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Soy Protein Supplementation Reduces Clinical Indices in Type 2 Diabetes and Metabolic Syndrome

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Purpose: Clinical trials have studied the use of soy protein for treating type 2 diabetes (T2D) and metabolic syndrome (MS). The purpose of this study was to outline evidence on the effects of soy protein supplementation on clinical indices in T2D and MS subjects by performing a meta-analysis of randomized controlled trials (RCTs).

Materials and Methods: We searched PubMed, EMBASE, and Cochrane databases up to March 2015 for RCTs. Pooled estimates and 95% confidence intervals (CIs) were calculated by the fixed-and-random-effects model. A total of eleven studies with eleven clinical variables met the inclusion criteria.

Results: The meta-analysis showed that fasting plasma glucose (FPG) [weighted mean difference (WMD), -0.207; 95% CI, -0.374 to -0.040; p=0.015], fasting serum insulin (FSI) (WMD, -0.292; 95% CI, -0.496 to -0.088; p=0.005), homeostasis model of assessment for insulin resistance index (HOMA-IR) (WMD, -0.346; 95% CI, -0.570 to -0.123; p=0.002), diastolic blood pressure (DBP) (WMD, -0.230; 95% CI, -0.441 to -0.019; p=0.033), low-density lipoprotein cholesterol (LDL-C) (WMD, -0.304; 95% CI, -0.461 to -0.148; p=0.000), total cholesterol (TC) (WMD, -0.386; 95% CI, -0.548 to -0.225; p=0.000), and C-reactive protein (CRP) (WMD, -0.510; 95% CI, -0.722 to -0.299; p=0.000) are significant reduced with soy protein supplementation, compared with a placebo control group, in T2D and MS patients. Furthermore, soy protein supplementation for longer duration (≥6 mo) significantly reduced FPG, LDL-C, and CRP, while that for a shorter duration (<6 mo) significantly reduced FSI and HOMA-IR.

Conclusion: Soy protein supplementation could be beneficial for FPG, FSI, HOMA-IR, DBP, LDL-C, TC, and CRP control in plasma.

Key Words: Soy, diabetes, body weight, blood glucose, lipid

INTRODUCTION

Diabetes has become a global public health challenge. The main characteristics of diabetes are chronic hyperglycemia and metabolism disturbances. And the main causes of them are defects in insulin secretion and insulin actin. Long periods of such metabolism disturbances may cause diabetes-related complications, such as heart disease and kidney disease.[1,2] The risk of cardiovascular disease (CVD) and stroke is 3–4 times greater in patients with type 2 diabetes (T2D) than in the general population.[3,4] Metabolic syndrome (MS) is a clustering of metabolic abnormalities that occur in individuals with impaired insulin sensitivity.[5-7] MS comprises pathological conditions that include insulin resistance, arterial hypertension, and so on, which promotes the development of CVDs.[8,9] The etiology of this syndrome is largely unknown; genetic, metabolic, and environmental factors, including diet, are thought to play a major role.[7,10] Foods that improve insulin sensitivity might also provide benefits to the metabolic abnormalities related with insulin resistance.[7,11] Studies on food groups are important, and there is a trend in the literature to verify the relationships between dietary patterns and cardiovascular risk factors.[8,12] On the basis of laboratory and observational evidence, several longitudinal studies in T2D and MS have examined the relationship between soy protein supplementation and risk

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factors for CVD, such as body weight, lipids, and glucose metabolism, although results are controversial. Some studies have suggested a reduction in fasting plasma glucose (FPG),[2,13] blood pressure,[8] low-density lipoprotein cholesterol (LDL-C),[7,13-15] total cholesterol (TC),[7,13,15,16] C-reactive protein (CRP),[13,17] triglyceride (TG),[13,15,16] fasting serum insulin (FSI),[7] and homeostasis model of assessment for insulin resistance index (HOMA-IR),[7] while others do not.[18,19]

Clinical trials have studied the use of soy protein for treating T2D and MS. The purpose of this study was to examine evidence on the effects of soy protein supplementation on CVD risk factors, such as body weight, FPG, and LDL-C, in T2D and MS subjects by performing a meta-analysis of randomized controlled trials (RCTs).

