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Original Research

A Complementary Therapy with Whey Protein in Diabetes: A Double-Blind Randomized Controlled Clinical Trial

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Abstract

Type 2 diabetes (T2DM) and its complications can cause severe morbidity and mortality. The researchers and clinicians' attention has been toward finding an efficient treatment for T2DM to decrease its heavy burden on the people and countries. Whey protein (WP) is a known glucose-lowering treatment of traditional Persian medicine. This randomized controlled clinical trial aimed to evaluate the efficacy of the WP on the improvement of the glycemic index of the patients with T2DM in Fars, Fasa, Iran. A total of 58 patients with T2DM met the inclusion criteria and were randomly assigned to one of two groups: intervention or placebo. For 12 weeks, they were given 1 sachet of WP or 1 sachet of placebo. Before and after the trial, fasting blood sugar (FBS), lipid profile, and liver enzymes were tested. Finally, 35 patients completed the study (18 in the whey group and 17 in the placebo group). The mean ± standard deviation of age, BMI, and the disease duration in placebo group were 52.1±9.2 years, 26.8±3.9 kg/m2 and 102.9±67.7 months and in WP group were 51.2±8.2 years, 25.7±3.7 kg/m2 and 74.2±51.1 months. There were no significant differences among the study groups at the beginning (P>0.05). Meanwhile, the WP and placebo groups were the same by means of the amount of anti-diabetic drugs that participants consumed (P=0.242). After 12 weeks FBS and hemoglobin A1C amounts showed remarkable decreases in the WP group compared to its starting point (P=0.011 and P=0.001 respectively); while in the placebo group, no significant difference was observed (P>0.05). No severe complications were reported in the two groups. In conclusion, we found that whey protein would be a promising complementary therapy to control hyperglycemia in the patients with T2DM.

Keywords: Whey protein; Diabetes mellitus; Type 2 diabetes; Complementary medicine

Introduction

Type 2 diabetes (T2DM) is a non-communicable disease which can cause dangerous complications for the patients such as digestive disorders, nephropathy, cardiovascular disease, neuropathy, and diabetic foot ulcer [1]. The prevalence of T2DM increased in the last decades, and annually, the incidence of age is decreasing in different countries [2]. Furthermore, expensive care and supportive treatments lead to a huge economic and health burden on society [3]. Therefore, attempts were improved to control the T2DM incidence and symptoms [4].

To date, sodium-glucose inhibitors (SGLT2), continuous glucose monitoring, glucagon-like peptide-1

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receptor agonists (GLP-1), and insulin pumps, on the other hand, have made significant progress in managing T2DM symptoms across the globe. However, various countries continue to see a rise in the number of cases and mortality [5]. Lack of effort, accessibility, and education might be the major reason for this condition, especially in low-income countries [5]. Moreover, different adverse effects are observed by present conventional treatments of hyperglycemia in diabetics. Therefore, developing new therapies with fewer adverse effects and more efficiency and accessibility is required [6].

In the last decades, several natural products demonstrated high efficiency in the management of diabetics [7]. Expanded sources of natural material in almost all regions encourage the health care systems to improve the application of natural-based treatments in the health policy of T2DM. Thus, researchers developed natural medications by regulating the frequency and components of the usual meals of diabetics [8].

Significant weight loss induced by recommended diets increases hunger and dysregulates the gastrointestinal hormones in patients with T2DM, respectively. Controlling the increased hunger and gastrointestinal secretions would therefore be a concern in diabetes care [9]. Some studies indicated that obeying high-protein diets, especially using dietary products in breakfast, would result in a significant weight loss and help the patients keep their appetite low [10].

Whey protein (WP) is a known glucose-lowering treatment of traditional Persian medicine [9]. Among different studied proteins, WP is one of the most potent proteins in inducing insulin secretion with a high rate of absorption and bioavailability [11]. This medication has been shown in recent research to reduce diabetes-induced inflammation and oxidative stress, as well as prevent additional T2DM problems [12]. In addition, WP effectively decreased hyperglycemia in diabetic individuals [13]. Some studies hypothesized that promising effects of WP on the secretion of insulin, glucagon, and GLP-1 would be the responsible pathway for glucose-lowering properties of WP in the long-term period [14].

The present study aimed to investigate the efficiency and safety of glucose-lowering effects of WP in patients with T2DM.

