Whey Protein in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

Zyrah Lou R. Samar, MD,[1] and Genecarlo Liwanag, MD[1]

Background. Type 2 diabetes mellitus (T2DM), the more prevalent type, is caused by a combination of insulin resistance and inadequate insulin response to hyperglycemia. Aside from pharmacologic interventions, medical nutrition therapy is an integral part of the management of patients with T2DM. Whey protein, which is one of the best protein sources, has been investigated for its applicability in improving glycemic control in patients with T2DM. This systematic review and meta-analysis was conducted to measure the magnitude of the effect of whey protein on glycemic control in T2DM. The aim of this review is to evaluate the efficacy and safety of whey protein in patients with T2DM. The results of this study will contribute to the possible non-pharmacologic treatment approaches in managing the disease.

Methods. A systematic electronic search for studies in the PubMed and Cochrane Collaboration databases was done. Included in this review were randomized controlled trials of whey protein enrolling patients with T2DM. Three reviewers independently searched, assessed and extracted data from the individual studies.

Results. A systematic literature search was conducted from April to September 2021 to identify eligible studies published between 2010 and 2020. The search was performed across online databases. The search yielded 21 randomized controlled trials after removing duplicates. Only five articles were included after reviewing the full text which met the criteria for selection.

Conclusion. Whey protein supplementation significantly reduced fasting blood glucose. However, it did not reduce post-prandial blood glucose, HbA1c level, and weight when compared with placebo. There has been a considerable heterogeneity across all studies, which may have contributed to or confounded its effects. A larger sample size and better inclusion and a more specific study may be included in the future reviews.

Keywords. *Whey protein, Diabetes, Nutrition, Fasting blood sugar, Post-prandial glucose, HbA1c, Weight reduction*

Introduction

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors.[1] Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production.[2] The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems, which impose a tremendous burden on the individual with DM and on the health care system.

In the Philippines, DM is now an epidemic. According to the International Diabetes Federation, the prevalence of diabetes is 6.3%, or 63,993,300.[3] DM remains the leading cause of end-stage kidney disease and predisposes an individual to a number of complications.[4]

According to the Diabetes Control and Complications Trial, prevention of nephropathy, neuropathy, and retinopathy can be achieved if there is tight glycemic control. Moreover, achieving normoglycemia in patients with type 2 DM (T2DM) would prevent its complications. Hence, in patients with T2DM, glycemic control as

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reflected by reductions in fasting blood glucose (FBG) and HbA1c would reduce the burden of the disease.[5] The current nutrient recommendation of the American Diabetes Association for the management of diabetes includes "a dietary pattern that includes carbohydrates from fruits, vegetables, whole grains, legumes and low-fat milk". Moreover, it stated that "ingested protein can increase insulin response without increasing plasma glucose concentrations."

Whey is a by-product of the cheese-making process and has been a source of amino acids. It consists of a heterogenous group of proteins, which includes beta-lactoglobulin, alpha-lactoglobulin, proteose peptone, immunoglobulins, and bovine serum albumin.[6] Moreover, it is high in branched-chain amino acids, particularly leucine, which is a potent insulin secretagogue.[7] Leucine allosterically activates glutamate dehydrogenase to enhance glutaminolysis. Long-term treatment of leucine improves insulin secretory dysfunction of human diabetic islets via up-regulation of adenosine triphosphate (ATP) synthase B sub-unit, an enzyme responsible for elevating the cellular ATP synthesis rate, which regulates B-cell metabolism.

Whey protein, when added to a meal, also appears to increase insulin secretion and decrease post-prandial blood glucose levels. It slows gastric emptying and stimulates incretin hormone secretion, which reduces post-prandial glycemic excursions. Moreover, whey protein stimulates beta cells to secrete insulin, which results in reduced post-prandial glucose excursions, ultimately leading to a potential adjunct in glucose control/therapy in patients with T2DM.[8]

Frid et al., in 2005, evaluated if meals with high glycemic index with whey proteins can cause an increase in insulin secretion in patients with T2DM. Subjects were given whey protein meal supplementation during breakfast and lunch. Results demonstrated that the insulin responses were higher in both breakfast by 30% and lunch by 57% in patients with whey supplementation. Moreover, post-prandial glucose-dependent insulinotropic polypeptide (GIP) was significantly higher in patients with whey supplementation. Hence, whey protein exerts its insulinotropic effect by increased GIP post meal.[9]

Why It Is Important to Do This Review

Nutrition therapy is now recognized as an integral part of T2DM management.[10] The potential use of whey protein in nutritional management of glycemia has been widely studied. Our study aimed to analyze all available published randomized controlled trials (RCTs) regarding the safety and efficacy of whey protein on FBG, post-prandial glucose, HbA1c, and weight of patients with T2DM.