MATERIALS AND METHODS

Literature search

A literature search was carried out in PubMed, EMBASE, and Cochrane databases to identify all relevant RCTs about the effects of soy protein supplementation on body weight, blood glucose, and other clinical indices in T2D or MS up to March 2015. We used the following medical subject heading (MeSH) terms and/or text words: "body weight" [MeSH Terms] AND "soy protein" [MeSH Terms]; "blood glucose" [MeSH Terms] AND "soy protein" [MeSH Terms]; and "insulin" [MeSH Terms] AND "soy protein" [MeSH Terms] et al. We only reviewed original articles in English. We searched all computer-identified publications, "Related Articles" on the same topic in PubMed, and the reference lists of the reviewed articles.

Criteria of inclusion

Any study that met the following criteria was included: 1) RCTs focusing on the effect of soy protein supplementation on body weight, blood glucose, or other clinical indices; 2) body weight, glucose plasma levels, etc. were presented as mean (±SD) instead of medians; and 3) subjects were diagnosed with T2D or MS patients. The definition of intervention was a diet with soy protein supplementation whose content was given. The control group comprised placebo controls. All human studies that met the above criteria were included, regardless of dose of supplementation and the length of follow-up.

Data extraction

Two investigators assessed the articles independently according to the inclusion criteria, and made a consistent decision. From each study, we obtained the following information: name of the first author, year of publication, sample size, means, and SD/SE.[20]

Statistical analysis

When the data were reported as standard errors of means (SEM), SD was obtained by multiplying SEM by the square-root of the sample size: $SD=SEM\times\sqrt{N}$. The change (Δ) was calculated by the following formula: $\Delta BW=BW_1-BW_2$, where BW is body weight, and BW_1 and BW_2 are the mean values of BW before and after treatment. The variance (consequently SD) of ΔBW was estimated as follows:[21,22] $\Delta SD^2=SD_1^2+SD_2^2-2r\times SD_1\times SD_2$, where ΔSD is the change in SD of BW levels, and SD_1 and SD_2 are the means of baseline and end SD value of BW. r is the correlation between the baseline and the end values. We assumed a correlation r of 0.5 as described previously.[22,23] Blood glucose and other clinical indices were calculated by the same method.

For each meta-analysis, the weighted mean difference (WMD) was generated by a fixed effect model with I^2 less than 50% and random effect model with I^2 more than 50%. The corresponding *p* values and 95% confidence intervals (CIs) of Z-statistics were also calculated. To examine potential publication bias, funnel plots and Egger's regression test were used. Sensitivity analyses were conducted by the One Study Removed method test. We adopted Duval and Tweedie's trim and fill to modulate the influence of unpublished studies on the summarized effects. Analyses were performed with Comprehensive Meta-Analysis software.[22]

RESULTS

Characteristics of studies and quantitative synthesis

A total of 1978 studies were identified from the primary computerized literature search for potentially relevant studies. Studies including reviews, animal experiments, duplicated

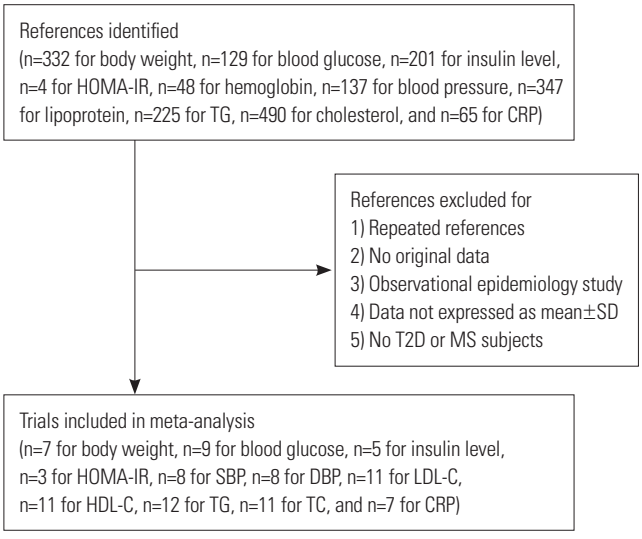

Fig. 1. Flow diagram of included/excluded studies. HOMA-IR, homeostasis model of assessment for insulin resistence index; TG, triglyceride; CRP, C-reactive protein; T2D, type 2 diabetes; MS, metabolic syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol.

