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ORIGINAL CONTRIBUTION

Effect of probiotics and synbiotics on blood glucose: a systematic review and meta-analysis of controlled trials

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Abstract
Purpose High fasting blood glucose (FBG) can lead to chronic diseases such as diabetes mellitus, cardiovascular and kidney diseases. Consuming probiotics or synbiotics may improve FBG. A systematic review and meta-analysis of controlled trials was conducted to clarify the effect of probiotic and synbiotic consumption on FBG levels.
Methods PubMed, Scopus, Cochrane Library, and Cumulative Index to Nursing and Allied Health Literature databases were searched for relevant studies based on eligibility criteria. Randomized or non-randomized controlled trials which investigated the efficacy of probiotics or synbiotics on the FBG of adults were included. Studies were excluded if they were review articles and study protocols, or if the supplement dosage was not clearly mentioned.
Results A total of fourteen studies (eighteen trials) were included in the analysis. Random-effects meta-analyses were conducted for the mean difference in FBG. Overall reduction in FBG observed from consumption of probiotics and synbiotics was borderline statistically significant (−0.18 mmol/L 95 % CI −0.37, 0.00; $p = 0.05$). Neither probiotic nor synbiotic subgroup analysis revealed a significant reduction in FBG. The result of subgroup analysis for baseline FBG level ≥7 mmol/L showed a reduction in FBG of 0.68 mmol/L (−1.07, −0.29; $\rho < 0.01$), while trials with multiple species of probiotics showed a more pronounced reduction of 0.31 mmol/L (−0.58, −0.03; $\rho = 0.03$) compared to single species trials.
Conclusion This meta-analysis suggests that probiotic and synbiotic supplementation may be beneficial in lowering FBG in adults with high baseline FBG (≥7 mmol/L) and that multispecies probiotics may have more impact on FBG than single species.

Keywords Probiotics · Synbiotics · Fasting blood glucose · Hyperglycemia

Introduction

Glucose is an irreplaceable source of energy for the human body [48] and a primary source of energy for the brain; therefore, its availability influences physiological processes [34]. A fasting blood glucose (FBG) level between 4.4 and 6.1 mmol/L is considered normal, and levels outside this range indicate medical abnormalities [1]. A continuous high level of FBG is termed hyperglycemia [16]. Among the several diseases associated with hyperglycemia, diabetes mellitus is the most common. Untreated continuous high FBG may lead to heart disease, eye, kidney, and nerve damage [45]. Hyperglycemia may be the result of genetic susceptibility or an unhealthy lifestyle [42, 65]. Although the genetic basis of hyperglycemia is yet to be identified, there is strong evidence suggesting that modifiable risk factors such as poor dietary behavior, obesity, and physical inactivity are the main non-genetic determinants [62].

While proper nutrition and regular physical activity (as the first line of therapy for hyperglycemia) have been

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shown to ameliorate hyperglycemia [33, 66], maintaining a healthy lifestyle is difficult [10]. Glucose-lowering medications may be recommended to control persistent hyperglycemia [1, 42]; however, pharmacotherapy is usually accompanied by side effects and their adherence is limited [10]. Recently, there has been an increasing interest in dietary constituents and supplements that can assist in reducing blood glucose (BG). Among these, the therapeutic use of probiotics (beneficial bacteria) and prebiotics (some types of fiber which stimulate the growth and/or activity of certain gut bacteria [36]) in clinical practice has been well studied [5, 9, 49]. Probiotics are live microorganisms shown to offer some health benefits when consumed in adequate amounts [51]. Dietary supplements that combine probiotics and prebiotics in a form of synergism are termed synbiotic. Synbiotics beneficially affect the host by improving the survival and implantation of live cultures in the gastrointestinal tract [36].

The composition of probiotic bacteria in the gut ecosystem has been shown to improve blood lipid profiles, hypertension, obesity, and general health [8, 21, 27, 32]. The gut microbiota plays a pivotal role in maintaining homeostasis in the human host, as well as in the pathogenesis of hyperglycemia [46]. The glucose-lowering effect of *Lactobacillus* and *Bifidobacteria* has been investigated in several human studies [3, 19, 20, 28, 52]. Some trials have suggested that probiotic or synbiotic consumption may prevent or reduce elevated BG in diabetic or non-diabetic participants [3, 19, 38]. A possible explanation is that the gut flora modification caused by probiotic bacteria stimulates glucose absorption by producing insulinotropic polypeptides and glucagon-like peptides [2]. However, other studies did not observe any improving effect of probiotics and synbiotics on FBG [28, 30, 31, 54]. Due to the inconsistency observed in the literature, the current systematic review and meta-analysis of controlled trials aimed to investigate the effectiveness of probiotics or synbiotics on human BG concentration. Furthermore, this study aimed to investigate the possible moderating influence of the dose, duration, and type of supplementation, and the baseline FBG levels on the overall effect of probiotic and synbiotic consumption on FBG level. The findings from this meta-analysis may provide further information on the effectiveness of probiotic and synbiotic consumption, their effective duration, and the dose of supplementation to convey health benefits and lower FBG.