Objectives

The primary objective of this study was to assess the efficacy of supplemental whey protein in controlling glycemic levels in patients with T2DM. The main outcome was to evaluate the effect of whey protein supplementation on reducing FBG levels. Additionally, the study aimed to investigate the impact of whey protein on weight reduction, post-prandial glucose levels, and HbA1c.

Methodology

The study protocol for this systematic review and meta-analysis has not been registered.

Search Strategy

Three authors conducted an electronic search at PubMed, Cochrane Central Register, and Herdin Plus with no language restrictions. The following keywords were used: "whey protein", "diabetes mellitus". The search included RCTs. The full search terms used are detailed in Appendix A.

Inclusion and Exclusion Criteria

In this meta-analysis, included studies in the search were published between 2010 and 2020. Inclusion criteria were as follows: (a) study designs were published RCTs; (b) whey protein, regardless of dose, was the intervention; (c) participants were 18 years old and older diagnosed with T2DM; (d) the study had intervention of minimum of 4 weeks; (e) the study had a placebo or control group; (f) FBG, post-prandial glucose, HbA1c, and weight were assessed.

The studies considered in this study were published between 2013 and 2023, RCTs, and published in English in academic journals or scholarly publication.

Data Extraction

Three authors independently reviewed titles and abstracts of the citations that resulted from the electronic search and excluded studies which failed to meet the inclusion criteria. Disagreements were resolved by discussion and resolved by consensus among the three authors.

The full-text versions of the selected papers in the initial screening were retrieved. The first author's name, publication year, study design, sample size, study period, whey protein, type of placebo or control groups, and outcome assessments were independently extracted.

Assessment of Quality

The methodological quality of the identified studies was independently assessed by three authors using the Cochrane Risk of Bias Tool. The following domains were categorized as having high, low, or unclear risk of bias: random sequence allocation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Disagreements between authors were resolved by consensus.

Statistical Analysis

The meta-analysis of the included studies was done using RevMan 5.3 software. We calculated the pooled mean difference with 95% confidence intervals (CI) comparing

intervention (whey) and control groups for each continuous outcome using random effects because the investigators hypothesized a significant heterogeneity among studies.

Results

Description of Included Studies

The search identified 533 potentially eligible studies, of which 397 studies were excluded based on title and abstract. Duplicates were identified and excluded. A total of nine studies were identified for full-text review. Five studies[11-15] involving 289 participants were included in the systematic review and meta-analysis. All articles were randomized and blinded, albeit two articles included were crossover studies. Search methodology is outlined in Appendix B. Characteristics of the included studies are listed in Table 1. A summary of risk of bias of included studies is shown in Appendix C. The included studies utilized varying dosages of whey protein from 17 g/day to 50 g/day during a time frame ranging from 4 weeks to 13 weeks.

Data Analysis

Quantitative analysis was conducted by pooling data into Review Manager 5.3 for meta-analysis using data gathered from included studies. The mean difference after treatment was used to assess the effects of whey protein vs. placebo in the following outcome measures: primary outcomes of FBG and hemoglobin A1c (HbA1c); secondary outcome, weight change. Heterogeneity was assessed using the chi-squared tests and the I^2 statistic. A significant chi-squared test ($p<0.05$) and an I^2 statistic of >50% indicated heterogeneity in effect sizes among the studies. Due to the presence of heterogeneity between the studies, the random-effects model with inverse variance heterogeneity was used to calculate the pooled effect size.

