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Effect of Vitamin C Therapy on Serum Parameters in Patients with Type 2 Diabetes Mellitus: Clinical Trial

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Abstract

Objective: Diabetes mellitus (DM) is a leading cause of morbidity and death worldwide. DM will affect 570.9 million people worldwide by 2025. The usefulness of vitamin C in improving diabetes control has been a point of contention.

Materials and Methods: This clinical-trial double-blind study with control groups was conducted on 164 patients with type 2 diabetes mellitus (T2DM). The intervention group received 1000 mg of oral vitamin C daily, and a placebo was administered to the controls. To analyze the obtained data, one-way ANOVA was used in SPSS software (version 20). A $P< 0.05$ was considered statistically significant.

Results: Fasting blood sugar (FBS), hemoglobin A1c (HbA1C), triglyceride (TG), and high-density lipoprotein (HDL) were improved significantly in the intervention group ($P< 0.05$), while the low-density lipoprotein (LDL) and cholesterol were unaffected ($P> 0.05$). HbA1C and LDL levels in the control group increased significantly ($P< 0.05$). Meanwhile, this group's HDL levels decreased considerably.

Conclusion: Our findings support the consumption of vitamin C to complement the primary treatment for DM. According to our results, vitamin C provides a clear benefit over a placebo in the treatment of diabetic patients' serum parameters.

Keywords: Clinical trial, Diabetes mellitus, Blood glucose, HbA1C, HDL, LDL, Ascorbic acid

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Introduction

Diabetes mellitus (DM) is a significant cause of morbidity and mortality worldwide. By 2025, DM will reach a global prevalence of 570.9 million (1). Type 2 diabetes mellitus (T2DM) accounts for 91.2% of diabetes diagnoses in the US (2). Patients with DM are at an increased risk of chronic kidney disease, cardiovascular disease, cerebrovascular diseases, infections, and numerous other complications. Researchers in recent years have established the role of free radicals in developing DM complications (3). Therefore, the addition of antioxidants to existing treatments for DM has been investigated (4-7). Ascorbic acid, commonly known as vitamin C, is an active antioxidant that protects diabetic tissues from oxidative stress and scavenges free radicals in the body (8). Additionally, the structural similarities between vitamin C and glucose could impact the transportation of glucose into specific cells (9). Since vitamin C supplements are affordable in many places, they could be a cost-effective addition to T2DM medications (10). (11). Ascorbic acid supplementation has also been shown to improve insulin resistance and regulate fasting blood glucose (FBS) and glycosylated hemoglobin (HbA1c) in some studies (12,13).

There have been disagreements regarding the effectiveness of vitamin C in the improvement of serum levels of FBS, HbA1c, and lipid profile, including high-density lipoprotein (HDL), low-density lipoprotein (LDL), cholesterol, and triglyceride (TG) of DM patients (5,7). One of the major drawbacks of the current literature is the low variation of vitamin C doses administered in clinical trials, especially the number of studies that investigated doses of 1000 mg or higher (13). Additionally, we aim to increase the number of participants to help elucidate vitamin C's effectiveness in ameliorating lipid profile and plasma glucose.

Materials and Methods

Study population

This randomized clinical trial was conducted on 164 DM patients selected by block randomization. The patients with DM referred to the Imam Reza Hospital, Mashhad, Iran, were selected from November 2018 to March 2019. The included participants were individuals diagnosed with T2DM at least 12 months prior to the study, those who received oral hypoglycemic medication regardless of dyslipidemia drugs, and those whose HbA1c levels were under 8. On the other hand, insulin-treated patients, pregnant females, individuals with a glomerular filtration rate under 60, and those who were unwilling to proceed with the experiment were excluded from the study.

Sample size

A total of 200 patients were investigated for inclusion in the study. At the end, 164 DM patients were enrolled. Figure 1 illustrates the flowchart of subject inclusion into the study.

Study design

The patients with DM were assigned to control (n=81) and intervention groups (n=81) by a computerized random allocation. In this study, sealed opaque envelopes were used to conceal the sequencing. The patients and the person responsible for data collection were blind to group allocation. The demographic characteristics, including age, gender, and body mass index (BMI), were recorded on the first visit, and serum levels of FBS, TG, cholesterol, LDL, HDL, and HbA1c were recorded for each patient. Subsequently, 360 pills of 250c vitamin C (Osvah pharmaceuticals, Tehran, Iran) and a placebo (Vitamin C and placebo matched in appearance, placebo was produced by the research center of faculty of pharmacy, Mashhad University of Medical Sciences) were given four times daily for three months

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to the intervention and control groups, respectively. Patients were asked to maintain their usual level of physical activity during the study. We contacted the patients at least once a month to ensure drug compliance was satisfactory during the study period. The subjects were given a contact number to call in case of any inquiries. A nutritionist provided the patients with a diet suitable for diabetic patients, including sufficient vitamin C levels. The patients were reassured that they could decide on to left the study any time. After three months of treatment, FBS, cholesterol, HbA1c, HDL, LDL, and TG serum levels were measured.

