 2011). Interestingly, in the case of rye, evidence of rapid gut fermentation is present as judged from early postprandial increment in breath

hydrogen excretion. Taken together, the botanical structure and intrinsic composition of fermentable substrates seems important for PPG at subsequent meals.

*Longer-term interventions:* Evidence from longer-term DF interventions in T2DM subjects shows that relatively high fiber levels can be consumed when given as unprocessed foods (legumes, vegetables, whole grain cereals) without causing gastrointestinal problems (Table 2). Both de Natale et al. (2009) and Chandalia et al. (2000) noticed improved glycemic control in T2DM subjects after feeding 4–6 weeks of diets supplying 50–53 g of fiber per day. No adverse side effects were reported. Studies lasting 6–12 months with diets containing low-GI foods have produced rather negative results on fiber effects, showing no effect on glycosylated hemoglobin levels in T2DM subjects (Jenkins et al., 2008a, 2008b; Wolever et al., 2008).

An 18-week randomized controlled intervention in healthy subjects having increased intake of insoluble cereal fiber, supplemented by cereal fiber extracts twice daily, significantly improved whole-body insulin sensitivity, as measured using euglycemic-hyperinsulinemic clamps (Weickert et al., 2011a, 2011b). A previous intervention by Pereira and colleagues showed comparable results when investigating the effects of whole grain diets on whole-body insulin sensitivity (Pereira et al., 2002). Interestingly, the consumption of insoluble resistant starch appears to result in comparable effects on insulin sensitivity in healthy adults (Robertson et al., 2003; Robertson et al., 2005) and in subjects with metabolic syndrome (Johnston et al., 2010). It is worth noting that in some studies different sorts of moderately fermentable insoluble cereal fiber and insoluble resistant starch resulted in comparable improvements of estimated insulin sensitivity 24 h after consumption of the cereal. Fiber/starch extracts consumed in a second meal test, indicated that colonic fermentation with the production of SCFA was not the key factor conveying improved insulin sensitivity in this setting (Weickert et al., 2005). Longer-term studies with isolated fiber products have yielded conflicting results. Schwab et al. (2006) gave 24–30 g soluble fiber in the form of sugar beet pectin or synthetic polydextrose mixed with drink for three months to 66 subjects of which 10 were T2DM subjects, the rest having problems with glucose metabolism (IGT, IFG). They found no effect on fasting or on PPG after a standardized breakfast. However, supplemental fructooligosaccharides (FOS), 20 g/d, given to subjects with idiopathic hyperglycemia reduced the glucose excursions (Sorensen and Johansen, 2010).

*Possible mechanisms of fiber effects:* Soluble viscous fibers play a marked role in managing postprandial glucose and insulin levels via forming viscous gels by absorbing water and thereby reducing gastric emptying (Marciani et al., 2001; Darwiche et al., 2003; Sanaka et al., 2007) and rate of glucose absorption (Dikeman and Fahey, 2006). Other suggested explanations why high viscosity products reduce PPG are altered intestinal motility, slower diffusion rate of starch digestion products and reduced  $\alpha$ -amylase accessibility (Leclere

et al., 1994). In addition, it has been shown in vitro that guar gum inhibits  $\alpha$ -amylase in a direct, noncompetitive way in the first stage of the enzymatic degradation of starch (Slaughter et al., 2002).

The mechanisms underlying the association of increased fiber intake with improved glycemic control in longer term studies (Hu et al., 2001; Schulze et al., 2007; Livesey et al., 2008) are not fully understood, but may include also colonic effects such as short chain fatty acid production by colonic fermentation and concurrent liberation of phenolic compounds in addition to the above mentioned altered postprandial gastric and small intestinal functions (Lappi et al., in press; Vitaglione et al., 2008). Improved whole-body insulin sensitivity by insoluble cereal fiber was suggested to be related to interference with the digestion and/or absorption of dietary protein and consequently reduced amino acid induced activation of the mammalian target of rapamycin (mTOR) S6 kinase 1 (S6K1) signaling pathway (Weickert et al., 2006, 2011a, 2011b) that directly results in insulin resistance both in animal models and human intervention studies (Krebs et al., 2002; Um et al., 2004; Tremblay et al., 2005). Further mechanisms that may be involved could be cereal-fiber induced binding of bile acids and fiber-induced effects on gut hormones and metabolite profiles but this will need to be investigated in future studies.

Thus, these results suggest that acute consumption of foods rich in soluble fiber or soluble fiber supplements is beneficial especially for the postprandial glycemic control but also for the insulinemic response. However, the number of studies investigating the effects of DF on acute glucose and insulin responses in T2DM subjects is still limited which limits interpretation of the effects. Moreover, the relevance of acute postprandial effects needs to be studied with regard to long-term health outcome; in this context also insoluble dietary fiber seem to play an important role by improving glucose and/or insulin homeostasis (Blaak et al., 2012).

#### *Gut Microbiota and Glycemic Control*

The gut microbiota is increasingly considered as a symbiotic partner for the maintenance of health. The human gut harbours vast numbers of bacteria, around  $10^{11}$  bacterial cells per mL of contents (Diamant et al., 2011; Qin et al., 2010). Specific strains of gut bacteria can be classified upon their sequence analogy into phyla, genus, species, and subspecies. More recently, Arumugam et al., have “clusterized” the gut microbiota of individuals from different countries and continents into three “enterotypes” identified by the variation at the level of one of the three following genera: *Bacteroides*, *Prevotella*, and *Ruminococcus* (Arumugam et al., 2011). Long-term dietary pattern may influence the proportion of those enterotypes, the *Prevotella* group being associated with carbohydrates and fiber intake (Wu et al., 2010). *Bifidobacterium* spp. represents an important and complex group of bacteria whose presence is often associated with

beneficial health effects (Boesten and de Vos, 2008; Turroni et al., 2009; Delzenne and Cani, 2011a, 2011b). The *Bifidobacterium* genus was poorly represented in the faecal samples of diabetic subjects compared with healthy individuals (Wu et al., 2010). Another interesting bacterial species is *Faecalibacterium prausnitzii*, which level is found to be decreased in subjects with diabetes compared to nondiabetic obese subjects. Additionally, *F. prausnitzii* is negatively associated with inflammatory markers measured in the serum of obese individuals before and after roux- and Y-gastric bypass surgery (Furet et al., 2010). Related to the gut microbiota, components of the bacterial membrane have been incriminated in the development of inflammation and this is associated with lipopolysaccharides (LPS), present in gram negative bacteria (for review, see Cani and Delzenne, 2011). The level of serum LPS is increased approximately two-fold in obese subjects and those with diabetes, or fed a high-fat diet. This is considered to involve processes including an increase in chylomicron formation (upon high fat diet feeding), a decrease in gut barrier integrity, and/or a decrease in alkaline phosphatase activity, which is the enzyme responsible for the cleavage of the LPS in the intestine. It is likely that the metabolic function of the gut microbiota could be important in the control of blood glucose, even if much of the data have been mainly obtained in animal studies. The promoting effect of the gut microbiota on intestinal glucose absorption has been suggested in germ-free mice colonized with the saccharolytic *Bacteroides thetaiotaomicron*: this effect supports the fact that events occurring upon bacterial fermentation may have an effect in the upper part of the gut, and can modulate digestible carbohydrates availability (Hooper et al., 2001). The short chain fatty acids produced upon carbohydrate fermentation in the gut, reach host tissues where they may act as metabolic regulators or substrates. If propionate acts as gluconeogenic substrate in the liver, it is also able, at least in vitro, to counteract gluconeogenesis from lactate, thereby decreasing hepatic glucose production. Dietary supplementation of butyrate can prevent and treat diet-induced insulin resistance in mouse. The mechanism of butyrate action is related to promotion of energy expenditure and induction of mitochondria function (Gao et al., 2009). On the other hand, the G-protein coupled receptors, GPR43 and 41, are both expressed in endocrine L cells in the colon, and when activated by their physiological ligands, the short chain fatty acids, they promote proglucagon expression, GLP-1 secretion, and could thereby control insulin secretion and glucose homeostasis (Tolhurst et al., 2012).

If the gut microbiota plays a role in the control of glycemia, it would be interesting to modulate the gut microbiota composition. The transplantation of gut microbiota from diabetic animals to germ-free mice transfers the diabetic and obese phenotype, thereby suggesting that the characteristics of the gut microbiota of diabetic individuals per se could play a role in the metabolic response to diet, and that gut microbial

transfer is effective (Delzenne et al., 2011). The proof of this concept has recently been shown in humans. An allogenic faecal transplantation assay was performed from a nonlean male donor to individuals with metabolic syndrome, and this “treatment” was shown to improve glucose tolerance and insulin sensitivity after six weeks. Specific changes in the gut microbiota composition were associated with the improvement of health (Vrieze et al., 2012). It is clear that dietary approaches influence the composition of the gut microbiota in humans and for this reason, the following sections will cover the potential interest of prebiotics and probiotics to control blood glucose levels.

### *Prebiotics and Blood Glucose Regulation*

Among dietary fiber, some oligo- and polysaccharides exhibit prebiotic properties, a concept originally described by Gibson and Roberfroid (1995) and recently revisited at the initiative of the ILSI prebiotic task force (Roberfroid et al., 2010). This “prebiotic concept” is defined as the selective stimulation of one or a limited number of microbial genus (era)/species/strain(s) in the gut microbiota that confer(s) health benefits to the host. Inulin-type fructans were the first studied prebiotics that have repeatedly demonstrated the capacity to stimulate the growth of bifidobacteria in both animals and in humans. Even if other bacteria may be promoted or modulated on fructan administration, there is no proof that the bifidobacteria are responsible per se for the health effect of fructans, the bifidogenic effect appears as the “microbial signature” of those prebiotics. Other oligosaccharides such as galactans, arabinoxylans and glucans have now been considered as dietary fibers with prebiotic properties (Delzenne et al., 2011).