Methods

Literature search

Online databases of PubMed (MEDLINE), Scopus, Cochrane Library, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched until February 2015. In order to find relevant papers, the following Standard Medical Subject Headings (MeSH) terms were used, from the beginning of the databases: probiotics, *Lactobacillus*, *Bifidobacterium*, cultured milk Products, yogurt, synbiotics, oligosaccharide, and inulin in combination with blood glucose, blood sugar, diabetes mellitus (DM), cardiovascular diseases (CVD), and metabolic syndrome.

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis: The PRISMA Statement was followed [39] as a guideline for conducting and reporting this systematic review and meta-analysis. This systematic review is registered with the International Prospective Register for Systematic Review (PROSPERO) with the registration number CRD42014014293.

Study eligibility and selection

Randomized controlled trials or quasi-experimental trials (non-randomized controlled trials), with the accessible text in English, which investigated the efficacy of probiotics or synbiotics (i.e., the presence of live culture) on the FBG of adults (age $\geq$18 years) were included. Studies were excluded if they assessed the mixture of probiotics and other supplements (such as micronutrients or other dietary constituents) unless a controlled arm was provided for the mixing ingredient. Controlled trials which investigated the effect of probiotics or synbiotics on pregnant or lactating women were excluded. Review articles and study protocols were not included. Studies where the dose of supplemented probiotic (colony-forming unit, CFU) was not mentioned clearly were excluded. Studies using sweeteners or their alternatives for supplementation were also excluded. Studies were also excluded if the postprandial effect of probiotics or synbiotics on FBG was examined.

The study process is illustrated in Fig. 1. Two researchers conducted the initial screening of studies based on the titles and abstracts. The next phase involved a review of abstracts and an examination of the full text based on the eligibility criteria. The decision regarding the inclusion or exclusion of articles was made through an agreement between the two researchers. A third researcher was involved in decision making in case of any disagreement between the first two researchers.

Quality assessment and data extraction

The methodological quality of included articles was assessed using the Rosendal scale [64]. An overall Rosendal score of 60 % was regarded as being of excellent methodological quality [29]. Studies were included if they had a Rosendal score of 50 % or higher. The

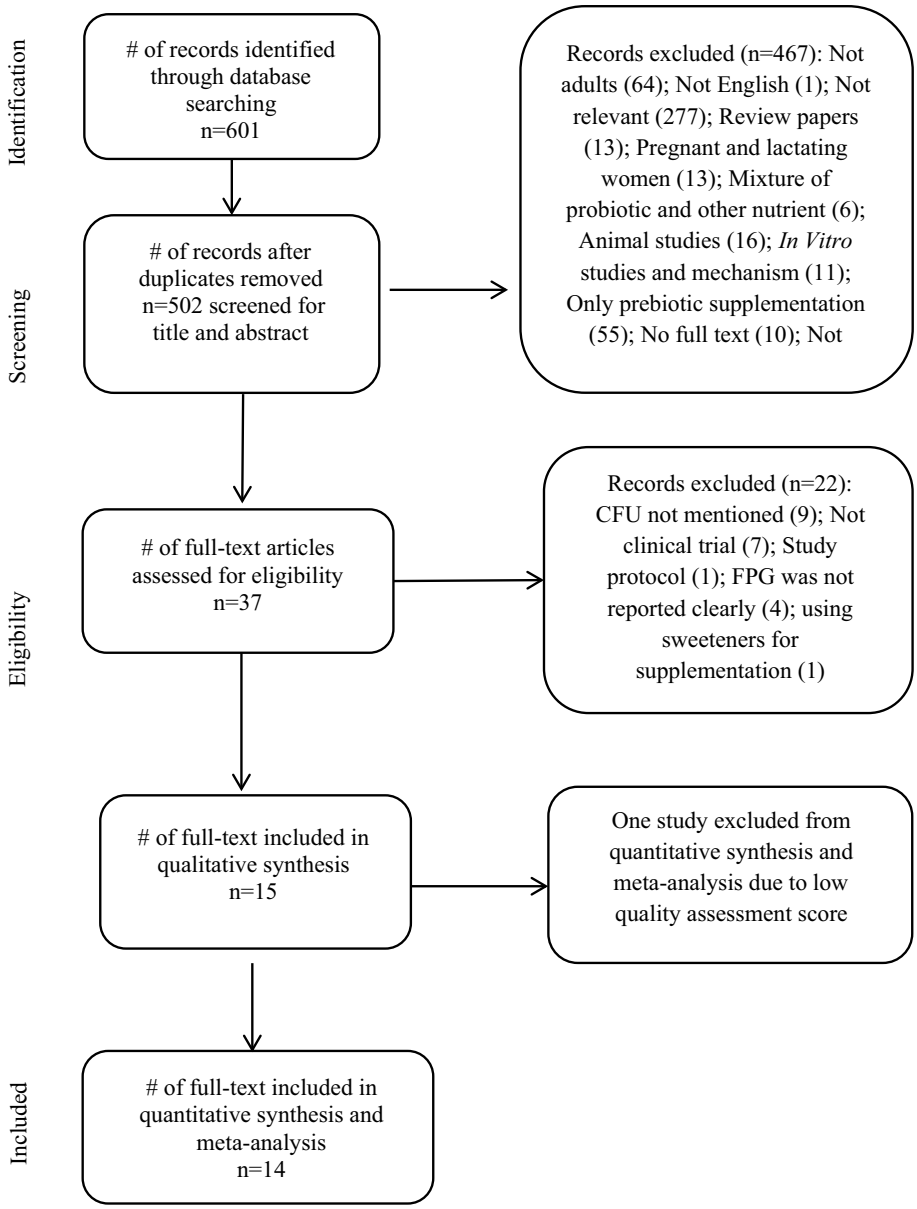

Fig. 1 Study flow diagram of systematic search of literature for the effect of probiotics and synbiotics on blood glucose

'checklist of items to consider in data collection' from the *Cochrane Handbook for Systematic Review of Interventions* [26] was followed to extract relevant data. The measurements reported for FBG were extracted as the main outcome. The preferred unit for reporting FBG in this study was mmol/L, and all measurements reported in mg/dl were converted to this preferred unit of measurement.