Table 1. Characteristics of included studies

Study	Study design	Participants		Intervention		Control	Outcome
		N	Age	Form of whey protein	Dosage of whey protein		
Jacubowicz, 2014[11]	12-week randomized, open label crossover clinical trial	15		Pre-meal drink with either 50 g [920 kJ (220 kcal)] whey protein concentrate dissolved in water	50 g whey	Water	• FBG • Post-prandial glucose • Insulin and C-peptide levels • Total GLP-1 • Intact GLP-1
Jacubowicz, 2017[12]	12-week randomized, open-label, parallel-arm clinical trial	56		Whey-based diet (dose)	28 g of whey	Carbohydrate -based diet	• FBG • HbA1c • Weight • BMI
Memelink, 2020[13]	13-week randomized, controlled, double-blind, parallel group trial	123		Whey protein drink enriched with leucine and vitamin D (test group) (dose)	21 g of whey	Isocaloric control drink	• FBG • 2h plasma glucose • HbA1c • Body weight • BMI • Total lean mass • Fat mass • Waist circumference • HOMA-IR

Watson, 2019[14]	12-week randomized, in single-blind group trial	79		"Shake"	17 g whey plus 5 g guar	"Shake" containing placebo	• FBG • 2h plasma glucose • HBA1c • Body weight • BMI • Waist circumference • HOMA-IR
Ma, 2015[15]	4-week randomized, single-blind, cross-over protocol	7		Formula	25 g chocolate flavored whey protein preload	25 g chocolate-flavored diet sauce as a placebo	• Post-prandial glucose • HBA1c • Weight • Gastric emptying time

Table 2. Characteristics of excluded studies

Study	Study design	Participants	Sample size	Intervention	Control	Outcome	Reason for exclusion
Bae, 2018	Randomized open-label study	15 T2DM patients and 15 individuals with normal glucose tolerance	15	Participants were randomly assigned to two groups and had PFB followed by breakfast (pre-meal PFB) or breakfast followed by PFB (post-meal PFB)	None	Plasma glucose concentration, plasma insulin concentration, plasma concentration of GLP-1	Population did not meet the inclusion criteria since it included subjects with normal glucose tolerance No control / placebo since it compared pre-meal PFB and post-meal PFB
Gaffney, 2017	A double-blind, randomized, placebo-controlled trial	Men with T2DM were recruited from local medical centers in Wellington	24	Whey protein beverage before and after 45 early-morning MMIT sessions for 10 weeks	Carbohydrate placebo before and after 45 early-morning MMIT sessions for 10 weeks	Glucose disposal rate	With high-intensity mixed-mode training as co-intervention Different outcome measured

Daly, 2014	A 6-month, two-arm, parallel, randomized controlled trial	Men and women aged 50 to 75 years with established type 2 diabetes	56	Resistance training program with no additional supplements	Resistance training program with whey protein and vitamin D group	The primary outcome measures will be changes in HbA1c levels and HOMA-2 of insulin resistance and β-cell function based on model-derived estimates using the validated HOMA-2 calculator	Intervention included supplementation other than whey protein
Mori, 2017	A randomized controlled trial	Participants were 200 community-dwelling older women aged 65–80 years	200	Exercise and whey protein	Exercise only	The following measures of physical function were evaluated: grip strength, knee extension strength, and gait speed. Grip and knee extension strengths were measured by hand-held dynamometry (T.K.K5401; Takei Instruments, Tokyo, Japan; μ-tus F-100; ANIMA, Tokyo, Japan)	Population did not meet the inclusion criteria since it included healthy, older women Different outcome measured in the study

Effects of the Intervention

Whey Protein on FBG

The primary outcome of intervention is its effect on FBG. Figure 4 illustrates the summary of the effect of whey protein vs. placebo in reducing the FBG of patients with T2DM. In the study of Huhman et al. in 2018,[16] the participants who received whey protein had higher FBG than those who received placebo. Meanwhile, in the four other RCTs,[11-14] those who received whey protein demonstrated reduction in FBG but with no significant differences as compared with placebo with the overall effect of Z=3.79 (p=0.0002). Overall result favors whey protein. Significant heterogeneity is noted across all studies I^2=99%.

Whey Protein on Post-Prandial Glucose

Two RCTs[14,15] were compared to determine the effect of whey protein on post-prandial glucose. The overall result favors whey protein; however, the overall treatment showed no statistical significance versus placebo (Z=1.93; p=0.05), there was significant heterogeneity seen between two study groups I^2=92%.