The modulation of gut microbiota by using dietary prebiotics in the control of blood glucose homeostasis has been evaluated in experimental animal models of hyperglycemia, associated or not with obesity (streptozotocin treatment rats, obese leptin deficient or leptin resistant mice of rats, high fat/ and or high glycemic index diet). The data have been detailed in a previous paper (Roberfroid et al., 2010). A decrease in postprandial or post-oral glucose tolerance test is observed in most of the models. The implication of gut peptides such as an increase in L cell differentiation leading to an increase portal GLP-1 may be involved in this effect, as shown in high fat fed mice or rats (Delzenne et al., 2011), or more recently in ob/ob mice (Everard et al., 2011). Data obtained in high-fat fed mice treated with fructan-type prebiotics revealed an improvement of hepatic insulin sensitivity and a decrease in fasting insulinemia that correlated with the increase in caecal *Bifidobacteria* (Cani et al., 2008). A more detailed genomic analysis of the gut microbiota in ob/ob mice treated with fructans as prebiotics highlighted novel bacteria that could be associated with the improvement of gut endocrine function (L cell number), such as *Faecalibacterium prausnitzii* or *Akkermansia muciniphila* (Everard et al., 2011). The increase in GLP-2 by L cells

occurring in prebiotic-treated mice could, in turn, reinforce the gut barrier integrity and thereby decrease inflammation in the liver tissue. This effect also contributes to improved glucose metabolism (Cani et al., 2009). However, in the Profimet study whole-body insulin sensitivity (Weickert, 2012) was significantly improved independent of various markers of colonic fermentation, SCFA profiles in faecal samples, and dominant groups of the gut microbiota (Weickert et al., 2011a, 2011b), indicating that further factors were involved in conveying improved insulin sensitivity upon the consumption of insoluble cereal fiber.

Few papers have been published, which have focused on the influence of prebiotics on glucose homeostasis in humans (Table 3). Luo et al. (1996) were the first to show that 20 g of short chain fructans given for four weeks in healthy subjects decreased basal hepatic glucose production, but had no detectable effect on insulin-stimulated glucose metabolism. In T2DM subjects, no significant modification of glucose homeostasis (plasma glucose level or hepatic glucose production) occurred in prebiotic-treated patients (Luo et al., 2000). In a similar study conducted in hypercholesterolemic patients, fructan-prebiotics reduced the PPI response, but the clinical relevance of this effect remains unclear (Giacco et al., 2004). A two-week supplementation with 16 g/day inulin-type fructans versus the same amount of maltodextrin as placebo, was able to increase GLP-1 production, and to lessen postprandial glucose response after a standardized breakfast (Cani et al., 2009a). Increases in gut peptides have also been shown in obese individuals treated with prebiotics. This effect was related to improvement of satiety, but the relation with glucose homeostasis was not reported in this study (Parnell and Reimer 2009). Glycemia was not significantly modified in obese individuals subjected to low-calorie diet completed with Jerusalem artichoke concentrate containing oligofructose as prebiotic, whereas an improvement of HOMA-IR was observed in treated obese adult women (Antal et al., 2008). If there are some positive effects of a prebiotic intervention, there is a lack of information relating the improvement of glucose response and to changes in gut microbiota composition and/or activity in humans or in diabetic/obese subjects. Those studies are needed to evaluate the relevance of microbiota in the management of glucose homeostasis.

#### *Probiotics and Blood Glucose Regulation*

A number of observations have led to speculation that probiotics, defined as “live microbes which, when administered in adequate amounts, confer a health benefit on the host” (FAO/WHO, 2002), may have potential benefits in the maintenance of healthy glucose metabolism. However, despite encouraging preclinical studies, the clinical research in this field is still only starting to emerge. In this review no human clinical studies assessing the effect of probiotic bacteria specifically on postprandial glycemia were identified. However, a limited number of clinical studies addressing the effect of probiotics

on related outcomes such as fasting glycemia and insulin resistance were identified.

Some studies have investigated the effect of probiotics on fasting glycemia. Moroti et al. (2012) reported that consumption of probiotics and fructo-oligosaccharides reduced fasting glycemia in elderly subjects with T2DM, whereas consumption of a placebo product did not. Similar results on probiotics were reported by Ejtahed et al. (2011; 2012), but Chang et al. (2011) and Schaafsma and coworkers (Schaafsma et al., 1998) did not observe reduced glycemia in their interventions. Probiotics combined with dietary counseling have also been suggested to improve glucose regulation during pregnancy (Laitinen et al., 2009). Probiotics may also regulate glucose by targeting insulin action; Andreasen et al. (2010) reported an improvement in insulin sensitivity in diabetic and nondiabetic volunteers following consumption of probiotics. A bilberry drink with oatmeal fermented with probiotics has also been suggested to lead to reduced insulin demand upon glycemic response (Granfeldt and Bjorck, 2011). In addition to human studies, several animal studies have yielded promising results on the efficacy of probiotics in the maintenance of healthy fasting and postprandial blood glucose levels and related outcomes (Andersson et al., 2010; Amar et al., 2011a, 2011b; Chen et al., 2011).

#### *Dietary Protein and Blood Glucose Regulation*

High protein diets appear to have beneficial effects on weight loss, body composition, and certain blood lipids, at least in the short term (Hession et al., 2009). Satiating effects of dietary protein, a reduced choice of foods, and an aversion against dietary fat in the absence of carbohydrates have all been attributed to better weight loss with high protein diets (Weickert et al., 2005). Lowering the percent protein of the diet from 15% to 10% increases total energy intake (Gosby et al., 2011), further indicating that a higher intake of dietary protein may help to reduce energy intake. In a recent review, it is concluded that dietary protein by acting on satiety and energy expenditure in negative energy balance may prevent weight cycling effects (Westerterp-Plantenga et al., 2012), indicating a beneficial role on weight regulation. Furthermore, a combination of high-protein and low glycemic load foods, in a hypo-caloric diet, significantly increased insulin sensitivity and decreased markers of inflammation in overweight and obese women with polycystic ovary syndrome (Mehrabani et al., 2012). Insulin resistance following amino acid infusion has been reported in healthy humans (Tremblay et al., 2005). One of the mechanisms of protein-induced insulin resistance appears to be inhibition of glucose uptake through phosphorylation of downstream factors of the insulin signaling cascade by the translation initiation factor serine-kinase-6-1 (S6K1) (Tremblay et al., 2005). On the other hand, it has been put forward that branched-chain amino acids (BCAA), in particular leucine, may help to counteract “anabolic” resistance” which may increase availability of AA for muscle protein synthesis,

reduce muscle protein breakdown, and enhance glucose disposal to help maintain blood glucose homeostasis in T2DM (Manders et al., 2012). Recent data on metabolomic profiling in obese adults have suggested associations between BCAA and future risk of T2DM (Newgard et al., 2009a, 2009b), whereas the opposite has been found in youth (Michaliszyn et al., 2012a, 2012b). In fact in youth increased plasma AA concentrations were positively associated with  $\beta$ -cell function. In animal models particularly the intake of BCAA appears to lead to unfavorable metabolic effects including insulin resistance, although in rodents the background of a high fat diet is required to promote these negative effects (Newgard, 2012).

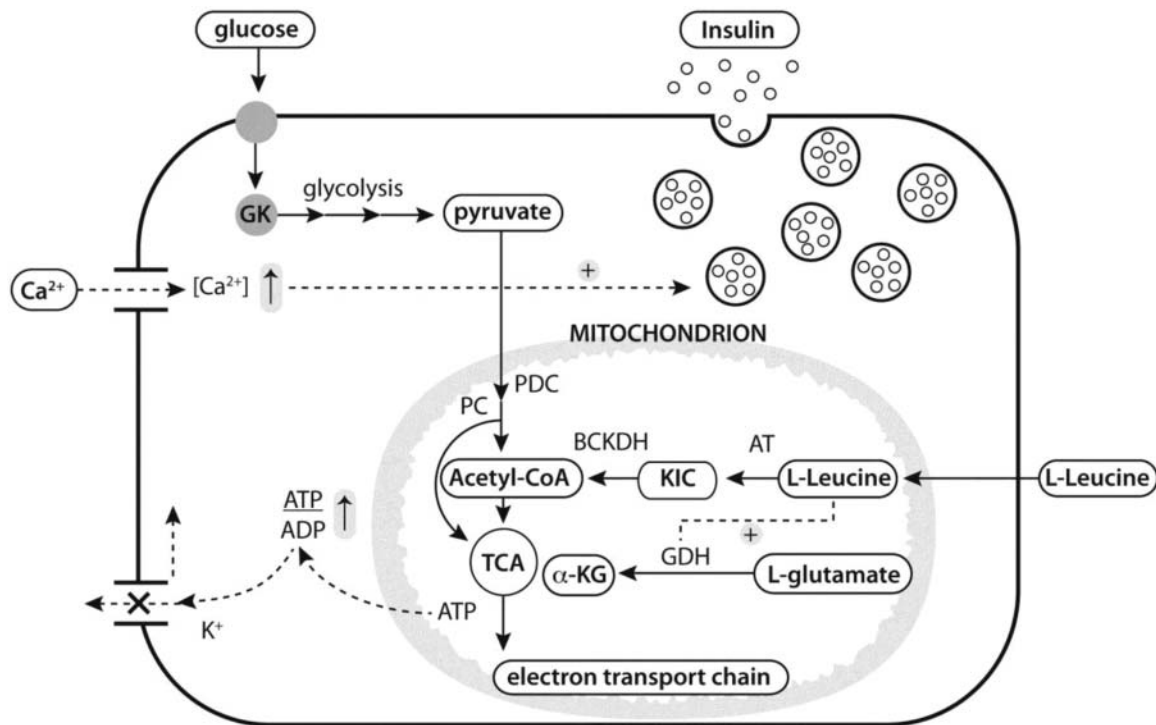
Longer term intake of high protein diets in human has been shown to result in whole-body insulin resistance (Linn et al., 2000; Weickert et al., 2006), associated with up-regulation of factors involved in the mammalian-target-of-rapamycin (mTOR)/S6K1 signaling pathway (Linn et al., 2000; Weickert et al., 2006), increased stimulation of insulin and glucagon within the endocrine pancreas, stimulation of gluconeogenesis (Linn et al., 2000; Weickert et al., 2006), and high glycogen turnover (Linn et al., 2000; Weickert, 2012). Furthermore, protein induced deterioration of insulin sensitivity has been observed in humans under conditions of restricted fat intake (30% of energy intake), both on whole-body and liver level, as measured using euglycemic hyperinsulinemic clamps combined with stable isotope techniques (Weickert et al., 2011a, 2011b). Interestingly, the way of protein administration seems to be of importance, and supplementation of insulin resistant rats with leucine through gavage, that is intermittent feeding, significantly lowered fasting glycemia compared with continuous administration through the drinking water (Zanchi et al 2012).