Data synthesis and analysis

The meta-analysis was conducted using RevMan software (Cochrane Review Manager, version 5.3). The effect of probiotics and synbiotics on FBG was presented as the mean difference of FBG between the intervention groups and control groups. For the one study which was not a controlled trial [28], a comparable parallel trial was considered as control. The mean and standard deviation (SD) of changes were reported in seven studies. The missing SD of change for the remainder of studies was imputed using the mean and SD of change reported in those seven studies. A correlation coefficient (r) of 0.68 was calculated. A DerSimonian and Laird random-effect model was used to conduct the meta-analysis as the studies were heterogeneous in terms of their methodology and design [18]. The I^2 index was used to assess the heterogeneity of the pooled effect. Low, moderate, and high heterogeneity was interpreted based on I^2 index of 25, 50, and 75 %, respectively [26]. A p value of less than 0.05 was considered a statistically significant effect.

Sensitivity and subgroup analysis

A one-by-one study sensitivity analysis was performed by assessing the effect of individual studies on overall results of meta-analysis. To analyze the robustness of the meta-analysis based on the computed SD of change, sensitivity analysis of different correlation coefficients ($r = 0.2$ and 0.8) was also performed.

Subgroup analysis was limited to trials reporting probiotics as the intervention compared with trials with synbiotics as the reported intervention. Intervention duration $\geq$8 weeks was compared with duration of <8 weeks. Dose dependency was analyzed by limiting the studies to those with a probiotic dose $\geq 10^{10}$ CFU per day, and the results were compared with those with less than 10^{10} CFU daily. The effect of the number of species (single species, multiple species) of probiotic was also assessed using subgroup analyses. Using fermented milk or yogurt as the probiotic source was compared with other supplements and foods as the source of probiotics. In another subgroup analysis, studies were compared in terms of the baseline FBG level of higher or lower than 7 mmol/L. To assess the influence of body weight on the meta-analysis results, the subgroup of studies with participants' mean baseline body mass index (BMI) $\geq$30 kg/m^2 was performed. The difference between subgroups was analyzed by assessing the heterogeneity between subgroups, and $p < 0.05$ was considered as significant difference.

Results

Overview of studies and study quality

Fifteen studies were included in the systematic review, of which fourteen (eighteen controlled trials, 1002 participants) were included in the final meta-analysis. The study by Ivey et al. [28] had 3 treatment arms and by Shakeri et al. [52] and Rajkumar et al. [50] had 2 treatment arms which were eligible for the study; therefore, 18 trials overall were included in the final meta-analysis. All included studies had a Rosendal score of more than 50 % except for Barreto et al. [6], which was excluded from the meta-analysis due to its low Rosendal score (Supplemental Table 1). The study by Ostadrahimi et al. [44] reported four different colony counts on the fermented milk product used in the intervention, on days 1, 7, 14, and 21 of the trial. Only the colony count measured for the first day of the trial was considered in this study.

The characteristics of the included studies are presented in Table 1. With regard to the participants' body mass index (BMI), three studies reported a significant reduction in BMI in the groups supplemented with probiotics [31, 53] and synbiotics [54] compared to the control group. Two studies did not report post-intervention BMI measurements [50, 54], and the rest did not report any significant change of body weight after intervention.

Ten studies [3, 19, 20, 28, 38, 43, 44, 52, 60] measured the dietary intake of participants, of which three [20, 38, 60] did not report the method of measurement. One study measured dietary intake only pre-intervention [28], while the other nine measured the dietary intake pre- and post-intervention. No significant changes were found in the nutritional intake of participants from pre to post. Eight studies reported that participants were advised to maintain their habitual diet and not to alter it during the intervention period [3, 19, 38, 44, 52, 54, 60].

Information on supplement protocol

As shown in Table 1, in three studies synbiotics were consumed as a source of live culture, one contained inulin [52], and two other contained fructo-oligosaccharide as a prebiotic [20, 54]. In three trials, volunteers were assigned to probiotic yogurt [19, 30, 38], while one trial used probiotic yogurt along with a probiotic capsule as the intervention [28]. Four studies used capsules [3, 20, 31, 50], and one study used tablets [54] as the source of probiotic. Ogawa et al. [43], Ostadrahimi et al. [44], and Tripolt et al. [60] used milk as the carrier. One study used bread [52], and another used cheese [53]. In six of the controlled trials, a single species of probiotic was supplemented to participants [30, 31, 43, 52, 53, 60]. Three studies used the combination of two *L. acidophilus* La5 and *B. lactic* Bb12 strains [19, 28, 38], while the remainder used multiple strains of probiotic bacteria. The total daily dose of probiotic consumption varied between 4.8×10^7 [44] to 1.5×10^{11} CFU [53], and the duration of supplementation varied between 3 [53] to 28 weeks [20]. All studies reported a good level of compliance. Except for four studies, which did not discuss adverse effects [28, 50, 54, 60], the rest of trials did not report any side effects of consuming probiotics or synbiotics.