Statistical analysis

The data were compared per protocol, and descriptive statistics were displayed as mean, standard deviation (SD), and percentage. T-test and Chi-square test were used to analyze the data. The means comparison was conducted using one-way ANOVA. All the analyses were performed using SPSS software (version 20; IBM, USA). P-values less than 0.05 were considered statistically significant.

Ethical considerations

The study protocol was reviewed and approved by the Ethics Committees of Mashhad University of Medical Sciences, Mashhad, Iran (Number: IR.MUMS. MEDICAL.REC.1397.249), and the study was registered at the Iranian Registry for Clinical Trials (code: IRCT20180627040253N1). Informed consent was attained from the subjects prior to inclusion in the study. Subjects were notified that they could opt-out at any time.

Results

A total of 200 diabetic patients were enrolled in the study; however, 162 cases were selected based on the inclusion and exclusion criteria (Figure 1).

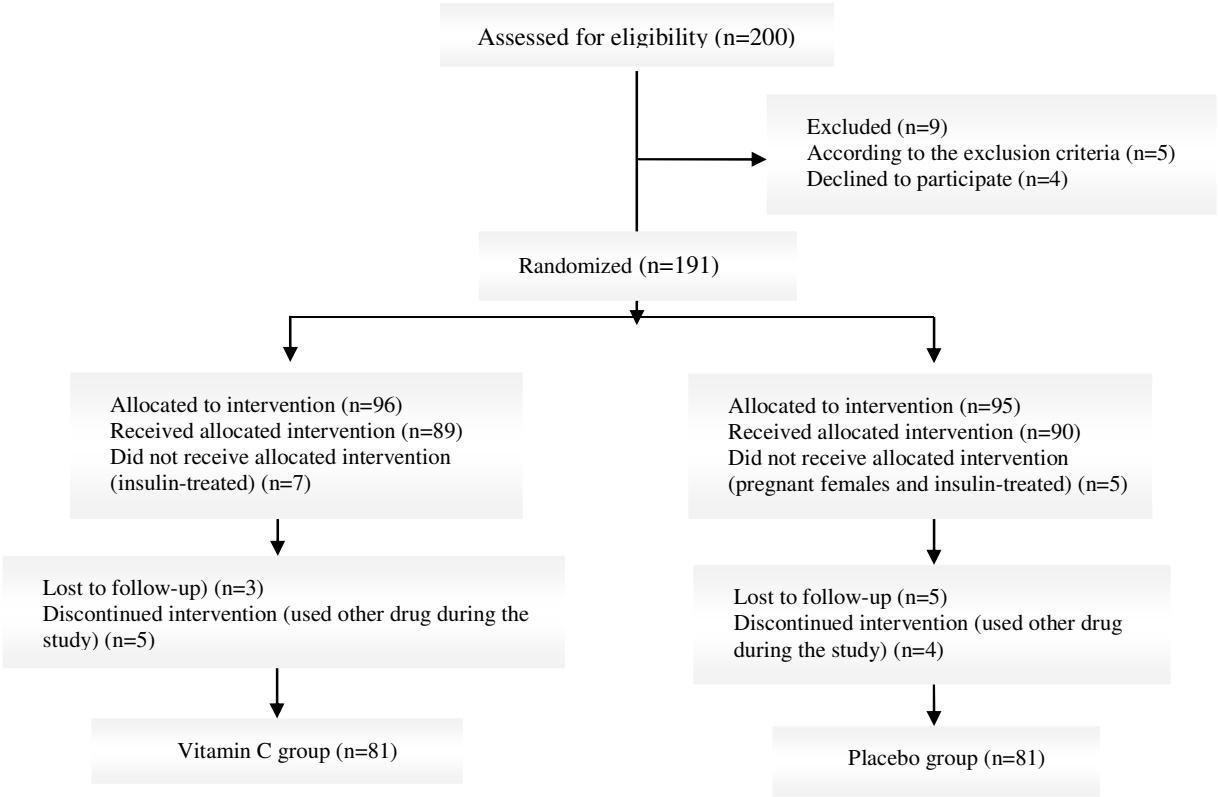

Figure 1. Flow diagram of the Patients

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The results of demographic characteristics are shown in Table 1. There is no significant difference between the control and intervention groups regarding age (*P*= 0.897), BMI (*P*= 0.960), and gender (*P*= 0.875).

A chi-square test was used for comparing gender between groups and T-test was used for comparing age and BMI between groups.