Materials and Methods

Study design and participants

This is a double-blind randomized controlled clinical trial. Participants were selected among the T2DM patients who came to the diabetic clinic of Fars, Fasa, Iran. The eligible participants were recruited into the study through face-to-face contact and signing informed consent after receiving comprehensive data about the study. Inclusion criteria were: the age between 30 to 65 years old, with hemoglobin A1c (HbA1C) > 6.4; weight < 100 kg; body mass index (BMI) < 35; no history of alcohol or drug addiction, steroids or antidiabetic herbal medications, and no medical disorders such as hypertension, renal failure, rheumatologic or liver diseases were included in the study. Exclusion criteria were: disagreement to participate in the study, having a FBS more than 270 mg/dL, consuming corticosteroid drugs during the study, and presence of any side effects.

This study was approved by the ethics committee of Fasa university of medical sciences (Code: IR.FUMS.REC.1396.313) and Iranian registry of clinical trials IRCT20140715018490N4. The CONSORT chart of this study is shown at figure 1.

Sample Size

Upon several clinical trials on WP (Ma-al-Jobon), a wide range from the sample sizes from 8 to more than 120 in the literature [12,13,15-19]. To determine the sample size in the study based on pilot studies, the rate of changes in fasting blood sugar (FBS) was considered 42±9/32 in WP powder group and 34±7/67 in control group. Considering 90% power and 95% confidence interval, the sample size in each group was estimated to be 24 patients, and finally with the possibility of attrition during the study, 5 cases were added in each group.

$$n_1 = n_2 = \frac{(S_1^2 + S_2^2)(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2}{(\bar{X}_1 - \bar{X}_2)^2}$$

Making drug and placebo sachets

WP powder was bought from Mani Mas Company, Fars, Fasa, Iran, and sachets containing 12.5 g of WP powder were prepared for the intervention group. Hence, sachets of caramelized corn powder (5 g each) were prepared for the placebo group. To blind the patients and the physician, the essence of orange was added to both sachets, and the sachet covers were the same in shape and color for both groups.

Randomization and blinding method

On the basis of a blocked randomization list, individuals were assigned to study groups. With a 1:1 allocation and random block sizes of 4, this list was constructed using Excel 2018 software. Each patient received a pack of sachets of intervention or placebo group based on the randomization list. Only the main researcher was aware of the codes on the sachets, while the physician and the patients were blind to them.