Meta-analysis results of the effect of probiotics and synbiotics on FBG

The meta-analysis of the effect of probiotics and synbiotics on FBG is presented in Fig. 2. There was an overall reduction in FBG observed from consumption of probiotics and synbiotics which was borderline statistically significant (−0.18 mmol/L 95 % CI −0.37, 0.00; $p = 0.05$). The subgroup analysis of probiotics did not result in a significant reduction in FBG (−0.17 mmol/L, 95 % CI −0.37, 0.03; $p = 0.10$). Subgroup analysis of synbiotics also failed to find a significant reduction in FBG (−0.35 mmol/L, 95 % CI −0.84 to 0.13; $p = 0.15$). A significant heterogeneity

Table 1 Characteristics of included studies evaluating the effect of probiotic and synbiotics consumption on FBG

Study/year	Design/location	Intervention/control (Duration, weeks)	Source (daily dose, CFU)	Supplement information probiotic/prebiotic	Participants (age, year)	Intervention *n* (M %); *n* control (M %)	Baseline FBG (mmol/L)
Asemi et al. [3]	R, PC, DB/Iran	Probiotic/Placebo (8)	Capsules (3.9×10^{10})	*L. acidophilus* + *L. casei* + *L. rhamnosus* + *L. bulgaricus* + *Bifidobacterium breve* + *B. longum* + *Streptococcus thermophilus*	T2D (35–70)	27 (30 %); 27 (30 %)	7.98 ± 3.08
Ejtahed et al. [19]	R, C, DB/Iran	Probiotic yogurt/Conventional yogurt (6)	Food (1.1×10^{8})	*L. acidophilus* La5 + B. *lactis* Bb12	T2D (30–60)	30 (37 %); 30 (40 %)	8.06 ± 2.49
Eslamparast et al. [20]	R, PC, DB/Iran	Synbiotic/Placebo (28)	Capsules (4×10^{8})	*L. Casei* + *L. rhamnosus* + *Streptococcus thermophiles* + *Bifidobacterium breve* + *L.acidophilus, Bifidobacterium longum and L. bulgaricus/Fructo-oligosaccharide*	MetS (38–56)[a]	19(39.5 %); 19 (39.5 %)	5.62 ± 1.12
Ivey et al. [28]	R, P, DB/Australia	Probiotic yogurt +probiotic capsule/Control milk + placebo capsule (6)	Food/Capsule (6×10^{9})	*L. acidophilus La5* + *B. lactic Bb12*	OW (60–76)[a]	40 (62.5 %); 40 (57.5 %)	5.53 ± 0.57
Ivey et al. [28]	R, P, DB/Australia	Probiotic yogurt + placebo capsule/Control milk + placebo capsule (6)	Food/Capsule (3×10^{9})	*L. acidophilus* La5 + *B. lactic* Bb12	OW (59–77)[a]	37 (67.5 %); 40 (57.5 %)	5.64 ± 1.01
Ivey et al. [28]	R, P, DB/Australia	Control milk + probiotic capsule/Control milk + placebo capsule (6)	Food/Capsule (3×10^{9})	*L. acidophilus* La5 + *B. lactic* Bb12	OW (58–72)[a]	39 (59 %); 40 (57.5 %)	5.59 ± 1.15
Jones et al. [30]	R, PC, multicenter, DB/Czech Republic	Probiotic yogurt/Placebo yogurt (6)	Food (1×10^{11})	*L. reuteri* NCIMB 30,242	Healthy (18–74)	59 (37 %); 61 (34 %)	5.18 ± 0.91
Jung et al. [31]	R, PC, DB/Korea	Probiotics/Placebo (12)	Capsule (6×10^{10})	*L. gasseri* BNR17	OB or OW (19–60)	28 (46 %); 29 (45 %)	5.73 ± 0.91
Mohamadshahi et al. [38]	R, C, DB/Iran	Probiotic yogurt/Conventional yogurt (8)	Food (1.1×10^{9})	*L. acidophilus* La5 + *B. lactic* Bb12	T2D + OB or OW (47–59)[a]	21 (24 %); 21 (24 %)	9.72 ± 2.58
Ogawa et al. [43]	PC, SB/Japan	Milk with probiotic/Milk without probiotic (4)	Food (1×10^{11})	*L. gasseri* SBT2055 (LG2055)	Hypertriacylglycerolemia (44–58)[a]	20 (75 %); 20 (75 %)	5.18 ± 0.64
Ostadrahimi et al. [44]	R, PC, DB/Iran	Probiotic fermented milk (Kefir)/Conventional fermented milk (8)	Food (4.8×10^{7})	*L. casei* + *L.acidophilus* + *Bifidobacteria*	T2D (35–65)	30 (60 %); 30 (53.3 %)	8.98 ± 3.20