Figure 4: Whey protein vs placebo on FBG

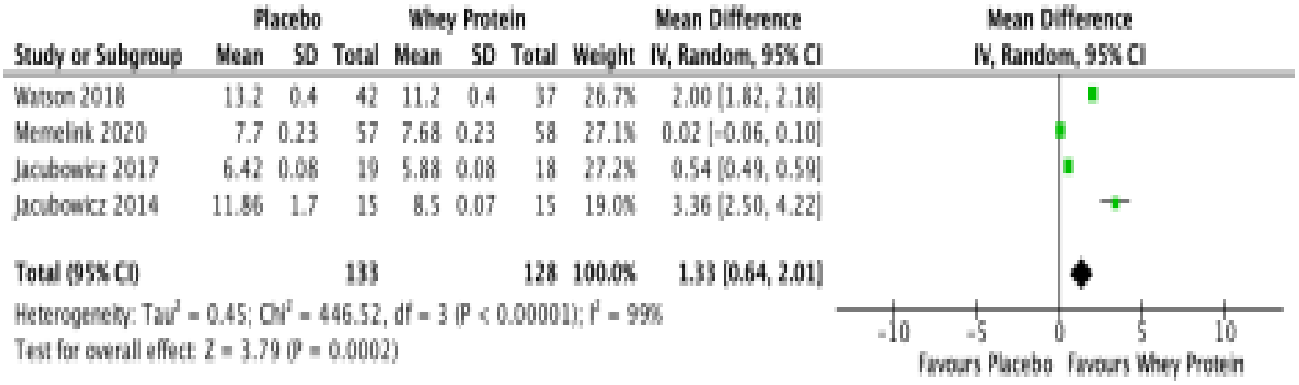
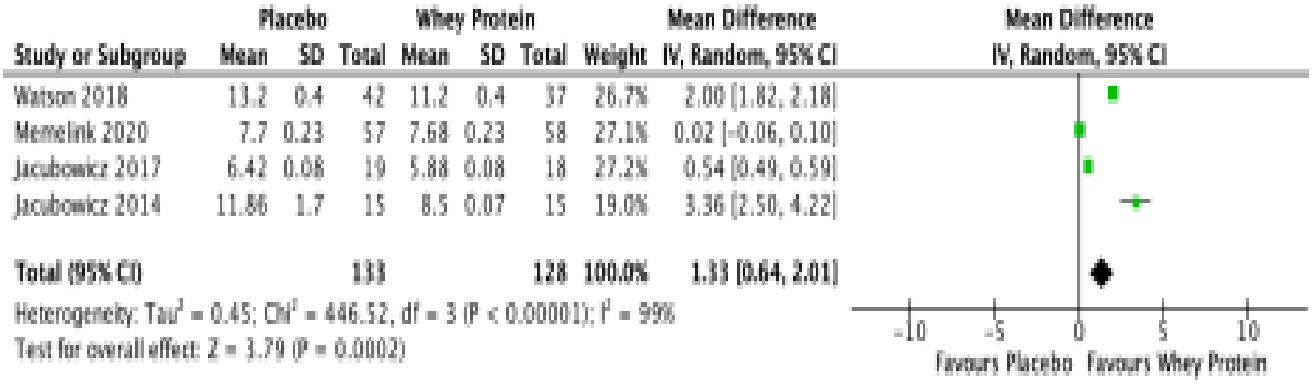


