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Probiotics, prebiotics, synbiotics and insulin sensitivity

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Abstract

Animal studies indicate that the composition of gut microbiota may be involved in the progression of insulin resistance to type 2 diabetes. Probiotics and/or prebiotics could be a promising approach to improve insulin sensitivity by favourably modifying the composition of the gut microbial community, reducing intestinal endotoxin concentrations and decreasing energy harvest. The aim of the present review was to investigate the effects of probiotics, prebiotics and synbiotics (a combination of probiotics and prebiotics) on insulin resistance in human clinical trials and to discuss the potential mechanisms whereby probiotics and prebiotics improve glucose metabolism. The anti-diabetic effects of probiotics include reducing pro-inflammatory cytokines via a NF-κB pathway, reduced intestinal permeability, and lowered oxidative stress. SCFA play a key role in glucose homeostasis through multiple potential mechanisms of action. Activation of G-protein-coupled receptors on L-cells by SCFA promotes the release of glucagon-like peptide-1 and peptide YY resulting in increased insulin and decreased glucagon secretion, and suppressed appetite. SCFA can decrease intestinal permeability and decrease circulating endotoxins, lowering inflammation and oxidative stress. SCFA may also have anti-lipolytic activities in adipocytes and improve insulin sensitivity via GLUT4 through the up-regulation of 5'-AMP-activated protein kinase signalling in muscle and liver tissues. Resistant starch and synbiotics appear to have favourable anti-diabetic effects. However, there are few human interventions. Further well-designed human clinical studies are required to develop recommendations for the prevention of type 2 diabetes with pro- and prebiotics.

Key words: **Probiotics: Prebiotics: SCFA: Insulin sensitivity: Clinical trials**

Introduction

The global diabetic population is rapidly growing from 382 million in 2013 to an estimated 592 million by 2035[1]. This situation imposes a great socio-economic burden on public health[2]. Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder of abnormal glucose and lipid metabolism, resulting in CVD, retinopathy, nephropathy, neuropathy, leg ulcers and gangrene[3]. The risk factors for T2DM include obesity, age, genetics, smoking, sedentary lifestyle and hypertension[2]. Recently, it has been proposed that changes in gut microbiota composition resulting from obesity could contribute to the pathogenesis of T2DM[4–8].

Probiotics and prebiotics may exert anti-diabetic effects through changes in microbiota[9–13]. Beneficial modification of the gut flora by probiotic and/or prebiotic treatment could be one dietary therapy for the prevention and treatment of T2DM.

PubMed, EMBASE, Cochrane and Scopus online database were searched for human intervention studies using the following terms: probiotic OR fermented OR yogurt OR cheese OR prebiotic OR inulin OR fructo-oligosaccharide OR synbiotic OR resistant starch OR gut microbiota, PLUS glucose OR glycemic OR hyperglycemia OR insulin OR insulin sensitivity OR type 2 diabetes Plus Human trial. Reviews were also utilised to clarify the potential mechanisms by which probiotics, prebiotics and synbiotics may alter insulin sensitivity.

Gut microbiota in individuals with type 2 diabetes mellitus and obesity

Most gut micro-organisms inhabit the large intestine that contains an estimated 10^{11-12} bacteria per g[14]. Gut microbiota can influence host adiposity and regulate fat storage[4,7,15–17].

The Bacteroidetes and the Firmicutes are groups of bacteria dominant in the human gut[8]. A correlation between changes in gut microbiota composition and obesity was reported in obese human subjects[8,18] and ob/ob mice[19], with lower microbial diversity, increased Firmicutes and decreased Bacteroidetes, and this obesity-associated gut microbiota had an increased capacity for energy harvest from the diet[19]. Germ-free wild-type C57BL/6J mice colonised with caecal microbiota from obese donors showed a significant increase (47 (SD 8·3) %) in body fat, compared with 27 (SD 3·6) % in mice colonised with a

Abbreviations: AMPK, 5'-AMP-activated protein kinase; ANGPTL4, angiopoietin-like protein 4; CFU, colony-forming unit; FIAF, fasting-induced adipose factor; FFAR, free fatty acid receptor; FOS, fructo-oligosaccharide; GLP-1, glucagon like peptide-1; GPR, G-protein-coupled receptor; GPx, glutathione peroxidase; HbA1c, glycated Hb; HOMA-IR, homoeostasis model assessment for insulin resistance; IGN, intestinal gluconeogenesis; LPS, lipopolysaccharide; MCP-1, macrophage chemoattractant protein-1; PBMC, peripheral blood mononuclear cell; PYY, peptide YY; SOD, superoxide dismutase; T2DM, type 2 diabetes mellitus.

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microbiota from lean donors over 2 weeks. During the 2 weeks, obese microbiota recipients consumed 55·4 (SD 2·5) g chow and gained 1·3 (SD 0·2) g fat, while the lean microbiota recipients consumed 54·0 (SD 1·2) g chow and gained 0·86 (SD 0·1) g fat, a difference of 2 % of total energy consumed[19].

Furthermore, composition of the intestinal microbiota in adults with T2DM was different from that in non-diabetic adults. The proportion of Firmicutes, Clostridia and bifidobacteria was significantly lower in diabetic adults than in non-diabetic adults[20,21].

Mucin-degrading bacteria such as *Akkermansia muciniphila* and *Desulfovibrio* were enriched in samples derived from T2DM patients[22]. In contrast, several recent studies showed that in mice, direct administration of *Akkermansia muciniphila*[23–27] or specific proteins isolated from the outer of membrane of *Akkermansia muciniphila* could prevent obesity, insulin resistance as well as atherosclerosis and a human study also showed that the abundance of *Akkermansia muciniphila* was associated with glucose homeostasis and body fat composition[28].

Vrieze *et al.*[29] investigated the effect of altering the gut microbiota on insulin sensitivity in subjects with the metabolic syndrome. Obese subjects given a small-intestinal infusion of faeces from lean donors (n 9) have shown improved peripheral insulin sensitivity after 6 weeks (median rate of glucose disappearance changed from 26·2 to 45·3 μmol/kg per min; $P < 0·05$), as assessed by the two-step hyperinsulinaemic–euglycaemic clamp method. These subjects also have shown a 2·5-fold increase in butyrate-producing gut microbiota, *Roseburia intestinalis*, compared with obese subjects reinfused with their own faeces (n 9). The faecal microbiota of obese subjects had lower microbial diversity, and contained higher amounts of Bacteroidetes and lower amounts of *Clostridium* cluster XIVa compared with faecal microbiota after lean donor infusion at 6 weeks[29].

Germ-free mice which are protected from diet-induced obesity had increased phosphorylated 5'-AMP-activated protein kinase (AMPK) in skeletal muscle and liver and increased fatty acid oxidation enzymes (acetyl CoA carboxylase; carnitine palmitoyltransferase), while germ-free knockout mice deficient in fasting-induced adipose factor (FIAF), a circulating lipoprotein lipase inhibitor, were not resistant to diet-induced obesity. Germ-free FIAF-deficient animals fed a Western diet showed decreased expression of the peroxisomal proliferator activated receptor-γ coactivator 1α (PGC1α) which is known to increase genes encoding regulators of mitochondrial fatty acid oxidation in the gastrocnemius muscle compared with germ-free $FIAF^{+/+}$ littermates, while there were no differences in phosphorylated AMPK levels between both groups. Consequently, germ-free mice were protected from diet-induced obesity through increased FIAF by inducing PGClα and also through elevated AMPK activity, implicating that obese gut microbiota can be responsible for decreased fatty acid oxidation and decreased FIAF/AMPK within the adipose tissue and liver[30].

The lipopolysaccharide (LPS) endotoxins, found in the outer membrane of some species of Gram-negative bacteria (for example, *Neisseria* spp. and *Haemophilus* spp.), induce signalling by binding to Toll-like receptor-4 present on endothelial cells, macrophages and monocytes. This promotes pro-inflammatory cytokines, chemokines, adhesion molecules and reactive oxygen species. An increase in LPS has been directly associated with insulin resistance[31]. Cani *et al.*[32] found in a mouse model that high-fat feeding changes gut microbiota with a marked reduction in some bacteria (*Lactobacillus* spp. and *Bacteroides–Prevotella* spp.), leading to an increased intestinal permeability, and LPS absorption. This increased metabolic endotoxaemia initiates adipose tissue inflammation (plasminogen activator inhibitor-1 and IL-1 mRNA), macrophage infiltration markers (macrophage chemoattractant protein-1 (MCP-1) mRNA, F4/80 mRNA) and oxidative stress (NADPHox mRNA, visceral adipose tissue and six transmembrane protein of prostate 2 (STAMP2, known to regulate nutrient-derived and inflammatory signals coordinately for metabolic homeostasis[33,34])).

Even though intestinal microbiota may play a role in the aetiology of obesity and insulin resistance, the relationship between the bacteria and these metabolic disorders remains a matter of debate and most publications merely report associations between intestinal microbial composition and metabolic disorders such as obesity and T2DM[35].