Table 1 continued

Study/year	Design/location	Intervention/control (Duration, weeks)	Source (daily dose, CFU)	Supplement information probiotic/prebiotic	Participants (age, year)	Intervention *n* (M %); *n* control (M %)	Baseline FBG (mmol/L)
Rajkumar et al. [50]	R, PC, DB/India	Probiotic capsule/Placebo capsule (6)	Capsule (1.12×10^{11})	*B. longum* + *B. infantis, B. Breve* + *L. acidophilus* + *L. paracasei* + *L. delbrueckii subsp. Bulgaricus* + *L. plantarum* + *Streptococcus salivarius subsp. thermophilus*	OW (40–60)	15 (50 %); 15 (50 %)	4.88 ± 0.056
Rajkumar et al. [50]	R, C/India	Probiotic capsule + omega-3 capsule/omega-3 capsule (6)	Capsule (1.12×10^{11})	*B. longum* + *B. infantis, B. Breve* + *L. acidophilus* + *L. paracasei* + *L. delbrueckii subsp. Bulgaricus* + *L. plantarum* + *Streptococcus salivarius subsp. thermophilus*	OW (40–60)	15 (50 %);15 (50 %)	4.82 ± 0.119
Shakeri et al. [52]	R, C, DB/Iran	Probiotic bread/Control bread (8)	Food (1.2×10^{10})	*L. sporogenes/Inulin*	T2D (35–70)	26 (19 %); 26 (19 %)	7.19 ± 2.05
Shakeri et al. [52]	R, C, DB/Iran	Synbiotic bread/Control bread (8)	Food (1.2×10^{10})	*L. sporogenes/Inulin*	T2D (35–70)	26 (19 %); 26 (19 %)	7.91 ± 3.25
Sharafedtinov et al. [53]	R, PC, P, DB/Estonia	Probiotic cheese/Control cheese (3)	Food (1.5×10^{11})	*L. plantarum* TENSIA	Mets + Arterial hypertonia (30–69)	25 (36 %); 11 (27 %)	7.16 ± 2.84
Shavakhi et al. [54]	R, PC, DB/Iran	Synbiotic +med/Placebo +med (24)	Tablet (1.9×10^{9})	*L. acidophilus, L. casei, L. rhamnosus, L.bulgaricus, Bifidobacterium breve, Bifidobacterium longum, Streptococcus thermophiles/ Fructo-oligosaccharide*	NASH (18–75)	31 (55 %); 32 (53 %)	5.48 ± 1.81
Tripolt et al. [60]	R, C,/Austria	Probiotic fermented milk/control (12)	Food (6.5×10^{9})	*L. casei Shirota*	MetS (40–62)[a]	13 (69 %); 15 (60 %)	6.1 ± 0.9

Values are presented as mean (SD) or mean of change (SD of change)

SB single blind, *DB* double blind, *T2D* type 2 diabetes, *MetS* metabolic syndrome, *OB* obesity, *OW* overweight, *NASH* nonalcoholic steatohepatitis, *C* controlled, *P* parallel, *PC* placebo control, *CO* crossover, *R* randomized, *FBG* fasting blood glucose, *CFU* colony-forming unit, and *M* male

[a] The age range presented for these studies is estimated from the mean (SD). The actual age ranges were not presented in the article