Figure 5: Whey protein vs placebo on post-prandial glucose



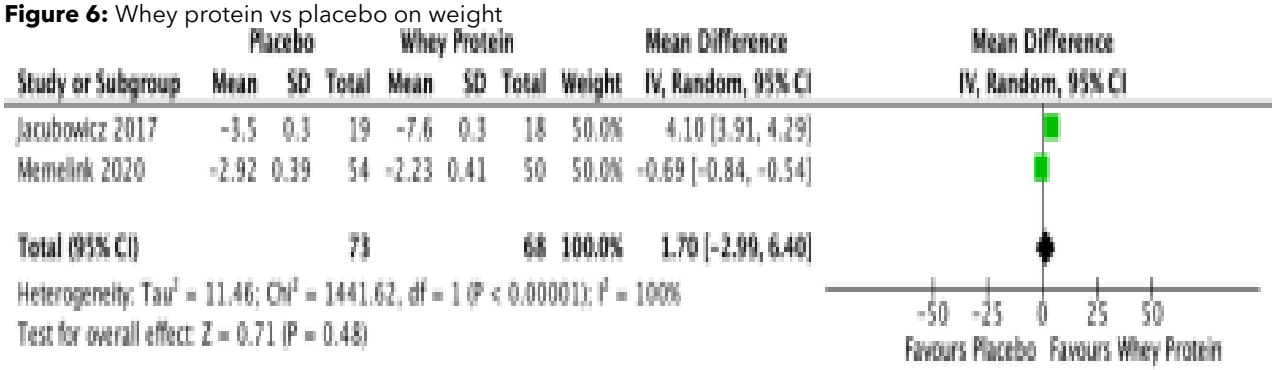
Whey Protein on HbA1c

Four published articles were compared to assess the effect of whey protein on HbA1c; overall result (Z=1.34; p=0.18) favors whey and touches the line of no effect. Significant heterogeneity exists across all study groups (I^2=98%).

Whey Protein on Weight

In Figure 6, the effect on the weight of whey protein vs placebo was compared. The values were nearing and touching the line of no effect, with a Z-score of 0.71 (p=0.48). Significant heterogeneity exists across both study groups (I^2=99%). Random effects model was used to account for the heterogeneity.

Figure 6: Whey protein vs placebo on weight



Discussion

Whey protein, as mentioned in various studies, has been shown to reduce post-prandial blood sugar levels through various physiological mechanisms by the following effects: enhancement of insulin activity and incretin secretion, reduction of gastric emptying time, appetite, and energy consumption.[11] The mechanisms mentioned may be beneficial in the management of T2DM.

Whey Protein on FBG

In the study of Huhman et al. in 2018, the participants who received whey protein had higher FBG than those who received placebo. Meanwhile, in the four other RCTs, those who received whey protein demonstrated reduction in FBG but with no significant differences as compared with placebo.[16]

Meals with whey protein determined whether it caused an increase in insulin secretion in patients with T2DM. Subjects were given whey protein meal supplementation during breakfast and during lunch. Venous blood samples were taken 4 hours after breakfast and 3 hours after lunch to determine blood glucose, serum insulin, GIP, and glucagon-like peptide 1 (GLP-1). Results showed that the insulin responses were higher in both breakfast by 30% and lunch by 57% in patients with whey supplementation. Moreover, it was noted that post-prandial GIP was significantly higher in patients with whey supplementation. Hence, whey protein exerts its insulinotropic effect by increased GIP post meal.[12]

Whey protein is rich in leucine, which exerts acute and chronic effects at multiple regulatory sites of glucose metabolism such as pancreatic B-cells, liver, muscle, and adipose tissue. Leucine allosterically activates glutamate dehydrogenase to enhance glutaminolysis. Long-term treatment with leucine improves insulin secretory dysfunction of human diabetic islets via upregulation of ATP synthase B sub-unit, an enzyme responsible for elevating the cellular ATP synthesis rate, which regulates B-cell metabolism.

Four RCTs were reviewed and analyzed in the study. Those who received whey protein demonstrated reduction in FBG but with no significant differences as compared with placebo with the overall effect of Z=3.57 ($p<0.000001$).[13,14,17,18] Overall result favors whey protein; however, considerable heterogeneity is noted across all studies (I^2=99%) and may not be clinically significant. In one study (Memelink 2020),[13] all participants were subjected to a hypocaloric diet (600 kcal/day) with exercise regimen thrice a week for 13 weeks; the results showed no significant difference in terms of FBG. The subjects included were obese, and according to the authors, the majority of the subjects did not reach the energy restriction target of 600 kcal/day and could have under-reported their energy intake. The heterogeneity may also be attributed in terms of differences in study group characteristics, i.e., population, outcome, comparison (e.g., whey dose, formulation, and duration of treatment).