Probiotics and effects of probiotics on glucose metabolism in human interventions

According to the FAO/WHO, probiotics are 'live microorganisms which, when administered in adequate amounts, confer a health benefit on the host'[36]. The requirement of adequate amounts differs between countries: products must contain at least 10^7 colony-forming units (CFU)/g of probiotic bacteria in Japan, at least 10^8 CFU/g probiotic bacteria in USA and 10^9 CFU/g probiotic bacteria in Canada. In general, $>10^6$–10^8 CFU/g, or $>10^8$–10^{10} CFU/d of viable cells are regarded efficacious[37,38], but the cell count levels recognised do not guarantee a health effect[38,39]. Moreover, it is suggested that the recommendation for CFU determination should be established using accurate and frequent assessments because the number of viable cells is reduced during production, processing and formulation[38].

Some of the species are: (1) lactic acid-producing bacteria (*Lactobacillus*, *Bifidobacterium*, *Streptococcus*); (2) non-lactic acid-producing bacterial species (*Bacillus*, *Propionibacterium*); (3) non-pathogenic yeasts (*Saccharomyces*; for example, *Saccharomyces boulfecesardii*, a non-colonising lactic acid-producing yeast); (4) non-spore-forming and non-flagellated rod or coccobacilli[40]. Over 100 *Lactobacillus* and over thirty *Bifidobacterium* species have been identified[40]. Lactic-producing *Bifidobacterium* and *Lactobacillus* are the predominant and subdominant probiotic groups[41].

Human interventions with probiotics are shown in Table 1. Ten interventions[10,12,42–49] have shown positive effects of probiotics on glucose control. Ten interventions[6,50–58] have shown no effect and two interventions have shown negative effects[59].

Patients with T2DM supplemented with probiotic yogurt experienced attenuated fasting glucose and glycated Hb (HbA1c) concentrations and increased erythrocyte superoxide dismutase (SOD), glutathione peroxidase (GPx) activities and total antioxidants, compared with the control group[10]. Pregnant women given a probiotic supplement (*Bifidobacterium lactis* Bb12 and

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Table 1. Summary of probiotic human intervention studies

Type	Probiotic stains and dose used	Design	Subjects	Period	Outcomes	No effects	Reference
Drink	400 ml/d of a rose-hip drink containing *Lactobacillus plantarum* 299 v (5×10^7 CFU/ml) *v.* 400 ml/d of a rose-hip drink without bacteria	C, PC, P, RD, DB	36 Healthy smokers aged 35–45 years Treatment (*n* 18) Control (*n* 18)	6 weeks	↓ SBP, fibrinogen and IL-6 within the treatment group *v.* baseline	Glucose, insulin, BMI, BP, lipids	Naruszewicz *et al.* (2002)[50]
Yogurt	Low-fat yogurt of 100 ml/3 × d containing *Streptococcus thermophilus* and *L. delbrueckii* subsp. *bulgaricus* plus *B. longum* BL1 *v.* low-fat yogurt of 100 ml/3 × d containing *S. thermophilus* and *L. delbrueckii* subsp. *bulgaricus*	RD, PC, SB, P	32 Adults with TC ranging from 220 to 280 mg/dl (5·7 to 7·3 mmol/l) Treatment (*n* 16) Control (*n* 16)	4 weeks	↓ TC, ↓ LDL-C, ↓ TAG	Glucose	Xiao *et al.* (2003)[51]
Capsule	Freeze-dried capsule (2×10^9 CFU/tablet) containing *L. fermentum v.* placebo twice daily	DB, PC, P	44 Subjects with HC aged 30–75 years Treatment (*n* 23) Placebo (*n* 21)	10 weeks		Glucose, TC, HDL-C, LDL-C, TAG	Simons *et al.* (2006)[52]
Capsule	(a) Diet supplemented with probiotics containing *L. rhamnosus* GG and *Bifidobacterium lactis* Bb12 dietary counselling (b) Diet/placebo (c) Placebo	RD, P, DB, PC	196 Pregnant women aged 25–35 years (a) (*n* 66) (b) (*n* 70) (c) (*n* 60)	20 weeks	↓ Glucose, ↓ insulin, ↓ HOMA, ↑ QUICKI	HbA1c	Laitinen *et al.* (2009)[42]
Capsule	Capsule with freeze-dried *L. acidophilus* (NCFM – ATCC 700396 (1 g; about 10^{10} CFU)) *v.* placebo (a mixture of silicon dioxide and lactose, ratio 1:1)	RD, P DB, PC	45 Males Treatment (*n* 21, 10 NGT, 3 IGT and 8 T2DM) Placebo (*n* 24, 12 NGT, 2 IGT and 10 T2DM)	4 weeks	↑ Insulin sensitivity by hyperinsulinaemic–euglycaemic clamp	TNF-α, IL-6, IL-Ira, hs-CRP	Andreasen *et al.* (2010)[43]
Capsule	$2{\cdot}9 \times 10^9$ CFU of *L. reuteri* NCIMB 30242 capsule *v.* placebo maltodextrin capsule twice daily	DB, PC, P	124 Adults with HC Treatment (*n* 62) Placebo (*n* 62)	9 weeks		Fasting glucose, BMI	Jones *et al.* (2012)[53]
Yogurt	300 g/d of yogurt containing *L. acidophilus* La5, *B. lactis* Bb12 with dose of $3{\cdot}98 \times 10^9$ CFU *v.* conventional yogurt	RD, P, DB, PC	60 Patients with T2DM aged 30–60 years, BMI <35 kg/m^2 Treatment (*n* 30) Control (*n* 30)	6 weeks	↓ Fasting glucose, ↓ HbA1c, ↑ antioxidant status	Insulin	Ejtahed *et al.* (2012)[10]
Capsule	10^{10} CFU of *L. salivarius* Ls-33 *v.* placebo daily	RD, PC, DB, P	50 Obese adolescents aged 12 to 15 years Treatment (*n* 27) Placebo (*n* 23)	12 weeks		Fasting glucose, insulin, HOMA-IR, C-peptide, TC, TAG, NEFA, hs-CRP, IL-6, TNF-α	Gøbel *et al.* (2012)[57]
Capsule	1500 mg probiotic capsule containing *L. acidophilus*, *L. bulgaricus*, *L. bifidum* and *L. casei* twice daily *v.* 1500 mg placebo capsule containing 1000 mg magnesium stearate twice daily	SB, PC, P	34 Subjects with T2DM Treatment (*n* 16) Placebo (*n* 18)	6 weeks		Glycaemic control, lipids, inflammatory markers	Yousefinejad *et al.* (2013)[54]
Capsule	Capsule containing 10^{10} CFU *L. gasseri* BNR17 and filler powder (50 % trehalose, 25 % skimmed milk, and 25 % FOS) *v.* placebo capsule containing filler powder. Six capsules per d taken	RD, PC, DB, P	50 Obese adults with BMI ≥ 23 kg/m^2 Treatment (*n* 22) Placebo (*n* 28)	12 weeks		Fasting glucose, insulin, BMI	Jung *et al.* (2013)[55]
Cheese	Hypoenergetic diet (1512 kcal; 6326 kJ) supplemented with 50 g probiotic cheese made with *L. plantarum* TENSIA added to the cheese milk in amounts of $1{\cdot}5 \times 10^{11}$ CFU/g before renneting *v.* 50 g control Edam-type cheese made with a starter C92. 50 g of each cheese was 175 kcal (732 kJ)	RD, DB, PC, P	36 Obese hypertensive subjects Treatment (*n* 25) Control (*n* 11)	3 weeks	↓ BMI, ↓ BP	Glucose, lipids	Sharafedtinov *et al.* (2013)[56]
Yogurt	Probiotic yogurt of 200 g/d containing *S. thermophilus*, *L. bulgaricus*, *L. acidophilus* LA5 and *B. animalis* BB12 with dose of 1×10^7 CFU *v.* conventional yogurt of 200 g/d containing only starter cultures of *S. thermophilus* and *L. bulgaricus*	RD, SB, PC, P	70 Primigravida pregnant women with singleton pregnancy at their third trimester Treatment (*n* 37) Control (*n* 33)	9 weeks	↓ Insulin, ↓ HOMA	Fasting glucose, BP	Asemi *et al.* (2013)[45]
Yogurt	300 g/d of probiotic yogurt containing a total of *L. delbrueckii* subsp. *bulgaricus*, *S. thermophilus*. *B. animalis* subsp. *lactis* Bb12 and *L. acidophilus* La5 with dose of $1{\cdot}11 \times 10^9$ CFU/d *v.* 300 g/d conventional yogurt containing *L. delbrueckii* subsp. *bulgaricus* and *S. thermophilus*	RD, P, DB, PC	40 Obese adults with T2DM, BMI ≥ 25 kg/m^2 Treatment (*n* 20) Control (*n* 20)	8 weeks	↓ HbA1c, ↓ TNF-α, ↓ hs-CRP, ↓ IL-6	Glucose	Mohamadshahi *et al.* (2014)[44]