In the short-term, these unfavorable effects on insulin resistance could be compensated by high protein diet induced weight loss, and, at least in physically active people, an increase of the lean muscle mass that is also mediated via the mTOR/S6K1 pathway. In the Diet, Obesity and Genes (DiOGenes) European multicentre trial with 548 completers, maintenance of weight loss was marginally better with the high protein diet despite controlled conditions, with no significant difference between groups in the full model (Larsen et al., 2010). Furthermore, DiOGenes revealed that both, a high protein intake or increased intake of high-GI carbohydrates, may increase low-grade inflammation (Gögebakan et al., 2011), which could be further related to worsening of whole-body insulin resistance (Möhlig et al., 2006). In further agreement that high protein-diets may have deleterious effects on glucose metabolism, a recent large prospective cohort with 10-years follow-up revealed that consuming 5% of energy from animal protein, but also from total protein at the expense of fat or carbohydrates increases diabetes risk as much as 30% (Sluijs et al., 2010). Furthermore, low carbohydrate high protein diets, used on a regular basis and without consideration of the source of proteins or the nature of carbohydrates

is associated with increased risk of cardiovascular disease (Lagiou et al., 2012), thereby suggesting a link between high-protein Western diets, cardiovascular risk and T2DM. Given these concerns further research is advised before high protein diets should be routinely introduced as a tool in the treatment of patients with T2DM or at risk of developing diabetes. However, in subjects with intact  $\beta$ -cell function protein/amino acid induced insulin resistance may be compensated by the also observed amino acid mediated increase in insulin secretion, as discussed in the next paragraph.

#### *Amino Acid Induced Insulin Secretion*

In a state of impaired glucose tolerance or T2DM, endogenous insulin secretion shows multiple abnormalities. Secretory defects include an attenuated early insulin secretory response to glucose, reduced ability of the  $\beta$ -cell to fully compensate for the degree of whole-body insulin resistance, impaired glucose sensing ability of the  $\beta$ -cell, and a shift to the right in the dose-response curve between glucose and insulin secretion, all of which are indicative of a progressive insensitivity of the  $\beta$ -cell to glucose (Polonsky et al., 1996). These defects involve glucose-sensing and signaling pathways in the  $\beta$ -cell. Even though insulin secretion in response to the prevailing glucose concentration may be blunted in T2DM subjects, insulin secretion in response to other stimuli remains functional (van Loon et al., 2003). Besides glucose, amino acids can also act as potent stimuli for the secretion of insulin from the pancreatic  $\beta$ -cell (Newsholme et al., 2005). In vitro studies using incubated primary islet cells or  $\beta$ -cell lines have described strong insulinotropic properties for arginine, leucine, isoleucine, alanine, and phenylalanine (Floyd et al., 1963; Sener et al., 1981; Pipeleers et al., 1985; Blachier et al., 1989; Malaisse et al., 1991; Schwanstecher et al., 1998; Lajoix et al., 2001; Xu et al., 2001a, 2001b; Salehi et al., 2012). The various mechanisms, by which these amino acids promote and/or enhance insulin secretion from the pancreatic  $\beta$ -cell, are diverse and have not yet been fully elucidated (Newsholme et al., 2005). In the presence of glucose, amino acids like arginine seem to be able to stimulate insulin secretion by depolarizing the plasma membrane (Blachier et al., 1989). The latter results in the opening of voltage-activated  $\text{Ca}^{2+}$  channels, resulting in the influx of  $\text{Ca}^{2+}$ , which triggers insulin exocytosis (Newsholme et al., 2005). Other amino acids tend to induce their insulinotropic properties by activating the  $\text{Ca}^{2+}$  channels, through their cotransport with  $\text{Na}^+$  (Sener and Malaisse, 2002). Furthermore, similar to glucose-mediated insulin secretion (Dean and Matthews, 1970), intracellular catabolism of the metabolizable amino acids in the pancreatic  $\beta$ -cell will increase the intracellular energy status (ATP/ADP ratio), which closes ATP-sensitive  $\text{K}^+$  channels, leading to the depolarization of the plasma membrane (Dunne et al., 1990; Brennan et al., 2002; Newsholme et al., 2005). In addition, leucine-induced insulin secretion is mediated both through its oxidative decarboxylation, as well



**Figure 2** Overview of proposed mechanisms by which glucose and leucine stimulate insulin secretion. GK, glucokinase; PDC, pyruvate dehydrogenase complex; PC, pyruvate carboxylase; TCA, tricarboxylic acid;  $\alpha$ -KG,  $\alpha$ -ketoglutarate; AT, aminotransferase; BCKDH, branched-chain a-keto-acid dehydrogenase; GDH, glutamate dehydrogenase; KIC, a-ketoisocaproate. Adopted from van Loon et al; *Current opinion in clinical nutrition and metabolic care*, 2012, 15: 71–77.

as its ability to allosterically activate glutamate dehydrogenase (Newsholme et al., 2005; Xu et al., 2001a, 2001b). The latter has also been reported for other amino acids, like phenylalanine (Kofod et al., 1986). A simplified overview on some of the proposed mechanisms by which amino acids are likely to stimulate insulin secretion in the pancreatic  $\beta$ -cell is provided in Fig. 2.

In accordance with the *in vitro* data on incubated  $\beta$ -cells, *in vivo* studies in humans have shown increased plasma insulin concentrations following the intravenous infusion of amino acids in both healthy (Floyd et al., 1966; Floyd et al., 1970) and T2DM patients subjects (Floyd, 1968). In line with those findings, nutritional studies in humans already reported the synergistically stimulating effect of the combined ingestion of carbohydrate and protein on plasma insulin concentrations in the 1960s (Rabinowitz et al., 1966; Pallotta and Kennedy, 1968), which were later confirmed in both healthy (Nuttall et al., 1985) and T2DM subjects (Nuttall et al., 1984; Gannon et al., 1992; Gannon et al., 1998). A series of studies trying to define the *in vivo* insulinotropic potential of the ingestion of various free amino acids and protein in combination with carbohydrate, report a mixture containing a protein (hydrolysate) with the addition of free leucine to be most potential (van Loon et al., 2000a, 2000b). The latter was later shown to allow a two–four-fold greater increase in postprandial insulin release in both healthy and T2DM subjects when compared with the ingestion of carbohydrate only (van Loon et al., 2003; Manders et al., 2005; Manders et al., 2006a, 2006b;

Manders et al., 2008). Reduction in PPG was observed following intake of whey and soy protein with or without supplementation with amino acids (isoleucine, leucine, lysine, threonine, and valine) in healthy volunteers. This reduction was mediated by an early postprandial insulinaemia (PPI) response and correlated with presence of plasma GLP-1 (Gunnerud et al., 2012a, 2012b). Increased plasma amino acid concentrations was also shown to be positively associated with  $\beta$ -cell function relative to insulin sensitivity in adolescents (Michaliszyn et al., 2012a, 2012b).

The insulinotropic properties of amino acids, and leucine in particular, may be of relevance as a means to stimulate endogenous insulin release and, as such, to improve postprandial glycemic control in T2DM subjects (van Loon et al., 2003; Manders et al., 2006a, 2006b). In agreement, various studies have reported lower postprandial glucose concentrations in both healthy, normoglycemic and T2DM subjects following co-ingestion of protein (concentrate/hydrolysate) and/or free amino acids (Nuttall et al., 1984; Nuttall et al., 1985; Gannon et al., 1992; Gannon et al., 1998; Gannon et al., 2001; Frid et al., 2005). The greater postprandial insulin response following protein and amino acid co-ingestion has been proven functional, stimulating blood glucose uptake, and reducing postprandial hyperglycemia in T2DM subjects (Manders et al., 2005). Co-ingestion of a small amount of protein hydrolysate and leucine with each main meal can be applied to improve 24 h glycemic control by reducing the prevalence of postprandial hyperglycemia

(Manders et al., 2006a, 2006b) despite a higher energy intake. Protein and/or amino acid ingestion strongly stimulates postprandial insulin release in both healthy and T2DM subjects and, as such, can strongly affect postprandial glycemic control. Dietary intervention strategies to improve PPG should not only consider the glycemic load of a meal, but should also consider the protein/amino acid content of the meal.