In patients with diabetes, fasting blood hyperglycemia is associated with the development of macrovascular and microvascular complications, including retinopathy, neuropathy, and nephropathy.[19] This meta-analysis and systematic review has showed that whey protein may reduce FBG and has potential as a supplement for patients with diabetes who have difficulty in controlling their FBG.

Whey Protein on Post-Prandial Glucose

Post-prandial glucose homeostasis is controlled by numerous factors such as the composition of nutrients (the glycemic index and glycemic load), gastric emptying time, glucose absorption rate in the gut, secretion of incretin hormones (such as GLP-1, GIP), insulin secretion, glucose uptake by insulin-sensitive tissues, and endogenous glucose production.[20] Understanding the different physiologic responses of glycemic enables the clinician to do a targeted approach/therapy to patients with T2DM. In some studies, whey protein meal stimulates secretion of insulin, GLP-1, GIP, which reduces post-prandial glucose excursions.[21] In addition, a high-protein meal stimulates secretion of cholecystokinin and peptide YY, resulting in reduced gastric emptying time and reduced appetite, respectively.[4]

Aside from the insulinotropic effects of incretins, GLP-1 slows gastric emptying time, suppresses energy intake, and has a glucagon static effect, with resultant control of post-prandial glucose levels. An RCT compared whey protein and placebo given to patients with T2DM; results showed a modest increment in plasma GLP-1 after 1 week of whey feeding but not placebo feeding, with a mean difference of (0.6 ± 5 pmol/L) and (-1.2 ± 0.6 pmol/L), respectively.[14] Another study compared whey protein and placebo and noted that the ratio intact GLP-1/total GLP-1 was significantly higher throughout the post-prandial period after whey pre-load.[22] Higher plasma incretin levels were also associated with reduction in plasma glucose excursion.[23]

Two RCTs were reviewed and analyzed comparing the effect of whey protein vs. placebo on post-prandial glucose levels. They compared the peak glucose levels between whey protein and placebo. The study showed no statistical difference in glucose levels between the two groups, albeit the result may be due to a significant heterogeneity in terms of whey formulation, dosage, and form used in each study.

Ma (2015) investigated the effects of whey protein and placebo for 4 weeks. Subjects consumed a flavored drink containing whey vs. placebo for 4 weeks. The study did not statistically show significant difference in post-prandial glucose levels. Food recall for 3 days was done; the study did not mention a standardized diet, which might have confounded with the post-prandial glucose excursions.[15]

Whey Protein on HbA1c

The effects of whey protein in the review showed no statistical difference in reducing HbA1c in patients with T2DM. The study also showed significant heterogeneity across the study groups.

In 2017, Jacubowicz et al. conducted a study to determine whether whey protein can reduce body weight, post-prandial glycemia, and HbA1c in T2DM. They assigned 56 subjects diagnosed with T2DM to receive whey protein breakfast diet and either protein breakfast diet or carbohydrate breakfast diet for 12 weeks. The results showed that patients who were given whey protein breakfast ($p<.001$) had the highest reduction in HbA1c (11.5 ± 0.6 mmol/mol) as compared to those assigned to protein breakfast (7.1 ± 0.31 mmol/mol) and carbohydrate breakfast (2.9 ± _0.31 mmol/mol).[12] The effect of whey protein diet on HbA1c is attributed to its insulinotropic effects on glycemia over time.[24] In patients with diabetes, HbA1c <7% is associated with reduced risk of microvascular and macrovascular complications. However, results of this study showed that whey protein has limited effects on the reduction of HbA1c.

Whey Protein on Weight

In several studies, high-protein diets were found to promote weight reduction. The mechanism of weight loss in protein diets has been attributed to several physiologic glycemic homeostatic mechanisms.[25-27] The studies show contradicting results in the effects of whey protein on weight. In this review, whey protein use in reducing weight is statistically non-significant.

The study by Jacubowicz et al. was conducted as a randomized, open, parallel-arm clinical trial which included subjects with a mean weight of 90.5 ± 1.3 and were given 28 g of whey protein. Meanwhile, the randomized, single-blind, cross-over study of Memelink et al. included participants with a higher weight of 96.11 ± 1.97 and lower whey protein dose of 17 g. Hence, there are significant differences in the baseline weight and whey protein dose, which increased the heterogeneity for this outcome.