Table 1 *Continued*

Type	Probiotic stains and dose used	Design	Subjects	Period	Outcomes	No effects	Reference
Capsule	Probiotic capsule containing *L. salivarius* with dose of 1×10^9 CFU/d *v.* placebo capsule	DB, PC, RD, P	138 Pregnant obese women with mean BMI 33·6 kg/m^2 Treatment (*n* 63) Placebo (*n* 75)	4 weeks		Fasting glucose, insulin, HOMA-IR, lipids, hs-CRP	Lindsay *et al.* (2014)[6]
Capsule/ yogurt	(a) Probiotic yogurt + probiotic capsules (b) Probiotic yogurt + placebo capsules (c) Control milk + probiotic capsules (d) Control milk + placebo capsules Probiotic yogurt and a probiotic capsule contained *L. acidophilus* La5 and *B. animalis* subsp. *lactis* Bb12 with dose of $3{\cdot}0 \times 10^9$ CFU/d	DB, P, PC	156 Overweight adults aged over 55 years (mean: 67 ± 8 years old) (a) (*n* 40) (b) (*n* 37) (c) (*n* 39) (d) (*n* 40)	6 weeks	↑ HOMA-IR in probiotic yogurt, ↑ fasting glucose in probiotic capsules	Insulin, HbA1c	Ivey *et al.*. (2014)[59]
Capsule	$12{\cdot}5 \times 10^9$ CFU/capsule VSL#3 containing *B. longum*, *B. infantis*, *B. breve*, *L. acidophilus*, *L. paracasei*, *L. delbrueckii* subsp. *bulgaricus*, *L. plantarum* and *S. salivarius* subsp. *thermophilus v. n*-3 capsules *v. n*-3 + VSL#3 *v.* placebo (cellulose)	RD, DB, PC, P	60 Overweight (BMI > 25 kg/m^2), healthy adults, aged 40–60 years Treatment 1 (*n* 15) Treatment 2 (*n* 15) Placebo (*n* 15)	6 weeks	↓ Lipids, ↓ HOMA, ↑ hsCRP within VSL#3 and VSL#3 + *n*-3 groups *v.* baselines ↑ Lactobacilli and bifidobacteria in a VSL#3 group		Rajkumar *et al.* (2014)[46]
Yogurt	80 ml/d of fermented milk with *L. plantarum* ($1{\cdot}25 \times 10^7$ CFU/g) *v.* 80 ml/d of non-fermented milk	SB, PC,P	24 Postmenopausal women with the MetS Treatment (*n* 12) Placebo (*n* 12)	90 d	↓ Fasting glucose, ↓ homocysteine	Insulin, HOMA-IR	Barreto *et al.* (2014)[49]
Yogurt	200 g/d of fermented milk with 5×10^{10} CFU/100 g of *L. gasseri* SBT2055 (LG2055) *v.* fermented milk without LG2055	SB, PC,P	20 Subjects with hypertriacylglycerolaemia	4 weeks	↑ HbA1c, ↓ postprandial and fasting serum NEFA levels		Ogawa *et al.* (2014)[58]
Yogurt	600 ml/d of probiotic fermented milk containing *L. casei*, *L. acidophilus* and bifidobacteria with dose of $3{\cdot}4 \times 10^9$ CFU/d (at day 21) *v.* 600 ml/d of placebo conventional fermented milk	RD, P, DB, PC	60 Diabetic patients aged 35–65 years Treatment (*n* 30) Placebo (*n* 30)	8 weeks	↓ HbA1c, ↓ fasting glucose	TAG, TC, LDL-C, HDL-C	Ostadrahimi *et al.* (2015)[47]
Yogurt	300 ml of Cardi04 yogurt containing *L. helveticus* once daily	RD, P, DB, PC	41 Patients with T2DM Treatment (*n* 23) Placebo (*n* 18)	12 weeks	↓ Fasting glucose	HbA1c, lipids, hs-CRP, TNF-α	Hove *et al.* (2015)[12]
Capsule	Probiotic capsule containing three viable freeze-dried strains including *L. acidophilus* (2×10^9 CFU/g), *L. casei* (2×10^9 CFU/g) and *B. bifidum* (2×10^9 CFU/g) *v.* placebo (cellulose) once daily	RD, P, DB, PC	Primigravida 60 pregnant women with gestational diabetes aged 18–40 years Treatment (*n* 30) Placebo (*n* 30)	6 weeks	↓ Fasting glucose, ↓ insulin, ↓ HOMA-IR, ↓ HOMA for β-cell function, ↑ QUICKI, ↓ TAG, ↓ VLDL-C		Karamali *et al.* (2016)[48]

CFU, colony-forming unit; C, control; PC, placebo–control; P, parallel; RD, randomised; DB, double blind; SBP, systolic blood pressure; BP, blood pressure; SB, single blind; TC, total cholesterol; LDL-C, LDL-cholesterol; HDL-C, HDL-cholesterol; HC, hypercholesterolaemia; HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; ATCC, American Type Culture Collection; NGT, normal glucose tolerance; IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus; IL-Ira, IL-1 receptor antagonist; hs-CRP, high-sensitivity C-reactive protein; HbA1c, glycated Hb; FOS, fructo-oligosaccharide; MetS, metabolic syndrome; VLDL-C, VLDL-cholesterol.

Lactobacillus rhamnosus GG) and dietary counselling together had improved glycaemic control during and after pregnancy compared with the control/placebo group[42].

In sixty women with gestational diabetes, the daily supplement of a probiotic capsule, containing three viable freeze-dried strains including *Bifidobacterium bifidum* (2×10^9 CFU/g), *Lactobacillus acidophilus* (2×10^9 CFU/g) and *L. casei* (2×10^9 CFU/g), for 6 weeks showed improved insulin sensitivity as assessed by the homoeostasis model assessment for insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI), compared with a placebo capsule (cellulose). This probiotic supplementation also lowered TAG and VLDL levels, but this study did not measure HbA1c[48]. Moreover, oral supplementation of *L. acidophilus* NCFM (progenitor of the strain being used for complete chromosome sequencing in order to identify the relationship between genetics and probiotic functionality[60]) for 4 weeks improved insulin sensitivity as assessed by hyperinsulinaemic–euglycaemic clamp, compared with a placebo group, without changes in inflammatory markers such as TNF-α, IL-6, IL-Ira and high-sensitivity C-reactive protein[43].

On the other hand, one study of overweight adults[59] has shown conflicting results in that the intake of probiotic yogurt increased HOMA-IR ($P=0{\cdot}038$) and probiotic capsules significantly increased fasting glucose ($P=0{\cdot}037$) with no change in HOMA-IR[59] (*n* 77 for the probiotic group and *n* 79 for the probiotic capsule; the specific study design is shown in Table 1). The probiotics used were *Lactobacillus acidophilus* La5 and *Bifidobacterium animalis* subsp. *lactis* Bb12 (dose of $3{\cdot}0\times10^9$ CFU/d)[59].

A single-blinded clinical trial of thirty-four subjects with T2DM showed no effects on glycaemic control, lipid profiles and inflammatory markers between a placebo group (*n* 18; 1000 mg magnesium stearate) and a treatment group (*n* 16) who received 1500 mg probiotic capsules containing *Lactobacillus acidophilus*, *L. bulgaricus*, *L. bifidum* and *L. casei* twice daily for 6 weeks[54]. However, this study provided no counts of probiotics used.

In summary, given the mixed results from human interventions, it is still unclear if probiotics favourably influence glucose control. More human interventions are needed with more comprehensive and dynamic measures of insulin sensitivity, as most studies did not use these. It is also required to investigate the treatment effects of specific strain(s) at different dosages and durations on insulin resistance.

Other fermented food

Kimchi, made with napa cabbage and various ingredients (garlic, red pepper powder, onion, ginger, radish, fermented fish sauce and starch syrup), is a fermented traditional Korean food. Kimchi can give health benefits due to its high nutritional value and abundant bioactive compounds including dietary fibres, minerals, amino acids, vitamins, carotenoids, glucosinolates and polyphenols. Kimchi can be improved by additional ingredients and altered fermentation conditions[61]. Fermented kimchi mostly contains lactic acid-producing bacteria including *Lactobacillus plantarum*, *Lactobacillus brevis*, *Pediococcus cerevisiae*, *Streptococcus faecalis* and *Leuconostoc mesenteroides*, which could exert a probiotic effect[61].

Studies have shown beneficial effects of fermented kimchi on glucose metabolism in obese[62] and prediabetic individuals[63].

Fermented kimchi intake for 4 weeks decreased fasting glucose, fasting insulin, total cholesterol, MCP-1, leptin and the waist:hip ratio compared with fresh kimchi in a cross-over design of twenty-two overweight and obese patients. Fresh kimchi was defined as 1 d-old kimchi and fermented kimchi was defined as 10 d-old kimchi. The number of *Lactobacilli* in fermented kimchi was higher than in fresh kimchi ($4{\cdot}3\times10^9$ (SD $1{\cdot}2\times10^9$)/ml *v.* $1{\cdot}4\times10^7$ (SD 3×10^6)/ml)[62]. The consumption of fermented kimchi for 8 weeks decreased HbA1c, fasting insulin, HOMA and increased quantitative insulin sensitivity check index (QUICKI) and β-cell function compared with before fermented kimchi intake, in twenty-two adults with prediabetes[63].