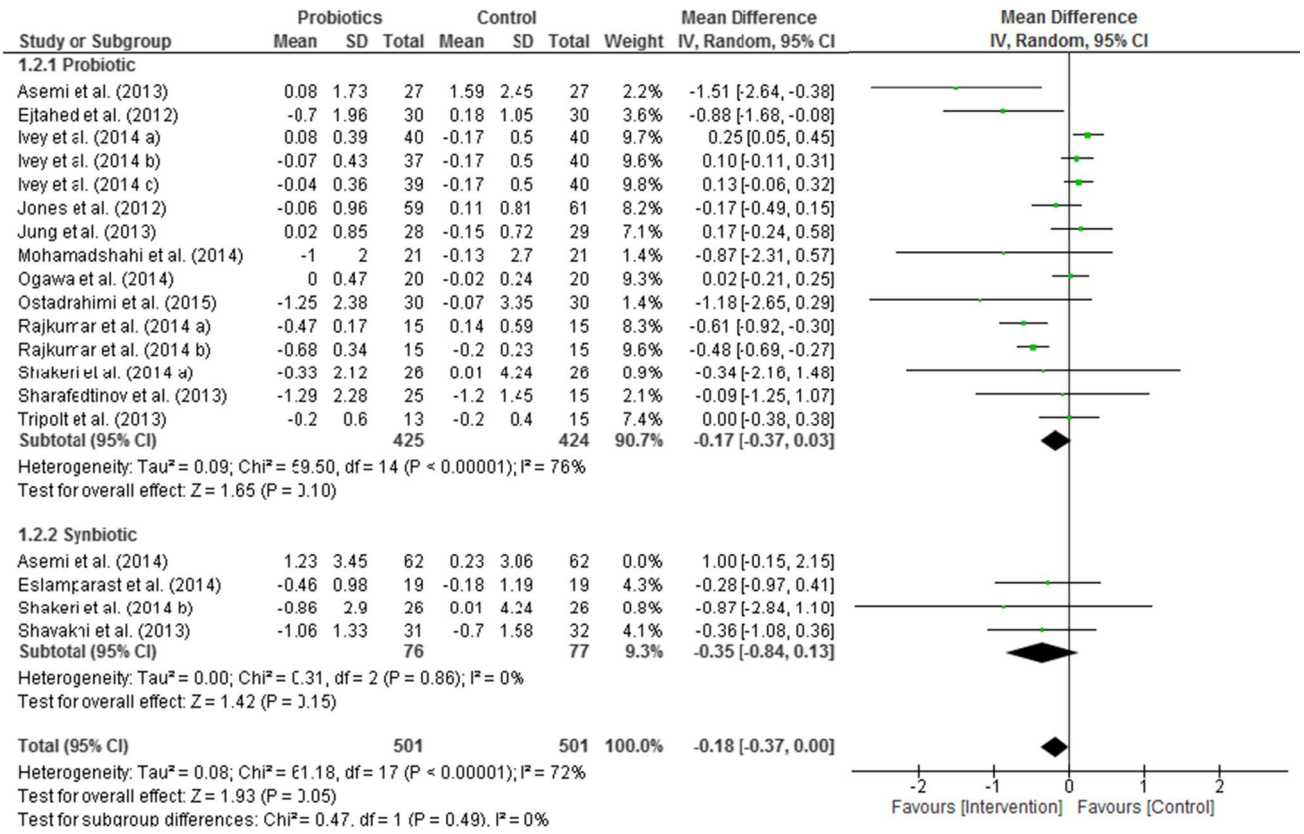

Fig. 2 Forest plot of the effect of probiotics and synbiotics consumption on FBG. A random-effect model was used to analysis the effectiveness of intervention. Effect of each trial was presented as weight (%), and mean difference and 95 % CI

was observed in the probiotics subgroup (I^2 = 76 %, p = < 0.01) and overall meta-analysis results (I^2 = 72 %, p = < 0.01). No heterogeneity was observed in the synbiotics subgroup (I^2 = 0 %, p = 0.86) (Fig. 2).

Sensitivity and subgroup analysis

The sensitivity analysis of individual studies was performed by excluding each study and evaluating the changes on overall results of the meta-analysis. Excluding the study by Ivey et al. [28] significantly improved the meta-analysis results on the FBG reduction effect of probiotics (overall effect −0.31 mmol/L, 95 % CI −0.52, −0.11). No significant effect on the overall meta-analysis or subgroup (probiotics and synbiotics) analysis results was observed by excluding other studies. Sensitivity analysis using alternative correlation coefficient (r = 0.2 and 0.8) was also conducted (Supplemental Table 2). Increasing the correlation from 0.68 to 0.80 increased the overall effect slightly, and reducing the correlation to 0.20 decreased it. However, since the correlation coefficient was calculated based on the SD of the change reported in the studies included in the analysis, the meta-analysis is robust to the imputed r = 0.68.

The subgroup analyses of the effect of duration, source, dose, BMI, and the number of probiotics species are presented in Table 2. Although the reduction observed after supplementation for duration ≥8 weeks was more pronounced than for duration less than 8 weeks, the reduction did not reach statistical significance. Consuming probiotics as supplements resulted in a higher reduction in FBG compared to fermented milk and yoghurt. Daily dose of probiotics supplementation ≥10^{10} CFU showed a higher reduction in FBG compared to dose <10^{10} CFU; however, the reduction observed was not statistically significant. The result of subgroup analysis for baseline FBG level ≥7 mmol/L showed a reduction in FBG of 0.68 mmol/L (−1.07, −0.29; ρ < *0.01*), while there was a nonsignificant trend observed with increasing FBG for the subgroup of studies with baseline FBG <7 mmol/L. The subgroup of trials with baseline BMI <30 kg/m^2 also showed a significant reduction in FBG of 0.25 mmol/L (−0.47, −0.03; ρ = *0.03*). The subgroup of studies with multiple species of probiotics showed a more pronounced reduction of 0.31 mmol/L (−0.58, −0.03; ρ = *0.03*) compared to those with single species. The subgroups of interventions as probiotics supplements, food, or a combination of probiotics and supplement showed more pronounced reduction

Table 2 Results of subgroup analysis of included randomized controlled trials in meta-analysis of the effect of probiotic and synbiotic on FPG