#### *Dietary Fatty Acids and Blood Glucose Regulation*

A significant positive correlation exists between circulating free fatty acid levels and insulin resistance in tissues. Twenty years ago, Storlien et al. (1991) reported that high saturated fat-fed rats developed insulin resistance, whereas those fed with diets high in n-3, with a low n-6/n-3 ratio, maintained insulin action at normal levels. Subsequent studies of platelet membrane phospholipid fatty acid content in Indian Asians who are at increased risk of metabolic syndrome showed a greater proportion of n-6 polyunsaturated fatty acid (PUFA) linoleic acid, and arachidonic acid in combination with a reduced proportion of the n-3 long chain (LC)-PUFAs, eicosapentanoic acid (EPA), and docosahexaenoic acid (DHA) in Indian Asians than in whites (Lovegrove et al., 2004). These effects have variably been attributed to PUFA-mediated alterations of the membrane phospholipid characteristics, such as fluidity (Rustan et al., 1997) or through the saturated fatty acid (SAFA)-driven accumulation of ceramide and diacylglycerol, which inhibit Akt/PKB activation. Latterly, an increase in ceramide content in skeletal muscles of obese insulin resistant humans (Adams et al., 2004) and in subjects who showed insulin resistance after lipid infusion (Straczowski et al., 2004) ends further support to its role, possibly through alterations in lipid raft formation and stability (Xu et al., 2001a, 2001b) or increased reactive oxygen species (ROS) generation from mitochondrial uncoupling. In vitro experiments have confirmed that the presence of the monounsaturated fatty acid, oleate, can divert palmitate away from ceramide synthesis and prevent ceramide accumulation and insulin resistance (Gao et al., 2009; Gao et al., 2012). Since dietary fat and the resulting plasma fatty acids profiles are correlated, dietary intervention is predicted to influence insulin resistance.

A systematic analysis of the literature for studies reporting on the impact on blood glucose and insulin of interventions on fatty acid intake in the diet of adult humans with either obesity or T2DM has been undertaken here. We have identified 20 relevant studies for inclusion in systematic review, of which 3 considered fatty acid length and degree of esterification (Scalfi et al., 1991; Li et al., 2008), 4 examined n-3 PUFAs (Zamboni et al., 1992; Brady et al., 2004; West et al., 2005; Madigan et al., 2000; Jans et al., 2012), 14 investigated effects of cis-MUFA (Lerman-Garber et al., 1994; Christiansen et al., 1997; McCargari et al., 1998; Madigan et al., 2000; Thomsen et al., 2003; Piers et al., 2003; Manning et al., 2004; West et al., 2005; Lefevre et al., 2005; Paniagua et al., 2007; de Natale

et al., 2009; Sloth et al., 2009; Li et al., 2010; Lopez et al., 2011; Jans et al., 2012) three considered trans-MUFA (Christiansen et al., 1997; Lefevre et al., 2005; de Natale et al., 2009) with 7 describing effects of SAFA (Rivellese 1996; Christiansen et al., 1997; Thomsen et al., 2003; Piers et al., 2003; Manning et al., 2004; Devaraj et al., 2008; Lopez et al., 2011). In total, dietary effects on postprandial glucose or insulin were reported in 689 participants. Key features of these studies are reported in Table 4. Overall, there was no effect of varying triacylglycerol, diacylglycerol or chain length on insulin resistance in study participants although some benefits for lipid metabolism were noted. In contrast, closer examination of PUFA intervention studies showed mixed results; one study reported a decrease in PPI concentration ( $n = 10$ , 12 weeks PUFA intervention) whereas a second reported no benefit ( $n = 18$ , US T2DM subjects, single PUFA meal) a third ( $n = 11$ , T2DM subjects in Ireland, two weeks PUFA intervention) reported higher PPI concentrations after compared with post-MUFA diets and a fourth reported improved AUC over 6 h for glucose and insulin after PUFA and MUFA compared to SFA ( $n = 10$ , Dutch insulin resistant, single meal). The variability in duration of dietary change may be significant in determining effect, with benefit being observed in the study with longest intervention. In the two studies that described an investigation of trans-MUFA, one did not show any significant difference to MUFA in outcomes and the second showed comparable effects to a saturated fatty acid diet. This is consistent with a review by Thompson et al. (2011) that there is very little convincing evidence that habitual exposure to dietary trans-fatty acid as part of a standard western diet has a significant contribution to risk of diabetes or insulin resistance. However, studies in FABP2Thr54 carriers (at increased risk for T2DM complications) have shown increased postprandial glucose following trans-MUFA challenge compared to noncarriers of this allele (Lefevre et al., 2005). The majority of studies identified systematically in this present review have described cis-MUFA interventions on insulin resistance involving 277 subjects in 12 studies. Only 24 subject interventions showed no significant benefit, with the remaining 10 studies of 253 participants describing significant reductions in either postprandial glucose and/or insulin compared to control diets. Taking the systematic analysis of dietary fatty acid modulation together strongly supports the benefit of replacement of fats with MUFAs in the diet of T2DM or obese insulin-resistant subjects for the improvement of their glucose/insulin metabolism.

#### *Impact of Micronutrients on Blood Glucose Levels*

##### *Dietary Vitamins and Glycemic Control*

Micronutrients are nutrients required in small quantities for a whole range of physiological functions, but which the organism itself cannot produce. Micronutrients include dietary trace minerals, which are generally less than 100 mg day<sup>-1</sup> and vitamins.

Vitamins, organic molecules that are vital for normal physiology in any organism, are known to improve health when supplemented during specific deficiency states. However, less is known of the clinical value for supplementing to improve the outcomes of diseases that are associated with lower plasma vitamin levels. Concerns exist that vitamin supplementation for health benefit may be distributed according to a bell-shaped curve, where deficiency contributes to disease but excessive vitamin intake may also have adverse health outcomes for some individuals. However, the association between vitamin E and all cause mortality is now disputed (Gerstl, 2009). A number of clinical trials are registered presently that are investigating vitamin supplementation in early diabetic states to prevent onset of T2DM, or in T2DM subjects to improve outcome measurements such as HbA<sub>1c</sub> level. A limited number of studies have completed which describe vitamin effects on PPG or PPI and these are summarized and discussed.

The complex of B vitamins serves as cofactors principally associated with metabolism and circulating plasma levels of B vitamins are reduced in some diabetic populations (Mitri et al., 2011; Page et al., 2011). Thiamine (vitamin B1) is an essential coenzyme for the transketolase enzyme and the dehydrogenase complexes for pyruvate,  $\alpha$ -ketoglutarate, and branched-chain keto acids which is at lower plasma concentration in T2DM (Page et al., 2011). Benfotiamine, a lipid-soluble allithiamine derivative that has better intestinal absorption and improved bioavailability than thiamine, has been shown to afford postprandial benefit on vascular function following meals rich in advanced glycation end-products in T2DM. Plasma glucose levels were lowered in the benfotiamine supplemented group but not significantly in the postprandial period after an AGE meal (Stirban et al., 2006), but the effects of benfotiamine on PPG were significant after a cooked meat meal (Stirban et al., 2007). The pharmacologic effects of niacin (nicotinic acid; vitamin B3) on cholesterol lowering were first reported in 1955 (Altschul et al., 1955). It is potent in lowering fasting triglycerides and postprandial triglycerides, however, extended-release niacin increased postprandial insulin concentrations by 54% by 2 h after a high-fat meal indicating a decrease in insulin sensitivity (Plaisance et al., 2008). Nevertheless, there remain some significant benefits of niacin for management of cardiovascular complications and the most recent summarized evidence suggests that the cardiovascular benefit outweighs the reduction in glycemic control (Goldberg and Jacobson, 2008; Bays et al., 2011). However, it was observed that treatment with high dose, extended-release niacin did not reduce the risk of cardiovascular events (including heart attacks and stroke) in people with heart and vascular disease receiving intensive statin therapy (Boden et al., 2011). The cofactor, biotin (vitamin B7) works in synergy with insulin and independently increases the activity of glucokinase. No studies meeting the inclusion criteria for this review were identified using biotin supplementation alone. However, in moderately obese subjects with T2DM and with impaired glycemic control supplemented with chromium and biotin combination for four

weeks, glucose levels decreased at 1 h and 2 h and glucose area under the curve and fructosamine level were significantly decreased (Geohas et al., 2007).

As a lipid soluble vitamin whose levels are expected to correlate to an extent with lipid levels, the interpretation of the association that exists between plasma vitamin D and diabetes is complicated (Muscogiuri et al., 2011). Nevertheless, daily intake of a vitamin D-fortified yogurt drink (500 IU vitamin D3), either with or without added calcium, improved glycemic status in T2DM patients measured as HOMA-IR (Nikooyeh et al., 2011). In contrast, supplementation with cholecalciferol did not improve glycemic control in T2DM whose serum 25-hydroxyvitamin D levels were in the normal range at baseline (Jorde and Figenschau, 2009). Similarly, non-T2DM subjects with lower than normal plasma vitamin D levels did not show any difference in glucose homeostasis post glucose tolerance test (Tai et al., 2008). Using <sup>2</sup>H NMR analysis of monoacetone glucose (MAG) after tracer administration to understand what effect vitamin D3 may have on hepatic glucose metabolism revealed no changes in the percentage contribution of glycogenolysis (O'Sullivan et al., 2011). At present there is a lack of evidence to support any intervention with vitamin D on PPG and this was compounded by the early termination of the Thiazolidinedione Intervention with vitamin D Evaluation (TIDE) randomized controlled trial due to concerns over increased cardiovascular events with rosiglitazone (Punthakee et al., 2012).