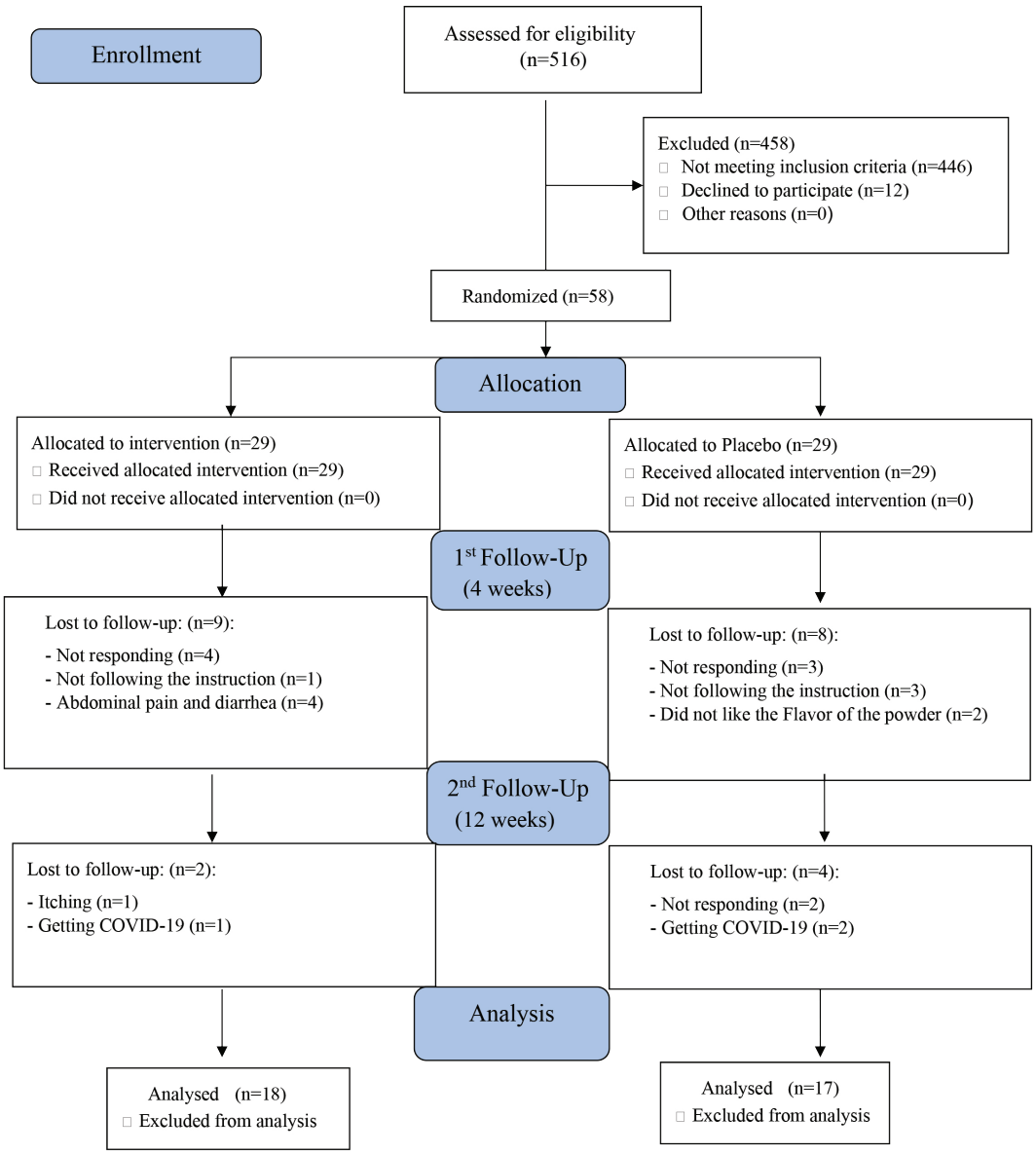

Figure 1. CONSORT Flow Diagram

Intervention

All participants received a sachet of WP powder (12.5 g each) or caramelized corn powder (5 g each), and were asked to dissolve sachets in 150 to 200 mL of hot water and drink it before breakfast for 12 weeks [12,15,20].

Measurements

After taking demographic and basic information of participants, a blood sample was taken from everyone and FBS, 2 hour postprandial sugar (2hpp), lipid profile (cholesterol, Chol; low-density lipoprotein-cholesterol, LDL-C; high-density lipoprotein-cholesterol, HDL-C; triglyceride, TG) and liver function (serum glutamic oxaloacetic transaminase, SGOT; serum glutamic-pyruvic transaminase, SGPT; Alkaline phosphatase, ALP) were assessed. Then, they were asked to consume one sachet in the morning for 4 weeks. After 4 weeks, the patients were checked in terms of how to use the medicine and possible side effects, and then the same drug boxes were given to them for additional 8 weeks. At the end of the study (after 12 weeks), the participants were visited, and all the starting laboratory tests were repeated. Meanwhile, every probable adverse effect was recorded during and at the end of study.

Statistical Analysis

The data were presented by mean ± standard deviation. Comparison of variables between control and intervention groups was done using independent t-test and Chi-squared (X2) distribution based on the variables. Before-after analysis was done with paired t-test. A P<0.05 was considered the significant level. All analyses were done in IBM SPSS 24 (IBM SPSS, Chicago, Ill)

Results

Out of 516 initially assessed individuals, 70 had the inclusion criteria; 12 of them did not accept to enroll in the study. After taking the informed consent, 58 individuals were recruited to the study (29 in each group). Among them, 17 participants at the first follow-up (9 from WP group and 8 from the placebo group) and 6 at the second follow-up (2 from WP group and 4 from the placebo group) were excluded from the study, and 35 finished the study protocol (Figure 1). The demographic and basic information is shown in table 1. There were no significant differences among the study groups at the beginning (P>0.05). Meanwhile, WP and placebo groups were the same regarding the amount of antidiabetic drugs that participants consumed (P=0.242), gender distribution (64.3% females in both groups, P=1), and disease duration (74.2±51.1 months for WP group compared to 102.9±67.7 for the placebo group, P=0.093).

Table 1. The comparison of demographic and basic outcome measures between two groups at the beginning of the study.

Variable	Placebo (n=29)		Whey (n=29)		P-value
	Mean	SD*	Mean	SD	
Age (Year)	52.1	9.2	51.2	8.2	0.698
BMI[1] (Kg/m^2)	26.8	3.9	25.7	3.7	0.288
FBS[2] (mg/dl)	182.2	56.1	181.7	52.5	0.595
Hb A1C[3] (%)	9.26	1.98	9.04	1.7	0.552
SGOT[4] (mg/dl)	20.0	6.5	19.9	7.3	0.545
SGPT[5] (mg/dl)	23.5	13.9	28.3	9.2	0.204
ALP[6] (mg/dl)	194.1	48.6	198.5	55.5	0.766
Total Chol.[7] (mg/dl)	161.8	39.3	160.4	42.1	0.902
LDL[8] (mg/dl)	85.5	32.5	85.0	38.7	0.960
HDL[9] (mg/dl)	42.6	7.3	44.3	8.3	0.442
TG[10] (mg/dl)	169.0	72.7	176.7	88.9	0.728