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Table 1. Diabetes, Obesity, and MS Markers Level at Baseline and at the End of Soy Protein Supplementation

First author	Control group			Supplementation group		
	n	Baseline mean±SD	End mean±SD	n	Baseline mean±SD	End mean±SD
Diabetes markers						
FPG						
Azadbakht, et al.[13]	21	137±54	142±49	20	141±55	130±32
Azadbakht, et al.[13]	21	137±54	145±51	20	141±55	132±43
Azadbakht, et al.[13]	21	137±54	146±61	20	141±55	129±36
Azadbakht, et al.[13]	21	137±54	147±57	20	141±55	121±42
Liu, et al.[19]	60	6.3±0.89	6.2±0.74	60	6.4±0.74	6.2±0.76
Liu, et al.[19]	60	6.3±0.89	6.1±0.74	60	6.4±0.74	6.3±0.92
Kwak, et al.[2]	21	115.38±13.9	114.38±16.5	21	121.6±13.6	117.95±18.6
Kwak, et al.[2]	12	124.7±10.91	124.5±13.34	16	126.6±11.68	121.7±18.72
Azadbakht, et al.[7]	42	120±3.89	112±6.48	42	119±3.89	111±5.83
FSI						
Azadbakht, et al.[7]	42	14.3±0.58	14.2±0.58	42	14.2±0.58	13.3±0.26
Liu, et al.[19]	60	10.3±4.49	9.8±5.96	60	10.1±5.73	10.0±7.19
Liu, et al.[19]	60	10.3±4.49	9.4±5.72	60	10.1±5.73	9.7±5.68
Kwak, et al.[2]	21	10.57±2.8	11.15±4.2	21	11.9±7.5	17.2±27
Kwak, et al.[2]	12	9.73±2.84	10.9±3.19	16	12.3±6.28	19.3±30.72
HOMA-IR						
Liu, et al.[19]	60	2.90±1.40	2.71±1.72	60	2.94±2.12	2.78±1.88
Liu, et al.[19]	60	2.90±1.40	2.59±1.72	60	2.94±2.12	2.84±2.45
Azadbakht, et al.[7]	42	4.19±0.19	3.9±0.26	42	4.20±0.26	3.6±0.19
HbA1c						
Kwak, et al.[2]	21	6.42±0.6	6.45±0.6	21	6.70±0.6	6.65±0.6
Kwak, et al.[2]	12	6.77±0.38	6.78±0.48	16	6.83±0.68	6.78±0.64
Teixeira, et al.[24]	14	7.5±1.50	7.1±1.50	14	7.3±1.12	7.3±1.50
Obesity markers						
Weight						
Azadbakht, et al.[13]	21	72±8	71±9	20	71±9	70±10
Azadbakht, et al.[13]	21	72±8	73±10	20	71±9	72±9
Azadbakht, et al.[13]	21	72±8	69±9	20	71±9	73±10
Azadbakht, et al.[13]	21	72±8	73±10	20	71±9	71±10
Liu, et al.[19]	60	-0.11±1.55		60	-0.60±1.64	
Kwak, et al.[2]	21	65.8±8.9	65.8±9.3	21	62.6±6.7	62.4±7.1
Azadbakht, et al.[7]	42	70.0±5.83	70.1±5.83	42	70.0±5.18	70.7±5.83
BMI						
Simão, et al.[8]	15	36.32±6.53	36.51±7.07	15	38.30±8.37	38.41±8.37
Simão, et al.[8]	15	36.32±6.53	36.43±7.35	15	38.30±8.37	38.63±8.47
Simão, et al.[8]	21	24.8±1.7	24.8±1.9	21	24.1±2.3	24.0±2.4
WC						
Simão, et al.[8]	15	111.00±19.08	111.50±20.20	15	115.50±15.30	113.79±14.77
Simão, et al.[8]	15	111.00±19.08	110.67±20.06	15	115.50±15.30	113.57±14.11
Azadbakht, et al.[7]	42	91.5±4.54	91.9±5.18	42	91.4±4.54	91.5±5.83
MS markers						
SBP						
Azadbakht, et al.[13]	21	153±71	155±64	20	150±64	148±55
Azadbakht, et al.[13]	21	153±71	150±49	20	150±64	153±68
Azadbakht, et al.[13]	21	153±71	147±58	20	150±64	149±52
Azadbakht, et al.[13]	21	153±71	148±67	20	150±64	147±49
Simão, et al.[8]	15	137±27.50	128.92±25.08	15	135.79±14.19	128.79±13.06