High plasma and cellular nutrients promote the formation of reactive oxygen species (ROS) from membrane NADPH oxidase and mitochondria. It has been proposed that ROS play an important role in insulin resistance and, therefore, vitamins as dietary antioxidants may act as important mitigants of metabolic stress, promoting glucose and fatty acid utilization. Antioxidants frequently act in concert, at least in vitro, each operating within defined redox couples and transferring radicals to yield less reactive/damaging products. The principal dietary antioxidants include a number of vitamins (C-ascorbate, E-tocopherols and A-carotenoids) which are essential for human health, and phytochemicals such as lycopene. Recently, we have undertaken a meta-analysis and shown that HbA<sub>1c</sub> levels were significantly reduced by antioxidant supplementation, suggesting that antioxidants may have some benefit in protecting against the complications of T2DM (Akbar et al., 2011). Our analysis showed that vitamin C or E supplementation did not affect plasma glucose or insulin levels, and here we have supplemented these studies by examining the effect of antioxidant vitamins on postprandial glucose/insulin.

Four studies (Nappo et al., 2002; Carroll and Schade 2003; Evans et al., 2003; Neri et al., 2005) were identified that met inclusion criteria for the study investigating antioxidant effects in 77 subjects with all studies incorporating vitamin C, three also including vitamin E and one also including N-acetyl cysteine. Summary information is shown in Table 5. Supplement duration varied from immediately prior to the test fatty meal up to 14 days of supplementation prior to meal test. None of the



studies reported any benefit on plasma glucose excursions in the postprandial period following antioxidant intervention. More recent interest in vitamin E has been directed toward gamma tocopherol as the active constituent which is reported to have anti-inflammatory and gene regulatory effects. Masterjohn et al. (2012) have investigated effects of vitamin E supplementation enriched with (500 mg day<sup>-1</sup>) gamma tocopherol on PPG in 12 healthy, normoglycemic, college students. They did not see any benefit for AUC glucose or insulin following five-day ingestion of a supplement enriched in  $\gamma$ -tocopherol.

#### *Dietary Minerals and Blood Glucose Regulation*

Deficiencies of several dietary minerals (such as chromium, magnesium, and zinc) have been reported in T2DM subjects. As there is no evidence of beneficial effects of mineral supplementation on diabetic subjects without underlying deficiencies, the following review will be focused on the evidence of three most reported micronutrients on glucose control (Table 5).

**Chromium.** Chromium is a trace mineral which plays an important role in whole body glucose homeostasis by enhancing the binding of insulin to insulin receptor (Cefalu and Hu, 2004). Beneficial roles of chromium supplementation on glucose metabolism have been demonstrated in T2DM subjects. For example, chromium supplementation (500  $\mu$ g/d chromium picolinate) for four-months in T2DM subjects showed a significant reduction of fasting and postprandial glucose levels (Anderson et al., 1997; Cheng et al., 1999) and this beneficial effect existed after chromium supplementation for a 10-month period. Moreover, an acute chromium supplementation at 400  $\mu$ g and 800  $\mu$ g to a white bread meal showed a substantial reduction in PPG in young, apparently healthy adults compared with the white bread meal supplemented with a placebo (Frauchiger et al., 2004).

**Magnesium.** Magnesium is a mineral which plays important roles in glucose transport and, therefore, blood glucose metabolism. A reduced plasma magnesium levels has been often reported in subjects with T2DM. A previous study in young diabetes subjects in Bangladeshis showed that more than half the subjects were hypomagnesemic (Khan et al., 1999). Furthermore, a recent cross sectional study showed lowered mean magnesium intake, urine magnesium, plasma magnesium, and erythrocyte magnesium in T2DM subjects with poor glucose control (Sales et al., 2011). However, because the lack of randomized interventional studies, the role of magnesium in hyperglycemia in T2DM subjects is not clear and future studies are required.

**Zinc.** Zinc is a mineral that plays important roles in the synthesis and insulin sensitivity (Roth and Kirchgessner, 1981; Park et al., 1986; Brun et al., 1995). Previous studies have shown that plasma and tissue zinc concentrations in humans and animal models with T2DM are lower than in nondiabetic subjects due to the increased urinary zinc excretion by uncontrolled diabetes (Kinlaw et al., 1983). Supplementation of zinc

is found to be beneficial in alleviating the hyperglycemia of *ob/ob* and streptozotocin-induced diabetic mice models (Chan et al., 1998; Chen et al., 2000). Also, a randomized study evaluated the effect of zinc with other antioxidants on blood glucose in human diabetic subjects on long-term follow-up. They showed that oral zinc sulfate (22 mg/day) supplementation with a multivitamin/mineral preparation (vitamin A, vitamin D3, vitamin E, magnesium, manganese, copper, and selenium) for a four-month period significantly reduced both fasting and postprandial glucose levels in previously diagnosed (for at least two years) subjects from Sri Lanka with T2DM compared to the placebo group (Gunasekara et al., 2011). Another study in *ob/ob* mice also showed that administration (by gavage) of arachidonic acid plus zinc significantly increased glucose disposal in *ob/ob* mice and effectively decreased blood glucose levels in obese mice from acute treatment (30 min; 3 h) up to 14 days prolonged treatment (Hwang et al., 2002). Further human studies are required to fully evaluate the effect of zinc supplementation alone on glucose metabolism in diabetic subjects.

#### *Impact of Phytochemicals on Blood Glucose Regulation*

Phytochemicals are plant secondary metabolites broadly classified according to the pathway from which they are derived. Very few studies have directly attributed specific phytochemicals as to having an effect on PPG. Much of the data discussed concern the observation that a phytochemical-rich food has been effective in modulating the glycemic response and the foods include: berries, nuts, soy, cinnamon, seaweed, tea, ginseng, beans, chocolate, and the herbal extract "salacia" (Tables 6–8). The phytochemicals associated with fiber are an important and likely effective group and this has been discussed above. The most widely studied phytochemical rich foods studied for their effect on postprandial metabolism are berries, nuts, cocoa, and beverages (tea and coffee). This is due to their strong epidemiological association of these products with cardiovascular health.

The compounds that appear to be of particular importance are phenylpropanoid-derived and comprise predominantly the flavonoids and phenolic acids (Table 6). Many preclinical and in vitro studies have shown these molecules can attenuate the postprandial glycemic response, improve acute insulin secretion, and insulin sensitivity and these have been extensively reviewed (Hanhineva et al., 2012). No human studies to date have demonstrated a direct effect of the flavonoids or phenolic acids on PPG. However, resveratrol, a phenylpropanoid-derived stilbene found in grape skins has been shown to reduce plasma glucose and improve insulin resistance in volunteers with T2DM, when administered in a capsule (Brasnyo et al., 2011). The seed extract of grapes also had an effect on blood glucose regulation by lowering fructosamine in T2DM volunteers (Kar et al., 2009). In this study, an improvement in endothelial function, antioxidant status, and C-reactive

protein (CRP) was described. Other soft fruits found to decrease plasma glucose levels were fig (Serraclara et al., 1998), sea buckthorn berries (Lehtonen et al., 2010), and mixed puree containing blackcurrant, bilberry, cranberry, and strawberry (Torronen et al., 2010). Again, no direct effect of an individual phytochemical could be attributed. Few human studies have explored vegetables as a potential source of phytochemicals which could effect PPG. A *Flaxinius* species extract was found to have an acute effect postprandial glucose levels in healthy male volunteers (Visen et al., 2009). Another particularly phytochemical rich plant source found to effect PPG in healthy volunteers was seaweed (Goni et al., 2000). Seaweed is also a rich source of vitamins, minerals, and amino acids, and the causative effect needs further investigation.

Of the foods containing these phytochemicals, flavan-3-ol rich chocolate and tea are widely studied. In healthy and IGT volunteers (with no symptoms of diabetes) chocolate had an effect on blood glucose levels when in response to an OGTT (Grassi et al., 2005, 2008), although no effect was observed on insulin sensitivity measured by the glucose clamp method in mild-moderate hypertensive volunteers (Muniyappa et al., 2008). Tea is the second most commonly consumed beverage worldwide after water (Table 8). Results of epidemiological studies have suggested that consumption of tea (mainly green tea) could lower the risk of T2DM (Iso et al., 2006) as well as cardiovascular risk through decrease of CRP (Steptoe et al., 2007; Rebello et al., 2011), serum amyloid A and haptoglobin (De Bacquer et al., 2006). Maki and coauthors did not confirm the link between tea consumption and CRP, but daily users of green tea represented more than 80% of the sample, and they others were potentially coffee drinkers (Maki et al., 2010). So, it is difficult to see the clear link with CRP in a population where tea and coffee are consumed daily. Animal studies showed a clear effect of green tea extracts on the improvement of glucose tolerance either in induced diabetic rats or in genetic models of rodents with T2DM (Sae-tan et al., 2011). Despite preclinical evidence (Tsuneki et al., 2004), green tea, when consumed as a beverage had no effect on postprandial glucose or insulin response when consumed within a meal or one hour prior to a meal in healthy human volunteers (Louie et al., 2008; Josic et al., 2010). Green tea has been particularly studied for health interest because of its high content on polyphenolic compounds (especially catechins). Consumption of an epigallocatechin gallate (EGCG; > 97%) enriched extract by overweight volunteers also showed no change in glucose levels, insulin sensitivity or secretion (Brown et al., 2009). However, there was some correlation of green-tea phenolic intake and insulin levels in healthy humans (Fukino et al., 2005) and a catechin-rich green tea increased insulin levels in volunteers with T2DM subjects (Nagao et al., 2009). Another cross-sectional study linked green tea consumption to the lowering of fasting blood glucose and fructosamine (Maruyama et al., 2009). In a longer term study it was demonstrated that daily supplementation of green tea-extract powder (as an