*SD: Standard deviation

1. Body mass index 2. Fasting blood sugar 3. Hemoglobin A1C 4. Serum glutamic oxaloacetic transaminase 5. Serum glutamic-pyruvic transaminase 6. Alkaline phosphatase 7. Total Cholesterol 8. Low density lipoprotein 9. High density lipoprotein 10. Triglyceride

Outcomes

All the observed differences during the research period had no statistically significant difference between study groups, But, within groups, after 12 weeks, FBS amounts showed significant decreases in the WP group compared to the baseline vaalues (144.5±46.3 vs. 181.7±52.5, P=0.011); while in the placebo group, there was no significant difference in this matter (182.2±56.1 vs. 158.9±53.9, P=0.079). Moreover, at the end of study, the amounts of HbA1C showed a statistically significant decrease in WP group compared to the baseline level (7.8±2.06 vs. 9.04±1.7, P=0.001). Meanwhile, there was no significant correlation among any outcomes and age, disease duration, or BMI, neither between nor within study groups (P>0.05). The comparison between the initial and final amounts of main outcomes of the study between and within groups is shown in table 2.

Adverse effects observed during the intervention

There was no significant difference between the two groups in regard to adverse events (P=0.066). Four cases of abdominal pain and diarrhea (13.8%) and 1 case of itching (3.5%) were observed in the WP group; while in the control group, 2 cases of unpleasant flavor (6.9%) were seen. All side effects were self-limited and did not need any additional medical intervention.

Discussion

It was found that a twelve-week consumption of WP significantly reduces FBS level and HgA1C in comparison with placebo. Thus, according to several pre-

Table 2. The comparison of the main study outcomes within and between two groups at the starting point and end of the study (after 12 weeks).

Variable	Group	Before	After	Mean difference ±SD	P-Value*
FBS[1] (mg/dl)	Whey	181.7±52.5	144.5±46.3	-39.33±58.7	**0.011**
	Placebo	182.2±56.1	158.9±53.9	-34.17±59.6	0.079
	P- Value**	0.673	0.605		
HbA1C[2] (%)	Whey	9.04±1.7	7.82±2.06	-1.2±1.3	**0.001**
	Placebo	9.26±1.98	8.76±2.32	-0.5±2.5	0.433
	P- Value**	0.615	0.217		
SGOT[3] (mg/dl)	Whey	19.9±7.3	21.2±7.1	-1.8±5.9	0.208
	Placebo	20.0±6.5	19.24±6.0	0.88±4.3	0.411
	P- Value**	0.606	0.930		
SGPT[4] (mg/dl)	Whey	28.3±13.4	20.3±4.4	-3.72±10.4	0.150
	Placebo	23.5±13.9	20.1±9.0	2.9±15.7	0.452
	P- Value**	0.301	0.958		
Total Chol.[5] (mg/dl)	Whey	160.4±42.1	157.7±45.0	-2.05±16.5	0.604
	Placebo	161.8±39.3	146.3±55.7	-17.29±45.4	0.136
	P- Value**	0.919	0.511		
TG[6] (mg/dl)	Whey	176.7±88.8	141.2±60.2	-12.69±35.4	0.147
	Placebo	169.0±72.7	156.4±70.7	-11.47±47.2	0.333
	P- Value**	0.781	0.498		
HDL[7] (mg/dl)	Whey	44.3±8.3	45.3±5.8	1.14±3.7	0.211
	Placebo	42.6±7.3	44.00±7.2	0.05±5.1	0.963
	P- Value**	0.442	0.538		
LDL[8] (mg/dl)	Whey	85.0±38.7	88.3±34.3	-0.27±14.4	0.936
	Placebo	85.5±32.5	83.3±37.2	-2.82±21.6	0.597
	P- Value**	0.960	0.684		
2hpp[9] (mg/dl)	Whey	267.5±84.8	195.1±57.1	-72.44±107.7	**0.011**
	Placebo	277.1±72.4	234.8±77.2	-42.6±108.4	0.124
	P- Value**	0.692	0.099		

* The comparison within each group.
** The comparison between each group.
Data were presented as mean±SD.
(Mean difference = after – before)
1. Fasting blood sugar 2. Hemoglobin A1C 3. Serum glutamic oxaloacetic transaminase 4. Serum glutamic-pyruvic transaminase 5. Total Cholesterol 6. Triglyceride 7. High density lipoprotein 8. Low density lipoprotein 9. 2-hour post-prandial blood sugar

vious promising effects of the WP in glucose levels of diabetics, this study hypothesized that the WP would indicate glucose-lowering effects in the long-term period.