A randomised controlled clinical trial in twenty-four obese women showed that fermented kimchi intake (180 g/d) for 8 weeks altered gut microbiota composition, with a decrease in genus *Blautia* and an increase in *Prevotella* and *Bacteroides*, compared with fresh kimchi intake and up-regulated expression of genes related to the metabolic syndrome such as acyl-CoA synthetase long-chain family member 1 (ACSL1; involved in enhancing fatty acid degradation) and aminopeptidase N (ANPEP; involved in the regulation of pain, angiogenesis, inflammation and apoptosis)[64].

Very recently, Shin *et al.*[65] demonstrated metabolic pathways of kimchi action based on *in silico* modelling of published data. A total of 4351 genes were associated with kimchi metabolites. Of these, 283 genes were associated with carbohydrate metabolism. In all, 309 genes were associated with lipid metabolism and twenty-seven genes (especially *GNAS*, *CTNNB1*, *EDN1*, *RAC1* and adenyl cyclases (*ADCY1*, *ADCY2*, *ADCY5*) known to act as regulators of metabolic and cardiovascular function) are directly related with CVD. Twenty-three genes (especially *PTPRC*, *LCK*, *JAK3*, *ZAP70* and *VEGFA*) were related to immune diseases and twenty-five genes were related to endocrine and metabolic diseases[65]. In summary, these inconsistent findings with probiotic interventions might result from heterogeneity in probiotic strains and populations. Intervention studies should be designed with a specific group and a specific strain[66].

Potential mechanisms of action of probiotics

One potential mechanism of anti-diabetic effects is that certain probiotics facilitate production of SCFA (acetate (C_2), propionate (C_3) and butyrate (C_4)), leading to the secretion of incretin hormones which may influence glucose levels[9,67]. Yadav *et al.*[9] have demonstrated a potential mechanism of probiotics through butyrate-induced secretion of glucagon-like peptide 1 (GLP-1) in mouse models. In this study[9], VSL#3 consisting of *Lactobacillus casei*, *L. plantarum*, *L. acidophilus* and *L. delbrueckii* subsp. *bulgaricus*, *Bifidobacterium longum*, *B. breve* and *B. infantis* and *Streptococcus salivarius* subsp. *thermophilus* was used. The levels of the SCFA butyrate in the mouse faecal samples significantly increased after VSL#3 (daily oral dose of 5 mg/kg body weight), as measured by liquid

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chromatography–electrospray ionisation–tandem MS. Significantly increased plasma butyrate levels were observed in VSL#3-treated mice compared with PBS-treated control mice. For the measurement of butyrate-producing bacteria, gene expression of butyrate kinase was assayed after 2 and 4 weeks of oral administration. Gene expression of butyrate kinase increased at 2 weeks in VSL#3-treated mice. An increase in GLP-1 was observed in the human intestinal L-cell line NCI-H716 treated with butyrate[9]. GLP-1, an incretin hormone secreted by L-cells mainly in the ileum and large intestine, increases insulin secretion while glucagon is suppressed. GLP1 secretion results in delayed gastric emptying and reduced appetite, food intake and body-weight gain[68]. Lactic acid produced by lactic acid-producing bacteria can be converted to acetate or propionate by *Clostridium propionicum*, *Propionibacterium* ssp., *Desulfovibrio* ssp, *Veillonella* ssp. and *Selenomonas* ssp.[69] via methylmalonyl-CoA or acrylyl-CoA, and then to butyrate via acetyl-CoA by *Eubacterium hallii* (butyrate-producing species)[67].

Other potential mechanisms of anti-diabetic effects of probiotics could be associated with enhanced immunity and increased anti-inflammatory cytokine production, reduced intestinal permeability and reduced oxidative stress[10,11,70,71]. In a randomised, double-blind, controlled intervention, patients with T2DM consumed 300 g/d of yogurt (*L. acidophilus* La5, *B. lactis* Bb12 with a dose of $3{\cdot}98 \times 10^9$ CFU) for 6 weeks and experienced a reduction in fasting glucose and HbA1c and an increase in GPx and erythrocyte SOD activities and total antioxidant status, compared with the control (300 g/d of conventional yogurt). GPx and SOD are scavengers of reactive oxygen species[10].

Pre-incubation of HeLa cells with live *Lactobacillus reuteri* cells for 1–2 h inhibited translocation of NF-κB to the nucleus, inhibited degradation of IKKB (inhibitor of NF-κB kinase subunit β) and prevented expression of pro-inflammatory cytokines under NF-κB regulation. Live *L. reuteri* up-regulated nerve growth factor and inhibited constitutive synthesis and secretion of IL-8 induced by TNF-α in T84 and HT29 cells (human colonic adenocarcinoma)[70]. Nerve growth factor is known to play roles in the regulation of inflammation[72,73] and proliferation of pancreatic β-cells[74]. Metabolites of *Lactobacillus plantarum* 2142 down-regulated peroxide-induced elevation in pro-inflammatory cytokines IL-8 and TNF-α in the IPEC-J2 cell line (jejunal epithelia isolated from neonatal piglet)[71]. In streptozotocin-induced diabetic rats, probiotic dahi containing *Lactobacillus casei* and *Lactobacillus acidophilus* suppressed streptozotocin-induced oxidative stress in pancreatic tissues by preventing the depletion of glutathione, GPx and SOD, as well as by decreasing thiobarbituric acid-reactive substances and nitrite[11]. This finding implicates that probiotic dahi could delay streptozotocin-induced alteration in glucose homeostasis by exerting an antioxidant effect on β-cells[11].

Prebiotics and effects of prebiotics on glucose metabolism in human interventions

Prebiotics are non-digestible food ingredients that are not metabolised or absorbed while passing through the upper gastrointestinal tract and are fermented by bacteria in the colon and selectively enhance the growth and/or activity of one or more potential beneficial bacteria (for example, *Bifidobacterium* and *Lactobacillus*) in the digestive system[75–77].

Food sources of prebiotics are seeds, whole grains, legumes, chicory roots, Jerusalem artichokes, onions, garlic and some vegetables. Some prebiotics can be produced during the process of enzymic action or alcohol or cooking[77].

Prebiotics include fructo-oligosaccharides (FOS), galacto-oligosaccharides, lactulose and large polysaccharides (inulin, resistant starches, cellulose, hemicellulose, pectin and gum)[75]. Of these, researchers have given more attention to FOS[77]. Synthetic oligosaccharides such as galacto-oligosaccharies have shown better effects and fewer side effects than natural forms[77]. Oligofructose-enriched inulin can act across the whole colon. Oligofructose is a short-chain fructan (a polymer of fructose molecules) containing three to ten monosaccharides linked together. It is quickly fermented and completely metabolised in the ascending part of the colon, whereas inulin is a long-chain fructan containing nine to sixty-four monosaccharides linked together. It is fermented and metabolised in the descending colon[77,78].

Inulin-type fructans of 10–20 g/d can normalise glucose tolerance or lipid profiles[79–84]. FOS or inulin of 4 g/d is the minimal requirement for the enhancement of bifidobacteria growth but 14 g/d or more of inulin can cause intestinal discomfort[77].

In various animal studies, prebiotics have shown improved glucose metabolism[85,86]. However, a few human studies have demonstrated inconsistent findings. Human interventions of prebiotics are shown in Table 2.

Fructo-oligosaccharides

Seven studies have shown a favourable effect of FOS[87–93] on glycaemic control, while three studies of FOS[94–96] have shown no effect.

Forty-eight overweight or obese adults (BMI > 25 kg/m^2) in a randomised, double-blind, placebo-controlled trial received 21 g oligofructose per d or a placebo (maltodextrin) for 12 weeks. FOS supplementation decreased ghrelin, glucose and insulin, and increased peptide YY (PYY) compared with a placebo[90]. Yamashita *et al.*[87] have also demonstrated a beneficial effect of supplementation of 8 g FOS per d for 14 d on glucose metabolism in individuals with T2DM. They found reductions in fasting glucose, total cholesterol and LDL-cholesterol. The intake of short-chain FOS of 10·6 g/d for 2 months reduced postprandial insulin response with no significant alteration in postprandial responses of glucose, NEFA and TAG in mild hypercholesterolaemic adults, compared with placebo[88]. In a double-blind cross-over design, a daily consumption of 20 g FOS for 4 weeks decreased basal hepatic glucose production with no change in insulin-suppressed hepatic glucose production or insulin-stimulated glucose uptake using a hyperinsulinaemic clamp, compared with a daily consumption of 20 g sucrose in twelve healthy subjects[89]. However, in subjects with T2DM, supplementation of 20 g FOS had no effect on basal hepatic glucose production, fasting glucose and insulin concentrations[95], and on blood glucose and serum lipids[94].