Conclusion

In this review, it was demonstrated that whey protein supplementation significantly reduced FBG. However, it did not reduce post-prandial blood glucose, HbA1c level, and weight when compared with placebo. However, this clinically may not be significant, due to the aforementioned significant heterogeneity. Therefore, we recommend a future study on whey protein using a larger sample size to improve the validity and generalizability of the study. To reduce heterogeneity, future reviews should emphasize the use of standardized whey protein dosing, ensure consistent dietary protocols for both intervention and control groups, extend the duration of treatment, and focus on more specific studies with well-defined methodologies and treatment protocols.

Conflict of Interest

The authors of the study declare no conflict of interest in conducting the study.

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Appendix A. Search Strategy

PubMed

Search: ((((whey protein) OR (whey)) AND (diabetes)) OR (type 2 DM)) OR (DM) Filters: randomized controlled trial, in the last 10 years

((("whey proteins"[MeSH Terms] OR ("whey"[All Fields] AND "proteins"[All Fields]) OR "whey proteins"[All Fields] OR ("whey"[All Fields] AND "protein"[All Fields]) OR "whey protein"[All Fields] OR ("whey"[MeSH Terms] OR "whey"[All Fields])) AND ("diabete"[All Fields] OR "diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields] OR "diabetic"[All Fields] OR "diabetics"[All Fields] OR "diabets"[All Fields])) OR ("Type"[All Fields] AND "2"[All Fields] AND ("dyn med"[Journal] OR "dis mon"[Journal] OR "dis manag"[Journal] OR "dm"[All Fields])) OR ("dyn med"[Journal] OR "dis mon"[Journal] OR "dis manag"[Journal] OR "dm"[All Fields])) AND ((y_10[Filter]) AND (randomizedcontrolledtrial[Filter]))

Translation

Whey protein: "whey proteins"[MeSH Terms] OR ("whey"[All Fields] AND "proteins"[All Fields]) OR "whey proteins"[All Fields] OR ("whey"[All Fields] AND "protein"[All Fields]) OR "whey protein"[All Fields] Whey: "whey"[MeSH Terms] OR "whey"[All Fields]

Diabetes: "diabete"[All Fields] OR "diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields] OR "diabetic"[All Fields] OR "diabetics"[All Fields] OR "diabets"[All Fields]

DM: "Dyn Med"[Journal:__jid101152197] OR "Dis Mon"[Journal:__jid0370657] OR "Dis Manag"[Journal:__jid9802539] OR "dm"[All Fields]

DM: "Dyn Med"[Journal:__jid101152197] OR "Dis Mon"[Journal:__jid0370657] OR "Dis Manag"[Journal:__jid9802539] OR "dm"[All Fields]

Cochrane

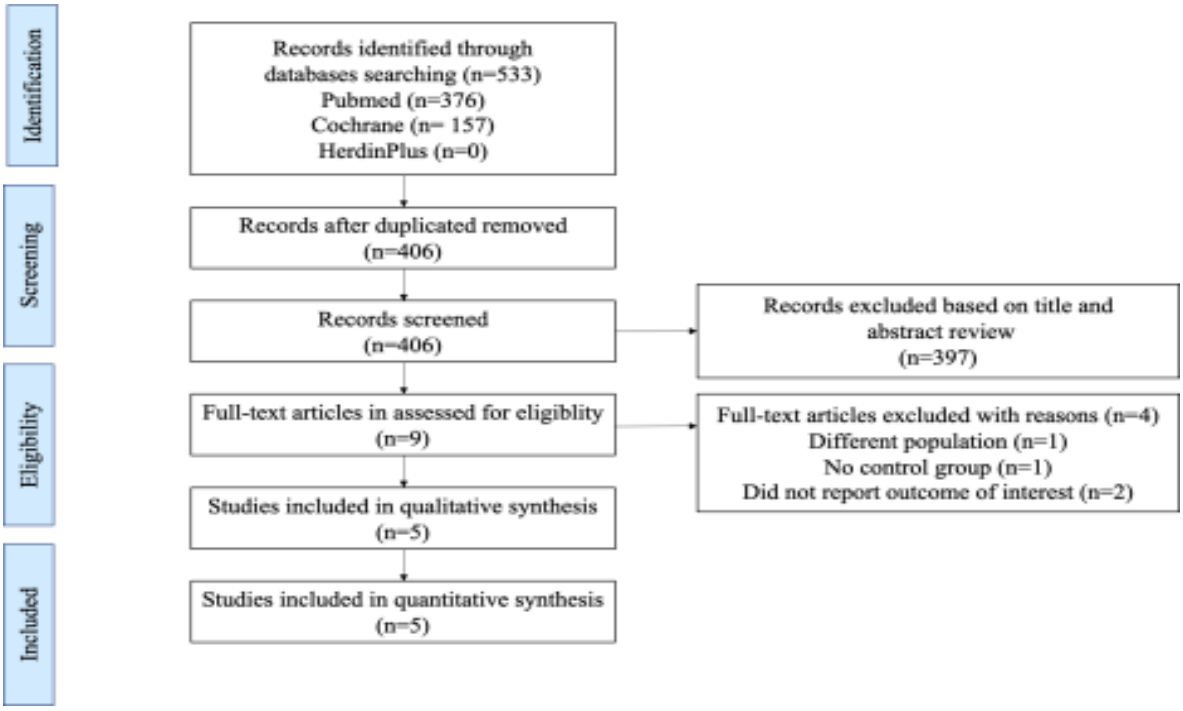
Search: ((((Whey Protein) OR (Whey)) AND (Diabetes)) OR (Type 2 DM)) OR (DM)