equivalent of 456 mg of catechins daily) for two months lowered the HbA1c levels in subjects with borderline diabetes (Fukino et al., 2008) and green tea was inversely associated with plasma C-reactive protein concentrations (Rebello et al., 2011). Some potential mechanism of action of the catechins could be the modulation of certain glucose metabolism enzymes in the liver (increase of glucokinase expression and decrease phosphoenolpyruvate carboxykinase), as well as lipid metabolism enzymes in the liver and adipose tissue (acyl-CoA oxidase-1 and carnitinepalmitoyl transferase-1), and potentially on some adipose and muscle glucose receptors (GLUT-4 mRNA or translocation) (Sae-tan et al., 2011). Other types of tea are less well studied (i.e., dark tea, Oolong tea). However, it was observed that black tea exhibited a late phase plasma glucose response in healthy humans with a corresponding increase in insulin (Bryans et al., 2007). In conclusion, controversial results have been obtained on the consumption of tea and its impact on glucose metabolism. Discrepancy of results may be due to type of tea. However, the interest of phenolic compounds present in green tea seems to be associated with a positive impact of glucose metabolism.

Coffee is among the most widely consumed beverages in the world (Table 8). Knowledge on both the positive and negative health effects of coffee has been shown and it has been extensively studied in relation to various diseases (Van Dam and Hu, 2005). Several systematic reviews associated the habitual consumption of caffeinated or decaffeinated coffee with a substantially lower risk in T2DM (Van Dam and Hu, 2005; Tunnicliffe et al., 2008; Floegel et al., 2012). Higher consumption of coffee was consistently associated with a lower prevalence of newly detected hyperglycemia, particularly postprandial hyperglycemia (Van Dam and Hu, 2005). Some interesting additional inverse associations were found between coffee consumption and inflammatory markers; CRP, Tumor Necrosis Factor alpha (TNF- $\alpha$ ) (Williams et al., 2008; Maki et al., 2010) and some interleukins (Wedick et al., 2011). The potential beneficial chronic effects of coffee may be related to antioxidant compounds including chlorogenic acid (Johnston et al., 2003; van Dam 2006; Tunnicliffe and Shearer, 2008). However, no direct link has been established so far. The acute effect of coffee may be different if consumed within a meal or before the meal, and if it is decaffeinated or caffeinated coffee. It has been shown that caffeinated coffee elicited acute insulin insensitivity when ingested around one hour before a carbohydrate meal compared to decaffeinated coffee (Moisey et al., 2008). Additionally, co-ingestion of caffeinated coffee with a high carbohydrate meal increased the blood glucose response, without modifying postprandial insulin response. Three hours later, an OGTT showed decreased insulin sensitivity after the caffeinated coffee compared to water of decaffeinated coffee (Moisey et al., 2010). Based on the current knowledge, the controversy between deleterious acute effect and beneficial chronic effect of caffeinated coffee has not been clarified. However, decaffeinated coffee

could be another alternative to provide a beneficial impact on the glycemic response.

Nuts in general contain very little available carbohydrate and, therefore, contribute little to the postprandial glycemic response. Addition of nuts (almonds, pistachios, and mixed nuts) to carbohydrate rich foods has been shown to blunt the glycemic response (Jenkins et al., 2006) in a dose dependent manner (Josse et al., 2007; Kendall et al., 2011a, 2011b) up to 55% (90 g) in healthy people (Table 8). Also, in T2DM subjects, mixed nut intake decreased the PPG response dose dependently, although the effect was half of the effect seen in nondiabetic subjects (Kendall et al., 2011a). In another study in T2DM subjects ingestion of 28 g almonds before a high-starch meal lowered PPG by 30%, but did not demonstrate this response in healthy volunteers. In contrast to the former studies, in this study, the control meal contained added fat (butter), and the amount of butter was reduced to compensate for the fat content of the almonds in the treatment meal. In impaired glucose tolerant adults, incorporation of whole almonds into a breakfast meal containing 75 g of carbohydrate also resulted in a lower PPG response and blunted the glucose levels throughout the day. The mechanism of action of nuts on PPG may be due to a reduction in gastric emptying rate as a consequence of the additional energy from fat and protein. However, when the energy and fat contents of meals were controlled, a reduction in PPG was observed (Cohen and Johnston, 2011). Alternatively, the phytochemicals in nuts (phytates and phenolics) could play a role by reducing amylase activity, the enzyme that hydrolyzes starch. Addition of nuts to meals resulted in decreased (Jenkins et al., 2006) (healthy volunteers) or unchanged (Cohen and Johnston, 2011; Mori et al., 2011) (IGT, DM2) insulin response and increased insulin levels after a second meal (Mori et al., 2011) (IGT). Furthermore, addition of nuts to a meal may result in less oxidative protein damage (Jenkins et al., 2006). Only a limited number of longer term trials with nuts on glycemic control have been conducted in people with T2DM. Three relatively small and short-term studies have generally not found significant improvements in markers of glycemic control with nut consumption (for overview, see, Kendall et al., 2010). However, a recent pilot trial in which ingestion of one serving of almonds 5 days week<sup>-1</sup> resulted in a 4% reduction of HbA1c (Cohen and Johnston, 2011). In addition a very recent well-powered study of 117 subjects with T2DM, consumption of mixed nuts (73 g/d) for 12 weeks significantly reduced HbA1c levels and improved blood lipid risk factors for CHD (Jenkins et al., 2011). Although, no compounds could be individually attributed to the effects observed, nuts are rich sources of phenolics and phytosterols, as well as macro- (e.g., MUFA) and micronutrients (e.g.,  $\alpha$ -tocopherol). More studies are required to make definite conclusions on the role of nuts in glycemic control.

With reference to more specific phytochemicals, various herbal extracts have been shown to be effective. This includes Ginseng, both Asian (*Panax ginseng*) and American (*Panax quinquefolius*) and Korean Red (*Panax ginseng*; heat treated) species (Table 8). The two most popular types of ginseng, namely *Panax quinquefolius* L (American ginseng) and *Panax ginseng* CA Meyer (Asian ginseng) are most widely studied with respect to their hypoglycemic effects. In a series of randomized, placebo controlled studies, American ginseng has been shown to reduce PPG by up to 39% in healthy volunteers (Vuksan et al., 2000a, 2000b; Vuksan et al., 2001; Dascalu et al., 2007) and up to 22% in T2DM subjects (Vuksan et al., 2000a; Vuksan et al., 2000c). In one study with healthy volunteers, only a trend for hypoglycemic effects was found and one study did not find any effects of American ginseng on PPG (Sievenpiper et al., 2003a). The effects of Asian ginseng are mixed, with some studies showing increasing (Sievenpiper et al., 2003a), no (Sievenpiper et al., 2003a, 2003b; Reay et al., 2006; Reay et al., 2009) or decreasing effects up to 29% (Sievenpiper et al., 2006; De Souza et al., 2011) on indices of PPG in healthy volunteers. The high variability in efficacy on PPG may be secondary to the variability in the ginseng source (species, batch, preparation, part of the plant, and variety) and its composition, as represented by the measured ginsenoside profile. For example, Korean red ginseng rootlets have been shown to decrease PPG (Vuksan et al., 2008), while the root body has not (Sievenpiper et al., 2006; De Souza et al., 2011). This inconsistency limits the generalizability of the effects from one ginseng source to another and thereby, the use of ginseng as a hypoglycemic agent by subjects with T2DM. However, it has been shown in a so called “acute to chronic testing model” that an acute clinical postprandial model used to select the most efficacious ginsenoside profile, dose, and time of administration is able to identify sources of ginseng with safety and efficacy on long term glycemic parameters in T2DM subjects (Vuksan et al., 2000d; Vuksan et al., 2003). Two other long-term studies in T2DM subjects, with some (methodological) limitations, also showed positive effects of ginseng on glycemic control (Sotaniemi et al., 1995). In 18 healthy volunteers (placebo controlled, double-blind, cross over study), 200 mg *Panax ginseng* extract during eight weeks had no effect on any gluco-regulatory parameter investigated. (Reay et al., 2009) The mechanism behind the hypoglycemic effects of ginseng are unknown but may include modulation of digestion of food and thereby carbohydrate absorption. Modulation of glucose transport and insulin secretion have also been proposed (Vuksan et al., 2000a). It is hypothesized that the ginsenosides may be responsible for the effect, but phytochemicals such as the alkaloids or other plant components may be involved. There have also been various studies on cinnamon with no conclusive results. A recent study where a cinnamon extract was administered to healthy volunteers had no effect on PPG (Markey et al., 2011). However, several human studies with the herbal extract of *Salacia oblonga* have demonstrated significant decreases in postprandial glucose levels in

both healthy and T2DM subjects (Collene et al., 2005; Heacock et al., 2004; Williams et al., 2007). The mechanism of action is considered to be through competitive inhibition of  $\alpha$ -glucosidase activity and two bioactive phytochemicals kotanol and salacinol have been isolated (Matsuda et al., 2005).