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Table 2. Summary of prebiotic human intervention studies

Source	Type and dose	Subjects	Design	Period	Outcomes	No effects	Reference
Inulin	50 g/d of rice-based ready-to-eat cereal containing (18 %) inulin *v.* 50 g/d of rice-based ready-to-eat cereal placebo	12 Healthy men with mean BMI 25·7 kg/m^2	CO	4 weeks	↓ TC, ↓ TAG, ↑ breath H_2, ↑ faecal lactic acid, ↑ bifidobacteria	Glyceamic responses, faecal and bile acid output, faecal SCFA, faecal pH	Brighenti *et al.* (1999)[83]
Inulin	10 g/d of inulin *v.* 10 g/d of maltodextrin placebo	54 Middle-aged subjects Treatment (*n* 27) Placebo (*n* 27)	RD, DB, PC, P	8 weeks	↓ Insulin at week 4 within the inulin group *v.* baseline ↓ TAG in the inulin group *v.* the placebo group at week 8	Fasting glucose	Jackson *et al.* (1999)[80]
Inulin	Diet supplemented with 10 g/d of inulin *v.* 10 g/d of maltodextrin placebo	Eight healthy subjects aged 23–31 years with BMI 19–25 kg/m^2	RD, DB, CO, PC	3 weeks	↓ TAG, ↓ hepatic lipogenesis	Glucose, insulin, glucagon, NEFA, lipids	Letexier *et al.* (2003)[84]
Inulin	Diet supplemented 11 % inulin-enriched pasta (100 g/d) *v.* wheat pasta (100 g/d) placebo diet	15 Healthy males	RD, DB, CO	5 weeks	↓ HbA1c, ↓ HOMA-IR, ↓ fasting glucose, ↓ fructosamine, ↓ gastric empting, ↓ TC, ↑ HDL, ↓ TAG		Russo *et al.* (2010)[81]
Inulin	Low-energy diet plus one of following treatments: (a) PMR alone; (b) PMR + 10 g/d of inulin; (c) 10 g/d of inulin alone; (d) control (no inulin or PMR)	110 Obese women aged 18–50 years with BMI ≥ 25 kg/m^2 (a) (*n* 28), (b) (*n* 23), (c) (*n* 30), (d) (*n* 29)	RD, C, L, P	12 weeks	↓ TAG	Glucose, TC, HDL-C	Tovar *et al.* (2012)[97]
Chicory root inulin	Diet supplemented with 1 pint (0·4732 litres) of low-fat vanilla ice cream made with 20 g/d of inulin *v.* the same diet supplemented with 1 pint of low-fat vanilla ice cream made with sucrose	12 Men with HC	RD, DB, CO	3 weeks	↓ TC, ↓ TAG	Glucose, insulin	Causey *et al.* (2000)[98]
Chicory inulin	Diet supplemented with 16 g/d of chicory-derived fructan/d *v.* diet with 16 g/d of maltodextrin placebo	10 Healthy adults with mean BMI 21·6 kg/m^2 Treatment (*n* 5) Placebo (*n* 5)	RD, DB, P, PC	2 weeks	↓ Postprandial glucose, ↑ breath H_2, ↓ hunger, ↑ GLP-1, ↑ PYY	Fasting glucose, insulin	Cani *et al.* (2009)[82]
Inulin and FOS	Yacon syrup with about 12·5 g/d of FOS *v.* placebo syrup containing 2·5 % tartaric acid, 1·8 % carboxymethylcellulose, 2·5 % saccharine and 10 % glycerine	35 Obese women with mean BMI 33·5 kg/m^2 Treatment (*n* 20) Placebo (*n* 15)	DB, PC, P	17 weeks	↓ Fasting insulin, ↓ HOMA-IR, ↓ LDL-C, ↑ satiety, ↓ BMI, ↓ waist circumference	Fasting glucose, TC, HDL-C, TAG	Genta *et al.* (2009)[92]
Inulin and FOS	16 g/d mixture of inulin and FOS (50/50) *v.* placebo maltodextrin. Dietary instruction given to all participants for weight loss	30 Obese women Treatment (*n* 15) Placebo (*n* 15)	DB, PC, P	12 weeks	↓ Post-OGTT glycaemia within the treated group, ↓ LPS ↓ *Bacteroides intestinalis*, *Bacteroides vulgatus* and *Propionibacterium* ↑ *Bifidobacterium* and *Faecalibacterium prausnitzii* ↓ *Bacteroides intestinalis*, *Bacteroides vulgatus* and *Propionibacterium*	HbA1c, fasting glycaemia, insulinaemia, post-OGTT insulinaemia, HOMA, adiponectinaemia, hs-CRP	Dewulf *et al.* (2013)[99]
FOS-enriched inulin	10 g/d of FOS-enriched inulin *v.* 10 g/d of maltodextrin placebo	52 Diabetic women with BMI > 25 but < 35 kg/m^2 Treatment (*n* 27) Placebo (*n* 25)	RD, PC, P	8 weeks	↓ Fasting glucose, ↓ glycosylated Hb, ↓ IL-6, ↓ TNF-α, ↓ LPS	hs-CRP, IL-10, interferon-γ	Dehghan *et al.* (2014)[78]
FOS	8 g/d of FOS *v.* 5 g/d of placebo sucrose	28 Patients with T2DM Treatment (*n* 18) Placebo (*n* 10)	RD, PC, P	2 weeks	↓ Fasting glucose, ↓ TC, ↓ LDL-C	NEFA, TAG, HDL-C	Yamashita *et al.* (1984)[87]
FOS	20 g/d FOS *v.* 20 g/d sucrose	12 Healthy subjects	RD, DB, CO	4 weeks	↓ Basal hepatic glucose production	Fasting glucose, insulin, lipids	Luo *et al.* (1996)[89]
FOS	15 g/d of FOS *v.* 4 g/d of placebo glucose	20 Patients with T2DM	RD, SB, CO	20 d		Glucose, lipids, TAG, NEFA, acetate	Alles *et al.* (1999)[94]
FOS	20 g/d of FOS *v.* 20 g/d of placebo sucrose	10 Patients with T2DM	DB, CO, no washout	4 weeks		Basal hepatic glucose production, fasting glucose, insulin, lipids	Luo *et al.* (2000)[95]
sc-FOS	10·6 g/d of sc-FOS *v.* 15 g/d of placebo maltodextrin and aspartame with tea and/or coffee	30 Adults with mild HC	RD, DB, CO	8 weeks	↓ Postprandial insulin response	Postprandial effects on glucose, NEFA, TAG	Giacco *et al.* (2004)[88]
FOS	Diet supplemented with 16 g/d of FOS *v.* diet with placebo 16 g/d of maltodextrin	Seven male adults with non-alcoholic steatohepatitis (mean BMI 29·1 kg/m^2)	RD, DB, CO	8 weeks	↓ Aminotransferases, ↓ AST after 8 weeks, ↓ insulin at 4 weeks	Insulin after 8 weeks	Daubioul *et al.* (2005)[91]