Table 1. Diabetes, Obesity, and MS Markers Level at Baseline and at the End of Soy Protein Supplementation (Continued)

First author	Control group			Supplementation group		
	n	Baseline mean±SD	End mean±SD	n	Baseline mean±SD	End mean±SD
Simão, et al.[8]	15	137±27.50	127.58±23.67	15	135.79±14.19	132.43±14.25
Azadbakht, et al.[7]	42	136±4.54	131±7.78	42	136±4.54	132±4.54
Kwak, et al.[2]	21	126.7±13.4	124.2±13.3	21	125.1±14.8	128.2±12.0
DBP						
Azadbakht, et al.[13]	21	91±41	95±36	20	96±23	92±32
Azadbakht, et al.[13]	21	91±41	96±42	20	96±23	90±26
Azadbakht, et al.[13]	21	91±41	94±39	20	96±23	94±33
Azadbakht, et al.[13]	21	91±41	93±43	20	96±23	93±29
Simão, et al.[8]	15	87.33±18.86	80.25±13.25	15	91.00±11.80	83.00±13.74
Simão, et al.[8]	15	87.33±18.86	89.25±15.57	15	91.00±11.80	80.07±10.46
Azadbakht, et al.[7]	42	87±0.65	84.0±3.24	42	87±1.30	85.0±3.24
Kwak, et al.[2]	21	74.5±9.7	74.3±9.5	21	73.6±10.8	75.1±8.8
LDL-C						
Liu, et al.[18]	60	3.81±0.88	3.62±0.76	60	3.94±0.90	3.77±0.77
Liu, et al.[18]	60	3.81±0.88	3.68±0.82	60	3.94±0.90	3.82±0.85
Azadbakht, et al.[13]	21	151±15	153±20	20	149±16	141±21
Azadbakht, et al.[13]	21	151±15	148±11	20	149±16	138±19
Azadbakht, et al.[13]	21	151±15	156±29	20	149±16	132±26
Azadbakht, et al.[13]	21	151±15	158±31	20	149±16	128±14
Azadbakht, et al.[15]	14	144.2±6.7	146.2±6.7	14	145±6.3	138.7±8.9
Kwak, et al.[2]	21	119.6±31.4	119.9±31.2	21	114.4±25.9	123.1±23.9
Teixeira, et al.[24]	14	2.50±0.63	2.51±0.71	14	2.61±0.75	2.55±0.75
Pipe, et al.[14]	29	2.98±2.15	2.90±0.65	29	2.95±0.65	2.78±0.70
Azadbakht, et al.[7]	42	143±5.18	134±21.39	42	142±3.89	127±15.55
HDL-C						
Liu, et al.[18]	60	1.65±0.30	1.57±0.31	60	1.66±0.37	1.63±0.37
Liu, et al.[18]	60	1.65±0.30	1.58±0.30	60	1.66±0.37	1.64±0.37
Azadbakht, et al.[13]	21	43±11	46±17	20	49±14	47±19
Azadbakht, et al.[13]	21	43±11	40±22	20	49±14	52±25
Azadbakht, et al.[13]	21	43±11	43±15	20	49±14	50±20
Azadbakht, et al.[13]	21	43±11	45±19	20	49±14	53±31
Azadbakht, et al.[15]	14	45.8±12.2	46.4±13.5	14	46.5±12.8	49.1±12.6
Kwak, et al.[2]	21	45.6±8.8	45.8±8.8	21	46.5±12.9	44.9±9.7
Teixeira, et al.[24]	14	0.92±0.19	0.89±0.22	14	0.96±0.22	1.00±0.19
Pipe, et al.[14]	29	1.16±0.27	1.12±0.22	29	1.19±0.27	1.14±0.27
Azadbakht, et al.[7]	42	31.0±2.59	33.3±4.54	42	32.0±2.59	34.0±4.54
TG						
Liu, et al.[18]	60	1.30±0.70	1.24±0.66	60	1.35±0.79	1.34±0.79
Liu, et al.[18]	60	1.30±0.70	1.28±0.74	60	1.35±0.79	1.39±1.02
Azadbakht, et al.[13]	21	238±39	235±45	20	249±51	239±42
Azadbakht, et al.[13]	21	238±39	239±36	20	249±51	236±40
Azadbakht, et al.[13]	21	238±39	228±42	20	249±51	231±37
Azadbakht, et al.[13]	21	238±39	232±49	20	249±51	224±43
Azadbakht, et al.[15]	14	240.5±61.6	243.7±61.0	14	242.5±60.0	232.6±62.1
Kwak, et al.[2]	21	128.1±47.1	129.1±67.3	21	128.1±81.4	126.6±87.0
Teixeira, et al.[24]	14	2.32±1.76	2.18±1.38	14	1.95±1.23	1.90±1.09
Pipe, et al.[14]	29	1.18±0.43	1.14±0.43	29	1.11±0.48	1.13±0.48
Anderson, et al.[16]	8	2.88±3.03	3.22±2.97	8	3.36±3.20	2.91±2.66
Azadbakht, et al.[7]	42	219±8.42	213±7.78	42	220±7.13	210±11.02