The mechanism of action of nonnutrients on PPG is mostly unknown due to poor classification of the phytochemical composition of the foods studied. Potential mechanisms are mostly based on in vitro, preclinical and human ex vivo data. Some general mechanisms that have been proposed include: inhibition/retardation of carbohydrate digestion, modulation of glucose release, uptake and absorption, stimulation of insulin secretion (pancreatic  $\beta$ -cells), activation of receptors, modulation of signaling/gene expression, inhibition of lipolysis, decrease in oxidative stress and inflammation. It may be that the level required of certain plant products may be too high to tolerate. For example, some interventions have been shown to be ineffective at sustainable product levels (Josic et al., 2010; Clegg et al., 2011) and the food may have to be provided as a purified extract. For this reason, herbs, spices, and certain plant extracts (with high phytochemical content) are likely to be more effective. There is also little consideration regarding the phytochemicals associated with fiber and protein rich plants such as cereal crops and soya. Phytochemicals bound to these fractions can be released within the gastrointestinal tract and influence PPG, but few studies address their metabolism and bioavailability. It is clear that phytochemical-rich foods have potential to influence PPG, but in order to understand the impact of individual components on glucose metabolism it will be essential that the bioactive metabolites are identified.

### ***Impact of Miscellaneous Food Components on Blood Glucose Regulation***

#### ***Low-calorie Sweeteners and Glycemic Response***

People with diabetes need to monitor their carbohydrate intake in order to control blood glucose levels. Low-calorie sweeteners are added to foods, beverages, and used as tabletop sweeteners to provide sweetness without the calories or carbohydrates. As a caloric sweetener replacement, they are added in smaller quantities; hence, they provide few or zero calories. Low-calorie sweeteners do not affect the glycemic response and can help control overall carbohydrate intake by substituting for higher energy yielding sweeteners (Duffy and Sigman-Grant, 2004; Fitch and Keim, 2012).

A recent review (Fernstrom et al., 2012) concluded that ingestion of low-calorie sweeteners by animals and humans does not cause the hypothesized changes in blood glucose or hormone levels. An animal study observed that rats given acesulfame-K, saccharin, stevia or sucralose by gavage showed no change in blood concentrations of GLP-1, GIP, and glucose. Also, low-calorie sweeteners by gavage did not influence the rise in blood glucose during an oral glucose tolerance test

(Fujita et al., 2009). The influence of drinking solutions containing acesulfame-K (165 mg), aspartame (165 mg), cyclamate (800 mg) or saccharin (75 mg) on blood insulin and glucose levels in human volunteers over the following 2 h in comparison with sucrose (30 g) or water controls was investigated (Härtel et al., 1993). In comparison with the water control, and in contrast to the dose of sucrose, it was concluded that the ingestion of acesulfame-K, aspartame, cyclamate or saccharin (at moderate doses) did not increase blood glucose and insulin over the 2-h study period.

Further information is available from clinical research on the more recently developed sweeteners such as sucralose and stevioside/rebaudioside A (commonly known as stevia). A high single oral dose of sucralose (1000 mg) given orally to individuals with noninsulin-dependent diabetes mellitus and individuals with insulin-dependent diabetes did not influence plasma C-peptide or glucose concentrations (Mezitis et al., 1996). A single oral dose of sucralose (10 mg/kg) did not affect the glucose-induced changes in blood glucose levels when given with a large test dose of sucrose (100 g) (Roberts, 1999). Furthermore, a randomized, double-blind, placebo-controlled study in which 128 subjects with T2DM were given either sucralose (667 mg/d for 13 weeks) or placebo showed no effect on fasting plasma glucose, HbA1c or fasting serum C-peptide, demonstrating no effect of chronic ingestion of sucralose on glucose homeostasis (Grotz et al., 2003). A similar effect was observed when the low calorie sweetener, stevioside/rebaudioside A was consumed in a chronic study by patients with diabetes (Maki et al., 2008).

In summary, the above randomized human studies that varied from 1 to 16 weeks in duration found no significant difference between the effects of low-calorie sweeteners and various comparisons (sucrose, starch or placebo) on standard measures of glycemic and in general did not detect clinically relevant effects (Table 9). Furthermore, in the last two years more data have emerged. Anton and colleagues (2010) looked at the effects of preloads containing stevia, aspartame, and sucrose on food intake, satiety, and postprandial glucose and insulin levels in both lean and obese individuals. They concluded that stevia preloads reduced postprandial blood glucose and insulin levels, suggesting stevia may assist with glucose regulation. Raben et al. (2011) looked at importance of exchanging sucrose for sweeteners, on risk factors for diabetes development. Healthy overweight subjects were randomized to consume drinks and foods sweetened with either sucrose or sweeteners as supplements to their usual diet. After 10 weeks, a diet rich in low-calorie sweeteners had no effect on postprandial glucose, insulinemia, and lipidemia. Lastly, a study by Brown (2012) concluded that drinking diet soda could increase the amounts of a hormone that has been previously shown to be beneficial for people with diabetes when it comes to appetite and insulin secretion. More research, however, is needed to determine if this finding may impact future treatment of individuals with diabetes (Brown et al., 2012). In conclusion, the use of low-calorie sweeteners and the products that contain

them by subjects, with or without diabetes, do not affect blood glucose and are tools to help people reduce and control their caloric intake. Reducing calories could help to attain and maintain a healthy body weight, and thereby lower the risk of heart disease and diabetes. Leading health groups such as American Heart Association, American Diabetes Association (Gardner et al., 2012), and the Academy of Nutrition and Dietetics (Fitch and Keim, 2012) also agree that substituting low-calorie sweeteners for added sugars in beverages and other foods has the potential to help people reach and maintain a healthy body weight and help people with diabetes with glucose control.

#### *Water and Glycemic Control*

Addition of water to a test meal resulted in a 40% increased glucose response in 12 well controlled T2DM subjects (Table 9). In poorly controlled diabetic subjects, however, no significant effect was found, probably due to the varying fasting glycemia in these subjects (Torsdottir and Andersson, 2009). In another study in T2DM subjects, similar glucose responses were found to test meals with either 90 or 600 mL of tap water (Gregersen et al., 1990).

#### *Alcohol and Glycemic Control*

Epidemiological studies showed a U-shaped relationship between alcohol consumption and T2DM in western countries (Carlsson et al., 2005), showing that moderate alcohol consumption is associated with an increase in insulin sensitivity (Facchini et al., 1994; Kiechl et al., 1996; Kroenke et al., 2003). However, it is also suggested that unhealthy diets which include alcohol consumption are associated to metabolic disease genesis. Alcohol consumption of 10 g was associated with an increase in Low-Density Lipoprotein (LDL) oxidation, which is implicated in the development of cardiovascular disease (Schroder et al., 2006). Some inconsistent results may be attributed to the difference in beverage types, drinking frequency, and other dietary factors. The specific interest of phytochemical content in some alcoholic beverages such as wine has been addressed above. In a recent prospective cohort study, moderate alcohol consumption from 0 to 11 g/day of ethanol as beer, wine or liquors has been studied in around 3000 postmenopausal women with T2DM (Rajpathak et al., 2010). It was found that an inverse association between quantity and frequency of alcohol intake in relation to incident CHD (Rajpathak et al., 2010), was consistent with previous results obtained with nondiabetic postmenopausal women (Joosten et al., 2008). In an acute setting, moderate alcohol consumption (around 20 g of alcohol) may decrease the glycemic response when consumed within the meal, or before the meal (around 2 h prior to ingestion), independently of the type of beverage (Brand-Miller et al., 2007). However, the consumption of moderate alcohol may not modify the glycemic response of the breakfast when consumed during dinner (Godley et al., 2009). One potential mechanism of action is the

inhibition of the gluconeogenesis and the decrease of glucose output from the liver, as well as potential inhibition of  $\alpha$ -amylase and  $\alpha$ -glucosidase. However, this transitory impact of alcohol on glycemia seems to produce deleterious metabolic and hormonal consequence in the long term. Animal studies showed that chronic alcohol consumption increased plasma glucose and serum leptin, resistin, and adiponectin which are involved in insulin resistance genesis (Pravdova et al., 2009). Thus, moderate alcohol consumption may have some metabolic interest, including improvement of insulin sensitivity, and the reduction of some cardiovascular risk factors, but some critical questions are pending regarding the potential beneficial quantity, and which type of alcohol.

#### *Vinegar/Acetic Acid and Glycemic Control*

The interest on the effects of vinegar on the glycemic response has been studied because of the organic acid content, mainly acetic acid. Several years ago, organic acids such as acetic and propionic acids were shown to lower the glucose and insulin responses when added to white bread meals in healthy subjects (Liljeberg and Bjorck, 1998; Darwiche et al., 2001; Östman et al., 2005). More recently, addition of vinegar in a carbohydrate rich meal decreased significantly the glycemic and insulin responses in T2DM subjects only after a high GI meal (Liatis et al., 2010). The blood glucose and insulin kinetics were not modified after the low GI meal. A recent paper did not confirm the decrease of glucose response in a sucrose supplemented rice meal with addition of acetic acid (Mettler et al., 2009). Although, the authors could not find a clear explanation to justify this result, it may be due to the elevation of glycemia with rice was not large enough to observe the decremental effect of acetic acid, as some rice have a low GI. The potential mechanism of action proposed for acetic acid to decrease postprandial glucose and insulin responses is by slowing down the gastric emptying phase (Liljeberg and Bjorck, 1998; Darwiche et al., 2001), but this was not confirmed (Hlebowicz et al., 2008). Thus, addition of vinegar or acetic acid in carbohydrate rich meal may have a short-term positive impact by decreasing the postprandial glucose and insulin responses of high GI meals. There is no information regarding this addition in longer term studies.