Table 2 *Continued*

Source	Type and dose	Subjects	Design	Period	Outcomes	No effects	Reference
FOS	(a) FOS-rich yacon syrup (0·29 g FOS/body weight per d) (b) FOS-rich yacon syrup (0·14 g FOS/body weight per d) (c) placebo	55 Obese slightly dyslipidaemic premenopausal women Treatment (*n* 40) Placebo (*n* 15)	DB, PC, P	120 d	↓ Fasting insulin, HOMA-IR, BMI and LDL-C within the yacon syrup at 0·14 g FOS/body weight per d *v.* baseline	Fasting glucose, TC, HDL-C, TAG	Genta *et al.* (2009)[92]
FOS	21 g/d of FOS *v.* 7·9 g/d of placebo maltodextrin	39 Overweight or obese adults with BMI > 25 kg/m^2 Treatment (*n* 21) Placebo (*n* 18)	RD, DB, PC, P	12 weeks	↓ Ghrelin, ↑ PYY, ↓ postprandial insulin, ↓ body weight, ↓ fat mass, ↓ energy intake	Postprandial glucose, GLP-1, GIP, leptin, lipids	Parnell & Reimer (2009)[90]
FOS	30 g/d of FOS *v.* 30 g/d of placebo cellulose	22 Healthy obese subjects with BMI 25–35 kg/m^2 aged 20–50 years Treatment (*n* 12) Placebo (*n* 10)	P, SB, PC,	6 weeks	↑ PYY, ↓ appetite	AST, ALT, GGT, glucose, insulin, HOMA-IR, HOMA % B, lipids, GLP-1	Daud *et al.* (2014)[96]
FOS	18 g/d of freeze-dried powdered yacon containing 7·4 g/d of FOS *v.* placebo (18 g/d of maltodextrin)	72 Elderly subjects aged > 60 years Treatment (*n* 37) Placebo (*n* 35)	RD, DB, PC, P	9 weeks	↓ Serum glucose within the treatment group *v.* baseline	Insulin, HOMA-IR, lipids, hs-CRP	Scheid *et al.* (2014)[93]
RS	60 g/d of RS (Novelose 260) *v.* placebo (0 g/d of RS)	10 Healthy adults	SB, CO, PC, P	24 h	↓ Postprandial glucose and insulin, ↑ insulin sensitivity by a minimal model approach	TAG	Robertson *et al.* (2003)[102]
RS	30 g/d of RS *v.* placebo (0 g/d of RS)	10 Healthy adults with mean BMI 23·4 kg/m^2	SB, CO, PC, P	4 weeks	↑ Insulin sensitivity by hyperinsulinaemic–euglycaemic clamp at 3 weeks, ↓ insulin AUC at 4 weeks, ↑ insulin sensitivity by MTT at 4 weeks	Fasting glucose and insulin by MTT at 4 weeks	Robertson *et al.* (2005)[100]
RS	Low β-glucan (low, medium and high RS) *v.* medium β-glucan (low, medium and high RS) *v.* high β-glucan (low, medium and high RS) *v.* glucose	10 Normal-weight and 10 overweight women	MTT		↓ Glucose and insulin AUC		Behall *et al.* (2006)[106]
RS	40 g/d of RS *v.* placebo (0 g/d of RS)	20 Insulin-resistant subjects	SB, RD, PC, P	12 weeks	↑ Insulin sensitivity by euglycaemic–hyperinsulinaemic clamp	Adiposity, lipids, inflammatory markers	Johnston *et al.* (2010)[103]
RS	15 g/d of HAM-RS2 *v.* 30 g/d HAM-RS21 *v.* control (0 g/d of HAM-RS2)	Overweight and obese adults (11 men and 22 women)	RD, DB, CO, C	4 weeks	↑ Insulin sensitivity in men by insulin-modified intravenous glucose tolerance test	Fasting glucose, insulin, HOMA-IR, hs-CRP, fructosamine adiponectin	Maki *et al.* (2012)[104]
RS	24 g/d of RS *v.* control (0 g/d of RS)	86 subjects both with the MetS and without the MetS	DB, CO, PC, P	12 weeks	↓ Cholesterol in subjects with the MetS, ↓ body fat composition	Fasting glucose, postprandial glucose, HbA1c	Nichenametla *et al.* (2014)[107]
RS	40 g/d of type 2 RS (HAM-RS2) *v.* placebo (0 g/d of RS)	17 Diabetic adults with mean BMI 30·6 kg/m^2 aged mean 55 years	SB, RD, CO	12 weeks	↓ Postprandial glucose by MTT, ↓ TAG, ↑ GLP-1, ↓ TNF α	Fasting glucose, insulin, HOMA-IR, insulin sensitivity, HbA1c, C-peptide, lipids, IL-6	Bodinham *et al.* (2014)[105]
RS	Barley kernel-based bread high in RS and NSP (37·6 g/d of total dietary fibre) *v.* white wheat bread (9·1 g/d of total dietary fibre)	20 Healthy middle-aged subjects	RD, CO	3 d	↑ Fasting GLP-1, ↑ postprandial PYY and GLP-2, ↑ breath H_2, ↑ fasting SCFA, ↑ insulin sensitivity, ↓ blood glucose and serum insulin responses to the standardised breakfast	Fasting glucose, insulin, HOMA-IR, inflammatory markers	Nilsson *et al.* (2015)[101]

CO, cross-over; TC, total cholesterol; RD, randomised; DB, double blind; PC, placebo–control; P, parallel; HbA1c, glycated Hb; HOMA-IR, homeostasis model assessment of insulin resistance; PMR, partial meal replacement; C, control; L, longitudinal; HDL-C, HDL-cholesterol; HC, hypercholesterolaemia; GLP-1, glucagon-like peptide-1; PYY, peptide YY; FOS, fructo-oligosaccharide; LDL-C, LDL-cholesterol; OGTT, oral glucose tolerance test; LPS, lipopolysaccharide; hs-CRP, high-sensitivity C-reactive protein; T2DM, type 2 diabetes mellitus; SB, single blind; sc-FOS, short-chain fructo-oligosaccharide; AST, aspartate aminotransferase; GIP, glucose-dependent insulinotropic peptide; ALT, alanine aminotransferase; GGT, γ-glutamyltranspeptidase; RS, resistant starch; MTT, meal tolerance test; HAM-RS2, high-amylose maize type 2 resistant starch; MetS, metabolic syndrome.

Inulin

Effects of inulin on glycaemic control have shown mixed results, with three interventions[80–82] showing a positive effect and four interventions[83,84,97,98] showing no effect.

In a parallel study of fifty-four subjects receiving 10 g inulin (*n* 27) or maltodextrin (*n* 27) daily for 8 weeks, insulin concentrations were lower at 4 weeks within the inulin group compared with baseline, but no differences were observed at weeks 4 and 8 in comparison with a placebo. No effect of inulin on fasting glucose concentrations was observed compared with a placebo[80]. However, in a cross-over study of twelve men with hypercholesterolaemia, a diet supplemented with 1 pint (0·4732 litres) of vanilla ice cream made with 20 g inulin for 3 weeks decreased total cholesterol and TAG but did not alter glucose and insulin, compared with the same diet supplemented with 1 pint of vanilla ice cream made with sucrose[98].

Oligofructose-enriched inulin

Three interventions have shown favourable effects on glycaemic control when a combination of FOS and inulin was used[78,92,99]. In a randomised controlled study of fifty-two women with T2DM, 10 g FOS-enriched inulin per d (*n* 27) for 8 weeks lowered fasting glucose and glycosylated Hb and improved inflammatory markers (IL-6, TNF-α) and decreased LPS, compared with a placebo (maltodextrin; *n* 25)[78]. Further research is necessary to clarify the effects of oligofructose-enriched inulin on glucose metabolism.

Resistant starch

Consumption of resistant starch improved insulin sensitivity in healthy subjects[100–102] or in subjects with the metabolic syndrome[103,104], and lowered postprandial glucose or insulin in individuals with T2DM[105] and women[106]. One study[107] showed no difference in glycaemic control. The 3 d intake of barley kernel-based bread rich in resistant starch and NSP increased fasting SCFA levels, gut hormones (fasting GLP-1, postprandial PYY and GLP-2) secretion and breath H_2 excretion, and improved insulin sensitivity (the Matsuda index) after consuming a standardised breakfast, compared with white wheat bread[101].

In summary, the effects of prebiotics (inulin or FOS or oligofructose-enriched inulin administration) on glucose and lipid metabolism are not clear, but resistant starch appears to have a favourable effect on insulin sensitivity.

Other potential prebiotics

Costabile *et al.*[108] suggested that whole-grain wheat could exert a prebiotic effect on gut microbiota composition. This double-blind, randomised, cross-over trial comparing 100 % whole-grain breakfast cereal of 48 g/d with wheat bran breakfast cereal of 48 g/d for 3 weeks showed that whole grain significantly increased the number of faecal bifidobacteria and lactobacilli compared with the wheat bran cereal. However, there were no significant differences in faecal SCFA, fasting glucose, insulin, total cholesterol, TAG or HDL-cholesterol for whole grain intake compared with whole bran[108].

Potential mechanisms of action of prebiotic-derived SCFA in insulin sensitivity

Microbial fermentation of prebiotics facilitates the production of SCFA (essential endproducts of carbohydrate metabolism) and enhances gut barrier function[109]. In a mouse model, a prebiotic treatment decreased intestinal permeability and increased GLP-2 secretion, and reducing the hepatic expression of inflammatory and oxidative stress markers and decreasing LPS during obesity and diabetes[109].

SCFA and free fatty acid receptors

SCFA in the intestine activate G-protein-coupled receptors (GPR), such as GPR41 (namely, free fatty acid receptor 3; FFAR3) and GPR43 (namely, free fatty acid receptor 2; FFAR2). These receptors are present on ileal and colonic enteroendocrine L-cells, adipocytes and immune cells[110]. Both GPR41 and GPR43 on intestinal epithelia L-cells trigger the secretion of gut hormones (GLP-1 and PYY). Leptin is also released from adipocytes when SCFA bind to GPR41. PYY, GLP1 and leptin can decrease appetite[111–114]. GLP-1 increases insulin secretion from pancreatic β-cells and decreases glucagon secretion from the pancreatic islets, which leads to lower glucose output from the liver and enhanced peripheral uptake of glucose. GLP1 may suppress appetite and food intake via the autonomic nervous system or the brain[75,115,116]. It is known that FFAR3 is activated by butyrate and propionate while FFAR2 is activated by acetate and propionate[117]. FFAR3 knockout mice showed that butyrate and propionate inhibited food intake, reduced high-fat diet-induced weight gain and glucose intolerance and enhanced gut hormone release. FFAR3 was necessary for the maximal induction of GLP-1 by butyrate, whereas FFAR3 was unnecessary for the effects on body weight and glucose-dependent insulinotropic peptide secretion[118]. FFAR3 and FFAR2 can be expressed in several cells such as adipocytes, endocrine cells (for example, pancreatic islets) and immune cells[119]. FFAR2 is highly expressed in immune cells (neutrophils and monocytes) and haematopoietic tissues, compared with FFAR3[120]. SCFA can exert potent roles in inhibiting lipolysis and inflammation, and regulating energy metabolism[119,120–122]. Ge *et al.*[121] demonstrated that when FFAR2 on adipocytes was activated by SCFA (acetate and propionate), adipocyte lipolysis and differentiation were inhibited, while in GPR43 knockout animals, this was not observed, suggesting that prebiotic fermentation could be detrimental with regard to obesity[121]. However, obese mice and human studies of prebiotics (especially, inulin-type fructans) have not shown this[123,124]. SCFA inhibited the production of MCP-1 and LPS-induced IL-10 in human monocytes, as well as LPS-induced TNF-α and interferon-γ in human peripheral blood mononuclear cells (PBMC: monocytes and lymphocytes (T-cells, B-cells and natural killer cells))[120].