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Table 1. Diabetes, Obesity, and MS Markers Level at Baseline and at the End of Soy Protein Supplementation (Continued)

First author	Control group			Supplementation group		
	n	Baseline mean±SD	End mean±SD	n	Baseline mean±SD	End mean±SD
TC						
Liu, et al.[18]	60	5.63±0.93	5.33±0.87	60	5.83±0.94	5.58±0.84
Liu, et al.[18]	60	5.63±0.93	5.43±0.92	60	5.83±0.94	5.67±0.87
Azadbakht, et al.[13]	21	218±38	221±45	20	225±48	216±39
Azadbakht, et al.[13]	21	218±38	225±53	20	225±48	209±35
Azadbakht, et al.[13]	21	218±38	227±56	20	225±48	207±38
Azadbakht, et al.[13]	21	218±38	228±48	20	225±48	201±35
Azadbakht, et al.[15]	14	197.0±47.2	200.5±48.9	14	201.4±45.2	188.7±41.0
Kwak, et al.[2]	21	190.8±29.8	191.5±33.1	21	186.5±31.8	193.3±29.2
Pipe, et al.[14]	29	4.67±0.97	4.53±0.81	29	4.64±0.86	4.43±0.92
Anderson, et al.[16]	8	4.96±1.39	5.12±1.39	8	5.32±1.53	5.01±1.33
Azadbakht, et al.[7]	42	238±6.48	228±5.83	42	239±5.83	217±3.24
CRP						
Liu, et al.[18]	60	1.24±3.11	1.08±2.42	60	1.01±2.06	1.16±2.54
Liu, et al.[18]	60	1.24±3.11	1.11±3.32	60	1.01±2.06	0.91±1.48
Azadbakht, et al.[13]	21	3.5±0.2	3.7±0.1	20	3.8±0.1	3.2±0.1
Azadbakht, et al.[13]	21	3.5±0.2	3.6±0.3	20	3.8±0.1	3.1±0.1
Azadbakht, et al.[13]	21	3.5±0.2	3.8±0.1	20	3.8±0.1	2.5±0.08
Azadbakht, et al.[13]	21	3.5±0.2	3.9±0.2	20	3.8±0.1	2.4±0.1
Azadbakht, et al.[17]	42	-1.7±0.6		42	-2.0±0.3	

MS, metabolic syndrome; FPG, fasting plasma glucose; FSI, fasting serum insulin; HOMA-IR, homeostasis model of assessment for insulin resistence index; HbA1c, hemoglobin A1c; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; CRP, C-reactive protein.

publications, lack of interest in the presently investigated relationship, and no soy protein supplementation were excluded. Finally, 7, 9, 5, 3, 8, 8, 11, 11, 12, 11, and 7 studies for body weight, blood glucose, insulin level, HOMA-IR, systolic blood pressure (SBP), diastolic blood pressure (DBP), LDL-C, high-density lipoprotein cholesterol (HDL-C), TG, TC, and CRP, respectively, were included in the meta-analysis (Fig. 1). Table 1 shows the means, SDs (pre/post or change), and number of participants for the supplementation and control groups.