Subgroups	Trials, *n*	Mean difference (95 % CI) of blood glucose, mmol/L	Test for subgroup difference
Intervention duration ≥8 weeks	$n = 9$	−0.29 (−0.63, 0.05; $\rho = 0.09$)	$I^2 = 0$ %, $\rho = 0.47$
Intervention duration <8 weeks	$n = 9$	−0.14 (−0.37, 0.09; $\rho = 0.23$)	
Source of probiotic: fermented milk or yoghurt	$n = 8$	0.00 (−0.18, 0.18; $\rho = 0.96$)	$I^2 = 58.7$ %, $\rho = 0.12$
Source of probiotic: other supplements and foods	$n = 10$	*−0.31 (−0.61, 0.00; $\rho = 0.05$)*	
Probiotic dose $<10^{10}$	$n = 9$	−0.00 (−0.19, 0.19; $\rho = 0.99$)	$I^2 = 86.4$ %, $\rho = 0.00$
Probiotic dose $\geq 10^{10}$	$n = 9$	*−0.29 (−0.55, −0.03; $\rho = 0.03$)*	
Baseline FBG ≥7 mmol/L	$n = 8$	*−0.68 (−1.07, −0.29; $\rho < 0.01$)*	*$I^2 = 91.7$ %, $\rho < 0.001$*
Baseline FBG <7 mmol/L	$n = 10$	0.09 (−0.00, 0.19; $\rho = 0.06$)	
Baseline BMI ≥30 kg/m^2	$n = 6$	0.02 (−0.25, 0.29; $\rho = 0.89$)	$I^2 = 55.8$ %, $\rho = 0.13$
Baseline BMI <30 kg/m^2	$n = 12$	*−0.25 (−0.47, −0.03; $\rho = 0.03$)*	
Single species of probiotic	$n = 7$	−0.01 (−0.16, 0.14; $\rho = 0.89$)	$I^2 = 70$ %, $\rho = 0.07$
Multiple species of probiotics	$n = 11$	*−0.31 (−0.58, −0.03; $\rho = 0.03$)*	
Supplementation	$n = 9$	0.16 (−0.19, 0.08; $\rho = 0.16$)	$I^2 = 0$ %, $\rho = 0.73$
Food based	$n = 9$	−0.13 (−0.33, 0.06; $\rho = 0.17$)	

Changes in blood glucose are presented as mean difference and 95 % confidence interval. Heterogeneity (I^2) is presented by %. A p value <0.05 is considered significant

p values <0.05 are presented in italic

BMI body mass index

in FBG, when probiotics were consumed as a supplement, although the reduction was not significant (Table 2).

Discussion

The current study systematically reviewed published results of controlled trials on the effect of probiotic and synbiotic intervention on FBG. The meta-analysis results of this study suggested that supplementation with probiotics and synbiotics, simultaneously, may reduce FBG. However, supplementation with probiotics or synbiotics alone did not change FBG significantly, which can be due to the lower number of trials included in each subgroup. Several studies have reported that gut microflora modification by probiotics may regulate glucose metabolism and improve related conditions such as T2DM, hyperglycemia, and metabolic syndrome [34, 41, 58, 68]. Hyperglycemia is associated with a greater risk of micro- and macrovascular diseases [57]. Therefore, effective approaches in maintaining a good control of FBG, even at a small level, may result in reduced adverse vascular outcomes as a consequence.

The mechanism of the effect of probiotics on the characteristics of T2DM such as glycemic benefits and anti-inflammatory effects are reported in several animal studies [41, 58, 69]. The modification of normal gut microbiota and regulation of host immune responses are proposed as the potential mechanisms of probiotic action [41]. The glucose-lowering effects of probiotics and synbiotics can be influenced by the complexity of the host microbiome interactions and the probiotic strain [28]. Some strains of *Lactobacilli* and *Bifidobacterium* have been shown to improve glucose tolerance and insulin resistance in animal models [14, 40]. The colonization of lactic acid bacteria in intestinal epithelium, their use of glucose, and the reduction in intestinal glucose absorption as a result are other suggested mechanisms of this action [68]. Moreover, both *Bifidobacteria* and *Lactobacillus* can inhibit the proinflammatory cytokine production responsible for pancreatic cell destruction and reduced insulin production [25].

Although the findings from animal studies are of great importance, they are not always translatable to humans, due to differences in their gut microbiome [67] and pathophysiology of hyperglycemia and insulin resistance [15]. There is an innate biological difference between species, as well as subsequent differences in glucose homoeostasis maintenance [28]. In addition, probiotic activities are highly variable and may be altered by various factors. The gene expression of probiotic bacteria is not only affected by interactions with other bacteria existing in the gastrointestinal tract, but it may also be affected by the genotype of the host organism [56]. The glucose-lowering effect of probiotics has been attributed to the metabolites of these bacteria which was demonstrated to affect biological signaling pathways, modulated genes involved in ubiquitination and proteasomal processes, and altered autonomic nerve activity

[59, 70]. Although not as frequent as animal models, there are some human clinical trials both supporting and refuting the glucose-lowering effect of probiotics on humans. One example of this is the study by Van Baarlen et al. [63], which showed that the consumption of probiotics directly affects human inflammatory status and other diabetes risk factors such as blood glucose.

The findings of this study suggested that the effect of probiotics or synbiotics consumption can be influenced by the baseline level of FBG. Subgroup analysis of this study showed that a higher reduction in FBG may be expected from individuals with baseline FBG level ≥7 mmol/L. Of the eighteen included trials, only eight recruited participants who had a high baseline level of FBG [3, 19, 38, 44, 52, 53, 60], of which six showed reduction in FBG after probiotic or synbiotic consumption. The increasing FBG trend observed for the subgroup of trials with baseline FBG <7 mmol/L can be explained by the weight of one study with three treatment arms [28] reporting higher reduction in FBG in placebo group compared to intervention.