Anti-inflammatory effects

Elevated pro inflammatory makers such as high-sensitivity C-reactive protein, TNF-α and IL-6 are increased in T2DM[78]. SCFA can suppress these inflammatory mediators[120,125–128].

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SCFA (acetate, propionate, and butyrate) decrease NO[125]. NO is produced by NO synthase which converts oxygen and arginine to citrulline and NO. NO acts as a vasodilator with beneficial effects on vascular health[129–132] and has an anti-inflammatory effect under normal physiological conditions[133]. However, NO participates in immune responses by cytokine-activated macrophages which produce NO in high concentrations[133].

SCFA suppressed LPS-stimulated TNF-α[126] from neutrophils and also suppressed TNF-α, IL-1β, IL-6 and NO in RAW 264·7 murine macrophage cells[127]. Moreover, SCFA (0·2–20 mmol/l) lowered the LPS-induced production of TNF-α and interferon-γ in human PBMC in a dose-dependent manner[120]. Butyrate suppressed IL-6 and TNF-α in interferon-γ-stimulated RAW 264·7 murine macrophage cells[128]. Studies[125,126,128] showed that anti-inflammatory effects of SCFA could be mediated by inhibiting the activation of NF-κB (a transcriptional factor involved in the inflammatory response and cell proliferation and TNF-α production[134]). Butyrate is a histone deacetylase inhibitor[134,135]. SCFA (propionate and butyrate) suppressed the release of LPS-stimulated TNF-α and down-regulated NF-κB by facilitating PGE_2 levels and cyclo-oxygenase-2 activities through inhibiting histone deacetylase in PBMC[134] and murine macrophage cell line RAW 264·7 cells[135]. Therefore, SCFA, especially butyrate, exert an anti-inflammatory effect via two potential signalling pathways of NF-κB and histone deacetylase inhibition.

Butyrate also decreased the levels of MCP-1 in a dose-dependent manner with or without LPS in human PBMC[120]. SCFA inhibited the expression of vascular cell adhesion molecule-1 induced by TNF-α and IL-1β in human umbilical vein endothelial cells[136–138]. Butyrate suppressed T-cell activation stimulated by antigen-presenting cells by down-regulating the expression of intracellular cell adhesion molecule-1 and lymphocyte function-associated antigen-3 in monocytes[139].

SCFA and angiopoietin-like protein 4

Angiopoietin-like protein 4 (ANGPTL4) is a 50 kDa prohormone secreted from brown and white adipose tissues, liver, skeletal muscle, intestine and heart. Human ANGPTL4 is mainly expressed in the liver. It is known as fasting-induced adipose factor because ANGPTL4 is up-regulated in white adipose tissue and liver during fasting[110,140], while human plasma ANGPTL4 concentrations are reduced after meal consumption[140]. ANGPTL4 is a lipoprotein lipase inhibitor and thus causes decreased uptake of fatty acids into tissue[110]. In mice, overexpression of ANGPTL4 decreased clearance of TAG-rich lipoproteins and increased circulating TAG levels[141]. A very recent study showed that inhibition of or a lower level of ANGPTL4 is associated with lower risk of CVD in mice and non-human primate models[142]. The suppressed ANGPTL4 may result in increased lipoprotein lipase activity and lipolysis[75,115].

On the other hand, lower serum ANGPTL4 levels are observed in subjects with T2DM compared with normal subjects. An inverse association between plasma glucose levels and HOMA-IR, and serum ANGPTL4 levels was found. These findings suggest that decreased ANGPTL4 could play a role in glucose tolerance[143].

ANGPTL4 induced by fatty acids via PPAR in various tissues appears to reduce cellular lipid overload, oxidative stress and inflammation[144,145]. The SCFA, especially propionate, inhibited lipid synthesis in the presence of acetate as a source of acetyl-CoA in hepatocytes[146]. Propionate and/or butyrate, but not acetate, activated ANGPTL4 production in intestinal (Caco-2, HT-29 and HCT-116) and hepatic (HepG2) cancer cell lines[147] and the entero-endocrine cell line HuTu-80 from the human small intestine[140].

ANGPTL4 is a downstream target gene of PPAR[75]. PPAR, transcription factors with three isoforms (α, β and γ) are a superfamily of nuclear receptors[148]. Fatty acids and lipid-derived substrates are their ligands. PPAR-γ agonists are used as T2DM treatment drugs. PPAR-α, present in liver, heart and skeletal muscle, promotes primarily hepatic fatty acid oxidation, ketone body synthesis and glucose sparing, while PPAR-γ, expressed in the lower intestine, adipose tissue and immunity cells, facilitates an increase in fatty acid storage in adipocytes[148].

Thiazolidinediones (TZD) are strong activators of PPAR-γ which improve insulin sensitivity and facilitate insulin-mediated suppression of gluconeogenesis in the liver and glucose uptake in the skeletal muscle[148,149]. However, PPAR-γ is expressed in adipose tissues but not in muscle, the main insulin-sensitive tissue[148]. Activation of PPAR-γ causes release of adiponectin from mature adipocytes, which stimulates AMP involved in the up-regulation of glucose transporters (especially, GLUT4) in skeletal muscle, the stimulation of increased fatty acid oxidation in mitochondria[148], as well as the down-regulation of gluconeogenesis in the liver[150], consequently leading to improved insulin sensitivity in skeletal muscle[148] and in the liver[149]. Metformin, a T2DM treatment medicine, is a stimulator of AMPK[148]. It is suggested that the combined use of PPAR ligands (for example, TZD) and SCFA could minimise weight gain from TZD releasing ANGPTL4[151].

SCFA and intestinal gluconeogenesis

One potential mechanism for SCFA to prevent T2DM involves intestinal gluconeogenesis (IGN) which is mediated by signalling of the periportal nervous system[152]. Hepatic gluconeogenesis and IGN play opposite roles in glucose homeostasis. IGN might be inversely associated with the risk of T2DM, as beneficial effects of IGN on a reduction in food intake, weight gain and hepatic glucose output, and on improvement in glycaemic control, have been shown[153–155]. In contrast, increased hepatic gluconeogenesis is related to the risk of T2DM[156,157]. The intestine produces approximately 20–25 % of total endogenous glucose in the fasted state[158]. Glucose produced by the intestine is sent to the portal vein. The periportal neural system in the portal vein walls detects glucose and sends a signal to the brain for the modulation of energy and glucose metabolism[158]. Interestingly, butyrate directly promotes IGN gene expression in enterocytes by increasing intracellular cyclic AMP levels in an FFAR2-independent manner[152]. Propionate binding to FFAR3 present in the portal nerves increases IGN gene expression through a portal hypothalamic neural circuit[152]. The benefit of this gut–brain neural circuits has been shown for portal glucose sensing

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Table 3. Summary of synbiotic human intervention studies