Body weight

Seven RCTs on body weight met our inclusion criteria. A total of 203 subjects with soy protein supplementation and 207 control subjects were identified (Table 2). Among the eleven studies, the duration of treatment varied from 8 weeks to 4 years. The overall effect on body weight in T2D and MS individuals was not significant (WMD, -0.072; 95% CI, -0.266 to 0.122; p=0.467; I^2, 0.000) (Table 2).

Diabetes markers

Blood glucose

Nine trials on the relationship between soy protein supplementation and blood glucose level met our inclusion criteria (Table 2). A total of 279 T2D or MS patients with soy protein supplementation and 279 control patients were included in this analysis. The duration of treatment varied from 8 weeks to 4 years. Overall, a significant result was detected (WMD, -0.207; 95% CI: -0.374 to -0.040; p=0.015; I^2=0.000) with the random-effect model in glucose level with soy protein supplementation. Subjects consuming soy protein for a longer duration (≥6 mo: WMD, -0.302; 95% CI, -0.536 to -0.068; p=0.012; I^2=0.000) had a notably lower glucose level than that for shorter durations (<6 mo: WMD, -0.110; 95% CI, -0.347 to 0.128; p=0.365; I^2=0.000) in the random-effect model (Table 2).

Insulin and HOMA-IR

Five trials with 199 soy subjects and 195 control subjects for the relationship between soy protein supplementation and insulin level were included in this meta-analysis (Table 2). A random-effect model was used to evaluate the influence of soy on insulin levels. A significant difference was found in insulin levels with soy protein supplementation (WMD, -0.292; 95% CI, -0.496 to -0.088; p=0.005; I^2=90.289). Subjects that consumed soy protein for a shorter duration (<6 mo: WMD, -0.390; 95% CI, -0.638 to -0.142; p=0.002; I^2=92.374) had notably lower insulin levels than those for a longer duration (≥6 mo: WMD, -0.088; 95% CI, -0.446 to 0.270; p=0.631; I^2=0.000) in the random-effect model (Table 2).

Three trials with 162 soy protein subjects and 162 control subjects for the relationship between soy protein supplementations and the HOMA-IR were included in this analysis (Table

Table 2. Subgroup Analysis of the Effect of Soy Protein Supplementation on Diabetes, Obesity, and MS Markers in T2D and MS Patients

	Trials	n (con/supp)	WMD (95% CI)	*p* value	I^2
Diabetes markers					
FPG					
Overall	9	279/279	-0.207 (-0.374 to -0.040)	0.015	0.000
Duration					
<6 mo	4	135/139	-0.110 (-0.347 to 0.128)	0.365	0.000
≥6 mo	5	144/140	-0.302 (-0.536 to -0.068)	0.012	0.000
FSI					
Overall	5	195/199	-0.292 (-0.496 to -0.088)	0.005	90.289
Duration					
<6 mo	4	135/139	-0.390 (-0.638 to -0.142)	0.002	92.374
≥6 mo	1	60/60	-0.088 (-0.446 to 0.270)	0.631	0.000
HOMA-IR					
Overall	3	162/162	-0.346 (-0.570 to -0.123)	0.002	91.173
Duration					
<6 mo	2	102/102	-0.504 (-0.790 to -0.218)	0.001	94.913
≥6 mo	1	60/60	-0.099 (-0.457 to 0.259)	0.587	0.000
Obesity markers					
Weight					
Overall	7	207/203	-0.072 (-0.266 to 0.122)	0.467	0.000
Duration					
<6 mo	2	63/63	-0.077 (-0.426 to 0.273)	0.667	0.000
≥6 mo	5	144/140	-0.070 (-0.304 to 0.164)	0.557	24.484
MS markers					
SBP					
Overall	8	177/173	-0.027 (-0.237 to 0.183)	0.799	0.000
Duration					
<6 mo	4	93/93	-0.032 (-0.320 to 0.257)	0.830	6.487
≥6 mo	4	84/80	-0.022 (-0.329 to 0.284)	0.886	0.000
DBP					
Overall	8	177/173	-0.230 (-0.441 to -0.019)	0.033	0.000
Duration					
<6 mo	4	93/93	-0.253 (-0.544 to 0.038)	0.089	48.021
≥6 mo	4	84/80	-0.205 (-0.512 to 0.102)	0.191	0.000
LDL-C					
Overall	11	324/320	-0.304 (-0.461 to -0.148)	0.000	45.995
Duration					
<6 mo	5	166/166	-0.160 (-0.375 to 0.056)	0.147	0.000
≥6 mo	6	158/154	-0.382 (-0.609 to -0.156)	0.001	57.827
HDL-C					
Overall	11	324/320	-0.047 (-0.202 to 0.107)	0.548	0.000
Duration					
<6 mo	5	166/166	-0.081 (-0.296 to 0.135)	0.463	0.000
≥6 mo	6	158/154	-0.012 (-0.235 to 0.210)	0.916	0.000
TG					
Overall	12	332/328	-0.094 (-0.248 to 0.059)	0.227	0.000
Duration					
<6 mo	6	174/174	-0.101 (-0.312 to 0.110)	0.347	0.000
≥6 mo	6	158/154	-0.087 (-0.310 to 0.136)	0.444	0.000
TC					
Overall	11	318/314	-0.386 (-0.548 to -0.225)	0.000	85.275