One study suggested that the glucose-lowering effect of probiotics may be more pronounced if combined with prebiotics in treatment [52]. This was not found to be statistically significant in this meta-analysis. The positive effect of prebiotics on the growth and culture of probiotic bacteria in/of the gut is well known. Prebiotics selectively stimulate the growth or the activity of one or multiple probiotics [37]. *Bifidobacterium* and *Lactobacillus* spp. in particular are known for a response to the administration of certain prebiotics. For instance, oligofructose (OFS) stimulates the growth of intestinal bacteria, specially *Bifidobacteria* [55, 61]. The effects of prebiotics on metabolism may be influenced by a diet-induced inflammatory state. High-fat diets have the ability to increase lipopolysaccharide (LPS)-containing gut microbiota and down-regulate the amount of *Bifidobacteria* as a result [11]. The accompanying inflammatory state, which is metabolic endotoxemia, may be associated with insulin resistance and weight gain [11, 14]. In a physiological situation, *Bifidobacteria* are capable of lowering LPS levels [24]. Human clinical trials demonstrate that OFS administration is able to normalize *Bifidobacteria* levels and normalize plasma endotoxin levels, therefore, improves glucose tolerance, and increases satiety and weight loss [13, 47]. The combination of OFS with *Lactobacillus Acidophilus* not only led to an increased *Lactobacilli* concentration, it can increase the *Bifidobacteria* concentration to an even higher extent than the *Lactobacilli* [23]. Evidence from animal studies also shows that high-fat-fed diabetic mice which were on OFS treatment exerted reduced glucose tolerance, body weight, and endogenous glucose production [12]. Thus, there is increasing evidence to support the hypothesis that prebiotics can influence gut microbiota composition and, as such, metabolic disturbances. The evidence, however, is limited, and a definite beneficial effect on metabolic disturbances remains to be showed in large prospective randomized controlled trials.

In addition, meta-analysis result of our study indicated that consuming probiotic bacteria in a form of supplements resulted in a higher but nonsignificant reduction in FBG compared to fermented milk and yoghurt. The difference observed may be due to the lactose content of fermented milk and yoghurt, which may increase FBG [22]. Consuming probiotics in daily doses $\geq 10^{10}$ CFU showed higher reduction in FBG compared with the daily doses $<10^{10}$ CFU. It is estimated that the human intestine contains more than 10^{14} bacteria from thousands of species [34]. Therefore, a higher dose of probiotics may be required to induce gut flora changes and beneficial effects on glucose metabolism. Based on our study's results, probiotic supplementation appears to be more successful when it is supplied for more than 8 weeks. This might also be due to the same reason that higher CFU of probiotic could confer better outcomes.

The subgroup analysis of studies with multi-strain probiotics showed a more pronounced reduction compared to those with single strain. Literature, in general, supports the use of multi-strain probiotics. Multi-strain probiotic seems to be more effective than single strains in most cases, which might be due to the synergistic interaction between different strains in multi-strains products, or a higher concentration of live cultures [17]. It is difficult, however, to draw a conclusion and directly compare the effectiveness of individual strain versus multi-strain probiotics, as every single strain of a multi-strain must be tested individually and each strain shows unique characteristics and effects. In addition, while mixing strains could result in synergistic effect in bioactivity of probiotics, it could cause mutual inhibition by the component strains which decrease probiotic efficacy [17].

The result obtained from subgroup analysis of trials with baseline BMI <30 kg/m^2 illustrates a significant reduction in FBG compared to those with higher BMI. The difference observed can be due to the low number of trials included in subgroups. However, it is possible that the beneficial effect of probiotics and synbiotics consumption is masked by the adverse effect of higher body weight and BMI. There is strong evidence suggesting increased body weight or BMI can induce insulin sensitivity and lower insulin production [7].

To the best of our knowledge, this study is the first to systematically review the effect of probiotics and synbiotics on FBG without restriction by health condition by pooling the results of individual control trials. This study investigated the effect of different dose and duration of probiotic and synbiotic supplementation on FBG. However, the current review has some limitations which need to be considered. The focus of the study was on FBG changes, which is the main assessment marker in glycemic control [4]. However, in the management of diabetes, other metabolic factors, such as glycated hemoglobin (HbA_{1c}) or postprandial glucose (PPG),

are also measured [4]. Although FBG levels are highly correlated with HbA_{1c} [4], the effect of consuming probiotics and synbiotics on other metabolic factors of glycemic control and diabetic management needs further investigation. Supplement administration varied between included studies in terms of the duration, supplement dose (CFU), and the type of the carrier. Ivey et al. [28] found that probiotic capsules and probiotic yogurt had different effects on glycemic biomarkers. The dose of the bacteria was less than 10^{10} CFU in most of the trials. It has been shown that probiotic dose can influence their efficacy and their influence on gut flora [35]. Hence, probiotic bacteria should be supplied in adequate amounts to trigger the targeted effect. Studies were also varied in terms of sample size. Lack of sufficient power to detect the observed differences in FBG was reported in some studies [28, 60]. Health conditions and the baseline characteristics of participants also varied, which may have influenced the meta-analysis outcome. Few studies reported higher baseline blood glucose in the group administered with probiotic compared to the control group [3, 30, 53], and this may have influenced the results of the study.

Conclusion

This systematic review and meta-analysis suggested that probiotic and synbiotic consumption may lower FBG levels in adults with baseline FBG $\geq$7 mmol/L and that multispecies compared to single species supplementation may be more successful. Future controlled studies at clinical or population level with a variety of sources and daily doses, and different durations of intervention are required to confirm the health benefit and the role of probiotic and synbiotic on glycemic control.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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