Yielded: 2184 searches, removed duplicates, manually selected studies by screening study title/abstract.

Herdin Plus

Search Term/s: ((((Whey Protein) OR (Whey)) AND (Diabetes)) OR (Type 2 DM)) OR (DM) Yielded: 0 searches

Appendix B. Search Methodology and Selection Process



Appendix C. Summary of Risk of Bias Among Included Studies

Figure 1. Risk bias graph of included studies

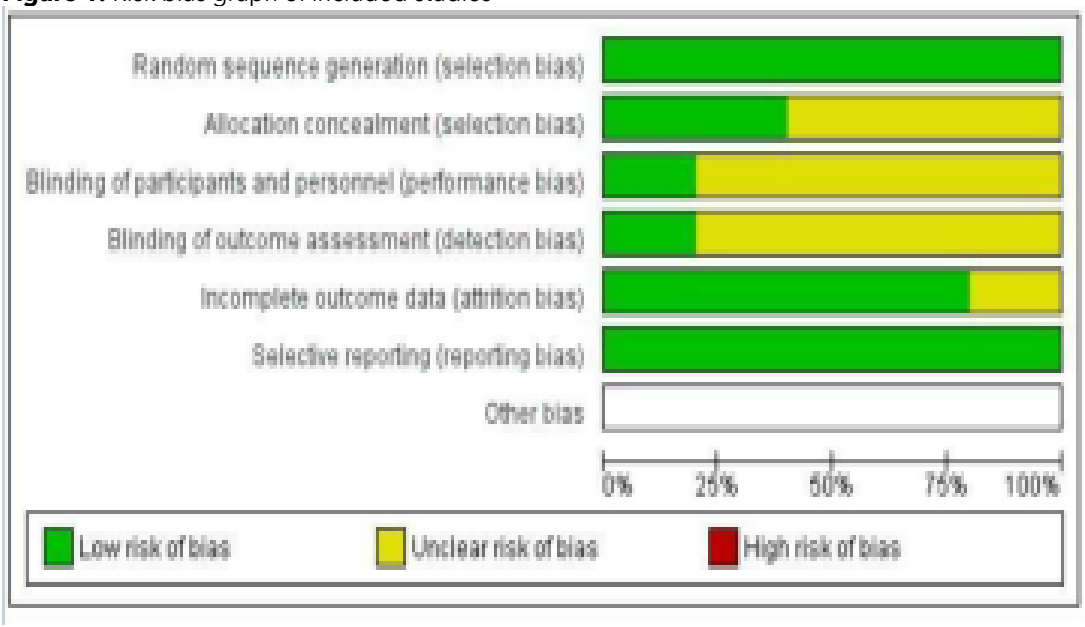


Figure 2. Risk Bias Summary of Included Studies