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Table 2. Subgroup Analysis of the Effect of Soy Protein Supplementation on Diabetes, Obesity, and MS Markers in T2D, and MS Patients (Continued)

	Trials	n (con/supp)	WMD (95% CI)	*p* value	I^2
Duration					
<6 mo	6	174/174	-0.443 (-0.666 to -0.220)	0.000	91.927
≥6 mo	5	144/140	-0.324 (-0.559 to -0.088)	0.007	26.703
CRP					
Overall	7	246/242	-0.510 (-0.722 to -0.299)	0.000	97.745
Duration					
<6 mo	2	102/102	-0.178 (-0.456 to 0.099)	0.208	85.463
≥6 mo	5	144/140	-0.971 (-1.298 to -0.645)	0.000	98.375

MS, metabolic syndrome; T2D, type 2 diabetes; FPG, fasting plasma glucose; FSI, fasting serum insulin; HOMA-IR, homeostasis model of assessment for insulin resistence index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; CRP, C-reactive protein.

2). A significant difference was detected (WMD, -0.346; 95% CI, -0.570 to -0.123; p=0.002; I^2=91.173). Subjects that consumed soy protein for a shorter duration (<6 mo: WMD, -0.504; 95% CI, -0.790 to -0.218; p=0.001; I^2=94.913) had notably lower HOMA-IR than that for a longer duration (≥6 mo: WMD, -0.099; 95% CI, -0.457 to 0.259; p=0.587; I^2=0.000) in the random-effect model (Table 2).

Metabolic syndrome markers

Systolic blood pressure and DBP

The SBP (soy n=173; control n=177) and DBP (soy n=173; control n=177) were measured in ten trials studies. Overall, SBP (WMD, -0.027; 95% CI, -0.237 to 0.183; p=0.799; I^2=0.000) was not significantly correlated, whereas a significant difference in DBP with soy protein supplementation was detected (WMD, -0.230; 95% CI, -0.441 to -0.019; p=0.033; I^2=0.000) in the random-effect model (Table 2).

LDL-C, HDL-C, TG, and TC

In eleven studies, LDL-C (soy n=320; control n=324), HDL-C (soy n=320; control n=324), and TC (soy n=314; control n=318) were analyzed, while TG (soy n=328; control n=332) was measured in twelve studies. Overall, significant differences were detected in LDL-C (WMD, -0.304; 95% CI, -0.461 to -0.148; p=0.000; I^2=45.995) and TC (WMD, -0.386; 95% CI, -0.548 to -0.225; p=0.000; I^2=85.275) with soy protein supplementation. Furthermore, as for LDL-C, longer duration (≥6 mo) seemed to be more effective (WMD, -0.382; 95% CI, -0.609 to -0.156; p=0.001; I^2=57.827), compared to a shorter duration (<6 mo) (WMD, -0.160; 95% CI, -0.375 to 0.056; p=0.147; I^2=0.000). However, no significant differences were detected in HDL-C and TG level with soy protein supplementation in the random-effect model (Table 2).

CRP

Seven studies investigated the association between CRP and soy protein supplementation (soy n=242; control n=246). Overall, a significant difference was detected in this analysis (WMD, -0.510; 95% CI, -0.722 to -0.299; p=0.000; I^2=97.745). On the basis of duration, we found a remarkable difference in the longer duration (≥6 mo) treatment group (WMD, -0.971; 95% CI, -1.298 to -0.645; p=0.000; I^2=98.375), compared with the shorter duration (<6 mo) treatment group (WMD, -0.178; 95% CI, -0.456 to 0.099; p=0.208; I^2=85.463) in the random-effect model (Table 2).