Dietary synbiotic intervention	Subjects	Design	period	Outcomes	No effects	Reference
200 ml of synbiotic shake containing 10^8 CFU/ml *Lactobacillus acidophilus*, 10^8 CFU/ml *Bifidobacterium bifidum* and 2 g FOS *v.* 200 ml of the synbiotic shake without bacteria	20 Adults with T2DM aged 50–60 years, 10/group	RD, P, DB, PC	15 d preingestion and 30 d ingestion	↑ HDL-C, ↓ glycaemia	TC, TAG	Moroti *et al.* (2012)[160]
14×10^9 CFU/tablet of probiotic capsule containing seven viable and freeze-dried strains of *L. acidophilus* (2×10^9 CFU), *L. casei* (7×10^9 CFU), *L. rhamnosus* ($1{\cdot}5 \times 10^9$ CFU), *L. bulgaricus* (2×10^8 CFU), *B. breve* (2×10^{10} CFU), *B. longum* (7×10^9 CFU), *Streptococcus thermophilus* ($1{\cdot}5 \times 10^9$ CFU) and 100 mg FOS *v.* placebo containing the same substance without bacteria	54 Adults with T2DM aged 35–70 years, 27 per group	RD DB, PC, P	8 weeks	↓ hs-CRP, ↑ GSH, ↓ fasting glucose		Asemi *et al.* (2013)[161]
Two tablets/d of 500 mg metformin + two tablets/d of protexin containing *L. acidophilus* (1×10^8 CFU), *L. casei* (5×10^8 CFU), *L. bulgaricus* ($1{\cdot}5 \times 10^8$ CFU), *L. rhamnosus* ($7{\cdot}5 \times 10^7$ CFU), *B. longum* ($2{\cdot}5 \times 10^7$ CFU), *B. breve* (5×10^7 CFU), *S. thermophilus* (5×10^7 CFU) and 350 mg FOS *v.* two tablets/d of 500 mg metformin + two tablets/d of placebo (120 mg of starch)	63 Subjects with NASH	RD, DB, PC, P	24 weeks	↓ Fasting glucose, ↓ TAG, ↓ cholesterol, ↓ BMI, ↓ ALT, ↓ AST		Shavakhi *et al.* (2013)[17]
Two sachets/d of Lepicol containing 2×10^8 CFU of strains of *L. plantarum*, *L. delbrueckii* ssp. *bulgaricus*, *L. acidophilus*, *L. rhamnosus*, *B. bifidum* and 3 g FOS/d *v.* control (usual care)	20 Subjects with NASH	OL, RD, C	26 weeks	↓ Liver fat within the synbiotic group *v.* baseline, ↓ AST within and between groups	Fasting glucose, TC, TAG, HDL-C, LDL-C, ALT, liver stiffness	Wong *et al.* (2013)[167]
Two tablets/d of protexin containing 2×10^8 CFU of strains (*L. casei*, *L. rhamnosus*, *Streptococcus thermophilus*, *B. breve*, *L. acidophilus*, *B. longum* and *L. bulgaricus*) and 250 mg FOS *v.* two tablets/d of placebo (250 mg maltodextrin)	52 Subjects with NAFLD	RD, DB, PC, P	28 weeks	↓ Fasting glucose, ↓ insulin, ↓ HOMA-IR, ↓ ALT, ↓ AST, ↓ GGT, ↓ hs-CRP, ↓ TNF-α, ↓ NF-κB		Eslamparast *et al.* (2014)[168]
Two tablets/d of protexin containing 2×10^8 CFU of strains (*L. casei*, *L. rhamnosus*, *S. thermophilus*, *B. breve*, *L. acidophilus*, *B. longum* and *L. bulgaricus*) and 250 mg FOS *v.* two tablets/d of placebo (250 mg maltodextrin)	38 Subjects with the MetS	RD, DB, PC, P	28 weeks	↓ Fasting glucose, insulin and HOMA-IR, ↑ QUICKI within the treatment group *v.* baseline	BMI, LDL-C, waist circumstance	Eslamparast *et al.* (2014)[163]
(a) 120 g/d of synbiotic bread containing *L. sporogenes* (1×10^8 CFU) and 0·07 g inulin as prebiotic per 1 g (b) Probiotic (c) Control bread	78 (or 81) patients with T2DM aged 35–70 years, 26 (or 27)/group	RD, P, DB, PC	8 weeks	↓ Insulin, ↓ HOMA-IR, ↓ HOMA for β-cell function, ↓ TAG, ↓ VLDL-C, ↓ TC:HDL-C, ↑ HDL-C, ↑ NO, ↓ MDA *v.* probiotic and control breads	Fasting glucose, QUICKI, hs-CRP, TC, LDL-C, TAC, GSH, catalase, liver enzymes, Ca, Mg, BP	Asemi and colleagues: Tajadadi-Ebrahimi *et al.* (2014), Bahmani *et al.* (2016), Shakeri *et al.* (2014)[164,170,171]
Synbiotic food containing *L. sporogenes* (27×10^7 CFU) and 1·08 g inulin per d *v.* control food (the same substance without probiotic bacteria and prebiotic inulin)	62 Diabetic patients aged 35–70 years	RD, DB, CO, C	6 weeks	↓ Insulin, ↓ hs-CRP, ↑ GSH, ↑ uric acid	Fasting glucose, HOMA-IR, TAG, HDL-C, TAC	Asemi *et al.* (2014)[165]
Synbiotic food containing *L. sporogenes* (18×10^7 CFU) and 0·72 g inulin per d *v.* control food (the same substance without probiotic bacteria and prebiotic inulin)	52 Pregnant women, primigravida, aged 18–35 years in their third trimester	RD, PC	9 weeks	↓ Insulin, ↓ HOMA-IR, ↑ QUICKI	Fasting glucose, hs-CRP	Taghizadeh & Asemi (2014)[166]
(a) Synbiotic group (4×10^9 CFU *L. salivarius* UBL S22 and 10 g/d of FOS) (b) probiotic (4×10^9 CFU *L. salivarius*) (c) placebo capsule (gelatin)	45 Healthy adults aged 20–25 years, 15/group	RD, PC, P, SB	6 weeks	↓ Fasting glucose within all groups *v.* baselines, ↓ insulin and ↓ HOMA-IR in probiotic and synbiotic groups *v.* placebo		Rajkumar *et al.* (2015)[162]
Synbiotic capsule containing *L. acidophilus* (2×10^9, *L. casei* 2×10^9, *B. bifidum* 2×10^9 CFU/g and 800 mg inulin	60 Overweight diabetic patients with CHD aged 40–85 years, 30/group	RD DB, PC, P	12 weeks	↓ Fasting glucose, ↓ insulin, ↓ HOMA for β-cell function, ↑ QUICKI, ↓ HDL-C		Tajabadi-Ebrahimi *et al.* (2017)[13]
Two tablets/d of protexin containing 2×10^8 CFU of strains (*L. casei*, *L. rhamnosus*, *S. thermophilus*, *B. breve*, *L. acidophilus*, *B. longum and L. bulgaricus*) and 250 mg FOS *v.* two tablets/d of placebo (250 mg maltodextrin)	50 Lean subjects with NAFLD	RD DB, PC, P	28 weeks	↓ Fasting glucose, ↓ TAG, ↓ TC, ↓ hs-CRP, ↓ TNF-α, ↓ NF-κB p65, ↓ hepatic steatosis, ↓ fibrosis, ↓ AST	HOMA-IR, insulin, QUICKI, HDL-C, LDL-C, ALT, GGT	Mofidi *et al.* (2017)[169]

CFU, colony-forming unit; FOS, fructo-oligosaccharide; T2DM, type 2 diabetes mellitus; RD, randomised; P, parallel; DB, double blind; PC, placebo–control; HDL-C, HDL-cholesterol; TC, total cholesterol; hs-CRP, high-sensitivity C-reactive protein; GSH, glutathione; NASH, non-alcoholic steatohepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; OL, open label; C, control; LDL-C, LDL-cholesterol; NAFLD, non-alcoholic fatty liver disease; HOMA-IR, homeostasis model assessment of insulin resistance; GGT, γ-glutamyltransferase; MetS, metabolic syndrome; QUICKI, quantitative insulin sensitivity check index; VLDL-C, VLDL-cholesterol; MDA, malondialdehyde; TAC, total antioxidant capacity; BP, blood pressure; CO, cross-over; SB, single blind.

initiated by a protein-enriched diet, resulting in decreased food intake[154].

IGN-deficient mice (with disruption of the glucose 6-phosphatase (G6Pase) catalytic subunit in the intestine) fed a SCFA- or FOS-rich diet showed no favourable effect on glucose and insulin with no change in body weight, compared with normal mice fed a SCFA- or FOS-rich diet[152]. Moreover, normal mice fed a high-fat/high-sucrose diet supplemented with FOS showed improved glucose and insulin tolerance and decreased fat mass, whereas these metabolic benefits were absent in IGN-deficient mice fed the same diet with FOS[152]. Therefore, IGN appears to be essential for the effect of SCFA on glucose homeostasis.

Synbiotics and effects of synbiotics on glucose metabolism in human interventions

A combination of probiotics and prebiotics is described as a synbiotic[77]. *Lactobacillus acidophilus* DSM20079 induced 14·5-fold more butyrate in the presence of inulin or pectin than in the presence of glucose[159].

Human interventions of synbiotics are shown in Table 3. Eleven of twelve studies of synbiotics have shown favourable effects on glucose metabolism[13,17,160–169]. Three[17,168,169] of four[17,167–169] studies in subjects with non-alcoholic fatty liver disease have shown a positive effect on glucose control. The Asemi research group conducted a randomised, double-blind, placebo-controlled trial in subjects with T2DM; the consumption of synbiotic bread (containing the probiotic *Lactobacillus sporogenes* (1×10^8 CFU) and 0·07 g inulin per 1 g as prebiotic) for 8 weeks improved insulin metabolism, lipid profiles and plasma NO and malondialdehyde levels, compared with the probiotic alone (*Lactobacillus sporogenes*; 1×10^8 CFU) and a control bread[164,170,171].

In summary, a very limited number of interventions have shown beneficial effects on glucose metabolism. More pronounced effects of synbiotics on glycaemic control and inflammation have been observed than with the use of probiotics alone[15].

Conclusion

Individuals with obesity or T2DM have been observed to have a different composition of gut microbiota. Altered gut microbiota may contribute to the development of T2DM. The composition of gut microbiota can be beneficially modified by probiotics and/or prebiotics to maintain glucose homeostasis. The potential mechanisms of action could involve insulinotropic and satiety effects mediated by gut hormones, GLP-1 and PYY, a β-cell-protective effect by reduced oxidative stress and lowered pro-inflammatory cytokines, anti-lipolytic activities and enhanced insulin sensitivity via GLUT4 through the up-regulation of AMPK signalling in tissues. An additional role of SCFA is in glycaemic control through IGN and mediated by the periportal nervous system. The antidiabetic effects of SCFA require further research. Use of resistant starch and synbiotics may become a diabetic nutritional strategy. Overall human interventions of probiotic and prebiotics showed mixed findings, so further work is required.

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