Cow's milk is one of the most important sources of different proteins. In the last decade, some studies indicated that higher consumption of cow's milk is associated with a lower risk of T2DM. Therefore, several further studies assumed that different isolated products of cow's milk would develop T2DM management [21]. Twenty percent of cow's milk contains WP, a lactoglobulin- and lactalbumin-rich protein [22]. Multiple trials repeatedly have been conducted to investigate WP medical applications in different diseases, such as hypercholesterolemia, cancer, and asthma [20, 23,24].

Similar to our results, several studies confirmed that WP is a promising natural glucose-lowering product for developing diabetic health. Also, a further adjustment in data analysis proved that the patients with

lower BMI, blood glucose level, and GLP-1 would benefit better from the therapeutic effects of WP [12]. For the first time, the present study showed that WP supplementation is a complementary therapy with low long-term adverse effects by examining liver and renal function during the trial. Our findings confirmed that 3 months of WP administration demonstrated no significant decrease in renal and liver function. On the contrary, some studies revealed that high-protein diets would cause serious damage to kidney function [25]. Therefore, this condition resulted in dose limitation in studies on the therapeutic application of different protein-based supplementations, such as WP [26]. On the other hand, various recent observations indicated no significant difference in kidney function among individuals with low- or high-protein diets [27]. Similarly, Almario et al. looked into the acute effects of WP on gastrointestinal hormone production after a meal. This research found that WP improves glucose control in T2DM patients with the fewest side effects [13]. Our results suggested that WP improves hyperglycemia in diabetics, but an uncontrolled level of blood glucose is not the most important issue of T2DM [28]. Several inflammatory- and oxidative-stress-mediated complications threaten the quality of life of diabetics, as well [29]. Therefore, chronic inflammation in adipose tissue develops insulin resistance for a long time [30]. To date, some studies developed promising supplementations, such as vitamin D, to control the inflammation mechanisms in the patients with T2DM, but we have a long way to achieve more acceptable therapeutic outcomes [31]. Moreover, long-term affordable elimination of a high level of the inflammatory factors would be one of the main goals of different trials via the lifestyle interventions.

In a recent 3-month randomized controlled trial conducted by Derosa et al., cysteine-rich WP decreased inflammatory factors, such as interleukin-6, tumor necrosis factor-α, and high sensitivity C-reactive protein in patients with T2DM. Moreover, the WP group showed a significant increase in oxidative stress agents, including superoxide dismutase, glutathione peroxidase, and glutathione, alongside positive effects on glucose and lipid metabolisms [19]. In contrast, although our findings supported the glucose-lowering effects of WP, the improvement of lipid profile was not statistically important. Therefore, further studies would be required to solve this controversy in the future.

Our research contained certain limitations, as well as some advantages. This was a well-designed randomized-controlled clinical study that followed T2DM patients for three months to see whether WP supplementation was safe and effective. Participants would feel uneasy if there was a lot of caramelized corn in the mix. Thus, as a result, the present study faced a limitation in the application of more amounts of placebo to increase the dose of WP and follow-up with appropriate blinding. Furthermore, previous studies indicated that the WP would negatively affect kidney function in the long-term applications [25]. Therefore, we administered low doses of WP to perform a safe follow-up of the patient in long-term period. The sample size of this study is not large, mainly due to the low number of eligible applicants. According to the acceptable safety of WP observed in the present study, further studies would try to investigate higher doses with a longer follow-up and bigger sample size to achieve more reliable findings.

Our studies had some limitations. One of the most important problems in carrying out the plan was the follow-up of patients during the COVID pandemic, which led to an excessive reduction in the number of patients and their lack of cooperation. Due to the effects that whey protein on kidney function, kidney tests should be considered in the next plans.

Conclusion

Our findings supported the confirmed promising glucose-lowering of WP in a long-term follow-up. Moreover, the result of the present study showed no significant clinical adverse effects or decrease in renal and liver function. Therefore, WP would be a promising complementary therapy to control hyperglycemia in the patients with T2DM. Further studies with bigger sample size, higher doses, and longer follow-up would be required to confirm these results in the future.

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Conflict of Interests

The authors declare that they have no competing interests.

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