DISCUSSION

In this meta-analysis, we found significant changes in FPG, FSI, HOMA-IR, DBP, LDL-C, TC, and CRP with soy protein supplementation, compared with the placebo control group, in T2D or MS population. In this meta-analysis, we collected a large number of references and stratified different subgroups.

Overweight and obesity are health problems that increase the risk of CVD and T2D. In this meta-analysis, we failed to show that soy protein supplementation could significantly reduce body weight in T2D or MS population. Soy protein supplementation seems to be ineffective in reducing body weight.

We also found that soy protein improved glycemic control. Compared with the control diet, HOMA-IR decreased significantly at the end of soy protein dieting. It is highly possible that a shorter duration (<6 mo) of soy protein supplementation is more effective in improving HOMA-IR than a longer duration (≥6 mo).

The notion that oral soy supplementation might have effects on lowering insulin levels has been reported previously.[7,13] In this meta-analysis, soy protein with or without soy isoflavone supplementation resulted in favorable changes in the descriptors for FSI. Furthermore, soy protein supplementation for a shorter term (<6 mo) seemed to be more effective in reducing FSI. Favorable effects of soy protein with or without soy isoflavone supplementation on FSI in T2D or MS patients need to be further confirmed.

Several reports have revealed that a shorter or longer duration of supplementation alters blood glucose level, compared with a placebo group.[7,13] In this meta-analysis, we found lon-

ger supplementation duration (≥6 mo) reduced blood glucose levels significantly. Therefore, longer duration of soy protein supplementation is better to reduce blood glucose.

In the present study, serum LDL-C was significantly reduced in soy protein consumption group, compared with a control group, which is consistent with the majority of prior soy intervention stdies in adults with T2D.[7,13,15] In contrast, in three other studies, serum LDL-C did not change significantly in adults with T2D following consumption of extracted soy protein.[2,18,24] Serum TC was significantly affected by soy protein consumption in the current meta-analysis study, which is consistent with previous soy intervention studies.[24] Serum HDL-C levels were not significantly affected by soy protein consumption in the current meta-analysis, which is consistent with previous studies.[2,7,13-15,18] In a few studies HDL-C was found to be significantly increased.[24] Overall, the majority of soy intervention studies in adults with T2D did not demonstrate effects on HDL-C; nevertheless, maintenance of HDL-C while reducing LDL-C concentrations may be regarded as a desirable outcome.

Serum TG was not significantly affected by soy protein consumption in the current meta-analysis, which is consistent with previous studies.[2,7,14,18] In contrast, however, some other studies on adults with T2D or MS did find significant reductions in TG.[13,15,16] The above conflicting results mean that serum TG should been further researched in future soy intervention studies in patients with T2D or MS.

It has been reported that circulating inflammatory markers levels are higher in diabetic patients.[13,25] Our findings suggest that longer term soy protein substitution in the diet decreases CRP significantly, compared with placebo. The improvements in inflammation status of soy protein group might result in a decline in CVD risk and also renal failure.[13,17]

When interpreting this meta-analysis, some limitations need to be considered. First, on the analyses of clinical indices, the large between-study heterogeneity in the effects of soy protein emerged. To identify the potential sources of heterogeneity, we conducted a sub-analysis, although we failed to find a clear explanation. Variability of experimental designs or exposition protocols may result in the conflicting results. Second, due to the limitations in quantity and size of experiments, the interactions among physical status, usage amount, and term of soy protein supplementation on body weight, blood glucose, and other clinical indices were not analyzed in this study. Therefore, larger and better designed intervention studies are still needed.

Soy protein supplementation could improve CVD risks and significantly improve glucose metabolism, compared with placebo, in T2D or MS patients. Furthermore, shorter supplement duration could significantly reduce FSI and HOMA-IR, whereas longer supplement duration could remarkably reduce blood glucose, LDL-C, and CRP. Hence, dietary soy protein supplementation might have a potential beneficial effect on diabetes. However, larger and more well-designed studies are recommended.

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