## **DISCUSSION**

Lifestyle modifications with the highest impact on the risk of diabetes and on blood glucose regulation in the long term are weight reduction and increased habitual physical activity. As for diet composition, the strongest correlation of a dietary component with reduced risk of developing T2DM is with insoluble and moderately fermentable cereal-based fiber (Hu et al., 2001; Schulze et al., 2007). Diets rich in fruit and vegetables, which are a good source of soluble/fermentable fiber, have also shown a protective effect. However, the evidence is

less consistent, particularly if their impact on the risk of T2DM is evaluated independently of their effects on body weight (Cooper et al., 2012). Many studies utilize soluble fiber in the context of a healthy diet and these have been shown to potentially play a role in managing daily glucose levels both in healthy individuals and individuals with impaired glucose metabolism. An additional factor, which appears to influence glycemic and insulinemic responses in addition to the amount of fiber in the diet, is the food matrix of carbohydrate rich foods. In particular, soluble fiber has been shown to alter the physical food form, structure, and viscosity of test foods (Tappy et al., 1996; Kim et al., 2009), impacting on the rate of carbohydrate digestion and absorption, which, in turn, is reflected in the postprandial glucose and insulin responses (Juvonen et al., 2011; Karhunen et al., 2010). The overall glycemic impact of foods may be markedly affected by the individual meal components. However, when single foods were ranked in relation to their glycemic index, they showed a similar ranking of blood glucose responses when included in a mixed meal (Robert and Ismail 2012). In general, the results suggest that carbohydrate foods that promote low but sustained blood glucose levels may be considered advantageous with regard to metabolic control of diabetes (Järvi et al., 1999), with acute consumption of foods rich in soluble fiber being beneficial for both postprandial glycemic control and the insulinemic response.

Despite encouraging preclinical studies demonstrating that control of glycemia is likely to involve interaction with gut microbes, evidence from human clinical studies is only just starting to emerge. There are some positive effects of including prebiotics in the habitual diet and a limited number of clinical studies addressing the effect of probiotics on related outcomes such as fasting glycemia and insulin resistance were identified. Amino acids function as nutritional signals regulating various metabolic processes and can stimulate secretion of insulin from the pancreatic  $\beta$ -cells (Newsholme et al., 2005), with intravenous infusion of amino acids resulting in increased plasma insulin concentrations (Floyd et al., 1966; Floyd et al., 1968; Floyd et al., 1970). In particular, leucine can strongly stimulate endogenous insulin release and has potential to improve postprandial glycemic control (van Loon et al., 2003; Manders et al., 2006a, 2006b). Protein and/or amino acid co-ingestion can improve PPG (Nuttall et al., 1984; Nuttall et al., 1985; Gannon et al., 1992; Gannon et al., 1998; Gannon et al., 2001). However, it should be noted that longer term intake of high protein diets has been shown to result in whole-body insulin resistance (Linn et al., 2000; Weickert et al., 2006). Although these unfavorable effects on insulin resistance could be compensated in the short term by high protein diet induced weight loss, anabolic effects resulting in increased lean/muscle mass, and an amino acid induced increase in insulin secretion in subjects with intact  $\beta$ -cell function, a clearer understanding of the impact of protein consumption on blood glucose levels is required. High fat diets are associated with reduced insulin sensitivity, whereas with lower fat intake the impact appears

to be dependent on the fatty acid composition. The data regarding dietary fatty acid modulation strongly supports the benefit of replacement of saturated fats with MUFAs in the diet of T2DM or obese insulin-resistant subjects for the reduction of insulin resistance and improvement of blood glucose levels.

Data regarding the impact of micronutrients on blood glucose regulation is beginning to emerge. Although, there is currently no data supporting the effect of vitamins on blood glucose levels it has been shown that plasma concentrations of B vitamins are reduced in some diabetic populations (Mitri et al., 2011; Page et al., 2011) and that regular vitamin D intake improved glycemic control in T2DM subjects (Nikooyeh et al., 2011). Reduced circulating levels of minerals such as magnesium and zinc have been observed in T2DM subjects (Kinlaw et al., 1983) and there is some evidence that mineral supplementation can be effective in improving glucose metabolism (Anderson et al., 1997; Cheng et al., 1999; Gunasekara et al., 2011). However, intervention data from human studies are severely limited. There is a large and increasing body of evidence to suggest that phytochemical-rich foods can improve glucose metabolism. Unfortunately, in general these studies suffer from poor characterization of the phytochemical composition of the foods studied and limited human interventions with single compounds and this decreased the strength of the data obtained.

Based on the evidence presented in this review, it is clear that dietary components can modulate blood glucose levels. Although closely related, fasting and postprandial blood glucose levels are regulated by mechanisms that are to some extent, different. In fact, while postprandial blood glucose concentrations are largely dependent on meal composition, fasting values are only minimally influenced by the amount and/or rate of glucose absorption during the previous meal, and reflect the rate of glucose production in the liver (the two key processes being glycogenolysis and gluconeogenesis). Among the various dietary constituents, the one with the strongest influence on blood glucose levels in the postprandial period is the amount of digestible carbohydrate in the diet. Digestible carbohydrates include monosaccharides (glucose, fructose), disaccharides (sucrose, lactose) and certain polysaccharides (starch), which are digested and absorbed in the human intestine, thus contributing to the glucose in flow to the blood stream. However, the impact of dietary carbohydrates on glucose metabolism depends not only on the amount consumed, as believed in the past, but also on some specific food properties which can profoundly influence the metabolic effects. Among these, also the food structure and some specific physico-chemical characteristics of carbohydrates present in the food can have a relevant role in modulating blood glucose response. The ratio between mono-, di- and polysaccharides is no longer regarded as important in relation to the effects on postprandial blood glucose since amylase and disaccharidase activities in the human duodenum are sufficient to hydrolyse starch and disaccharides within minutes. The meal content of

protein and fat, although able to influence postprandial glucose values, has limited practical significance because the magnitude of these effects is rather small.

More important are all dietary factors able to delay the process of digestion and/or absorption of carbohydrates in the intestine, thus reducing the glycemic response to carbohydrate-rich food. Although, the overall mechanisms of action are not yet clear, the nature of the effective dietary components suggests that they are likely to include delayed gastric emptying and accessibility of the available carbohydrates (Thomas and Pfeiffer, 2012). As already mentioned, soluble viscous types of fiber are those with the largest impact on the postprandial glucose and insulin response after a meal. The knowledge of nutritional factors influencing blood glucose metabolism in the fasting state is still not complete. Liver glucose production, the major determinant of fasting glucose levels, is under the control of insulin and, therefore, not adequately suppressed when insulin resistance is present; thus nutritional factors influencing fasting plasma glucose concentrations are primarily those acting on insulin resistance. The strongest corroboration of efficacy for dietary components improving glucose metabolism in the fasting state is available for nondigestible carbohydrates (i.e., dietary fiber, resistant starch and fructo-oligosaccharides) and MUFAs (as replacement of saturated fat) with weaker but substantial evidence that certain phytochemicals, predominantly phenolic compounds are likely to be effective. Nondigestible carbohydrates escape digestion in the small intestine and are fermented by colonic bacteria in the large bowel generating SCFAs and other metabolites such as phenolic compounds (Lappi et al., in press; Vitaglione et al., 2008). This may explain the available, albeit mostly preclinical evidence that suggests that the gut microbiota plays an important role in metabolic regulation of glucose metabolism. These metabolites could influence liver glucose production and, thus, the fasting glucose concentration. Moreover, they act as prebiotics influencing the composition of gut microbiota. Finally, alcohol intake also has significant, clinical effects on plasma glucose levels. In fact, alcohol acutely suppresses hepatic glucose production thus lowering plasma glucose levels. Conversely, if habitually consumed in large amounts it impairs insulin sensitivity, thus deteriorating glucose tolerance and increasing plasma glucose levels.

In conclusion, T2DM is a lifestyle illness that can be managed and prevented by reducing excess body weight, increasing physical exercise and modifying diet composition as outlined in this review. Intensive interventions should be undertaken in individuals at high risk and, in particular, in those with impaired blood glucose regulation, in whom they have proven to be effective. This is especially desirable since high blood glucose levels, even if they are below the diagnostic threshold for diabetes, are also linked with a high risk for CVD. Therefore, lifestyle

measures effective in improving blood glucose regulation are useful for prevention of cardiovascular disease as well as of T2DM. New emphasis on prevention might limit the dramatic worldwide increase in the incidence of T2DM expected in the next decades which is also going to impact on health and longevity of the population.

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### **DECLARATION OF INTEREST**

Ms Athanasia Baka is employed by ILSI Europe.

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### **ABBREVIATIONS**

PPG =	Postprandial glycemia
PPI =	Postprandial insulinaemia
T2DM =	Type 2 diabetes mellitus
GI =	Glycemic index
GL =	Glycemic load
GP =	Glycemic profile
DF =	Dietary fiber
HSH =	Hydrogenated starch hydrolysates
RS =	Resistant starch
SFA =	Saturated fatty acid
PUFA =	Polyunsaturated fatty acid
MUFA =	Monounsaturated fatty acid
TFA =	Trans fatty acid
EPA =	Eicosapentaenoic acid
DHA =	Docosahexaenoic acid
GG =	Guar gum
SCFA =	Short chain fatty acid
IGT =	Impaired glucose tolerance
IFG =	Impaired fasting glucose
GLP =	Glucagon-like peptide
GPR =	G-protein couple receptor

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