The median duration values of diabetes diagnosis in the intervention and control groups were 8 and 6, respectively. Moreover, the Mann-Whitney U test did not yield a significant divergence between the median values

Mann-Whitney U test The results of FBS, cholesterol, HbA1c, HDL, LDL, and TG serum levels are presented in Table 2. The findings show no statistically significant difference between the control and intervention groups in the mean levels of FBS prior to intervention. However, the treatment resulted in a significant decrease in the intervention group (*P*= 0.001). The intervention group had a significantly lower level of FBS after treatment. Serum FBS levels of the control group did not vary before and after treatment (*P*= 0.177). Measurement of HbA1C levels exhibited higher levels in the intervention group compared to the control group prior to treatment (*P*= 0.032). This disparity was insignificant after treatment (*P*= 0.791). Post-treatment HbA1C declined in the intervention group (*P*= 0.002) and increased in the control group (*P*= 0.037) in a significant manner. The serum level of TG was significantly higher in the intervention group than in the control group (*P*= 0.023). This difference became statistically insignificant post-treatment (*P*= 0.222). The serum TG level of the intervention group decreased significantly after the treatment (P=0.001); on the contrary, the change was insignificant in the control group (*P*= 0.332). The serum cholesterol level of the intervention group exceeded the control group both before (*P*= 0.001) and after (*P*= 0.001) treatment

Table 1. The baseline demographic characteristics of the two groups

Variable		Control (N=81)	Intervention (N=81)	*P*
Gender	Male N (%)	37 (45.1)	36 (43.9)	0.875
	Female N (%)	45 (54.9)	46 (56.1)	
Age[a] (Mean±SD)		52.20 (±13.29)	52.46 (±13.20)	0.897
BMI[a] (Mean±SD)		27.23 (±3.68)	27.21 (±3.43)	0.960
Median (range)		6 (1-35)	8 (1-30)	0.381

a: Independent T-test

Table 2. Comparison of the index of serum levels in the two groups

Variable		Intervention Mean (±SD)	Control Mean (±SD)	*P*[a]
FBS	Pre-intervention	130.32 (± 23.45)	130.71 (± 21.35)	0.911
	Post-intervention	123.46 (± 21.35)	132.56 (± 21.22)	0.007
	P[b]	0.001	0.177	
HbA1C	Pre-intervention	7.06 (± 0.63)	6.83 (± 0.71)	0.032
	Post-intervention	6.93 (± 0.65)	6.91 (± 0.75)	0.791
	P[b]	0.002	0.037	
TG	Pre-intervention	196.43 (±74.04)	173.26 (±53.46)	0.023
	Post-intervention	167.63 (±40.67)	176.65 (±52.62)	0.222
	P[b]	0.001	0.332	
Cholesterol	Pre-intervention	208.48 (±29.60)	179.70 (±31.35)	0.001
	Post-intervention	207.22 (±25.78)	182.40 (±36.73)	0.001
	P[b]	0.479	0.223	
LDL	Pre-intervention	117.02 (±16.09)	108.62 (±18.60)	0.002
	Post-intervention	116.11 (±14.93)	110.99 (±16.30)	0.037
	P[b]	0.339	0.007	
HDL	Pre-intervention	40.29 (±8.34)	41.34 (±7.61)	0.402
	Post-intervention	42.37 (±8.98)	40.16 (±6.81)	0.078
	P[b]	0.001	0.030	

[a] Paired T-test. [b] independent T-test

FBS, fasting blood sugar; Hb A1c, glycated hemoglobin; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein

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significantly. Changes in the cholesterol levels of both groups were insignificant. The significance of higher LDL in the intervention group before treatment (*P*= 0.002) persisted afterward (*P*= 0.037). Furthermore, the rise in the LDL level of the control group was significant (*P*= 0.007), while the changes in the intervention group were insignificant (*P*= 0.339). Our results demonstrated that the pretreatment levels of HDL were not significantly different between the study groups (*P*= 0.402). Moreover, comparing the post-treatment levels yielded no significant disparity (*P*= 0.078). On the other hand, the comparison of before and after treatment levels of HDL revealed a significant rise in the intervention group (*P*= 0.001) and a decline in the control group (*P*= 0.030).

The independent t-test of changes in FBS, HbA1C, TG, LDL, and HDL levels yielded a significant difference in the intervention group compared to the control group (*P*< 0.05). Comparison by the mean test resulted in no significant disparity between the intervention and control groups regarding the changes in cholesterol levels (*P*> 0.05).

Discussion

Pretreatment differences between the intervention and control groups were insignificant regarding age, BMI, gender, time since diagnosis of DM, FBS, and HDL. Meanwhile, pretreatment serum HbA1C, TG, cholesterol, and LDL levels were significantly greater in the intervention group than in the control group. The administration of vitamin C alleviated FBS, HbA1C, TG, and HDL in a statistically significant manner. No significant alteration in serum cholesterol and LDL was found after vitamin C treatment. The control group experienced a substantial rise in HbA1C and LDL.

Meanwhile, the HDL level of this group decreased significantly. Changes in the mean values of all studied variables while comparing the intervention and control groups were significant in favor of vitamin C administration, except for cholesterol. Our results validate the usefulness of vitamin C for DM as a supplement to principal treatment. Our study shows that vitamin C has a clear advantage over a placebo in improving the serum parameters of diabetic patients.

Hamed et al. studied the effects of vitamin C and vitamin E in addition to the regimens of 58 metformin-treated diabetic patients. They found that treatment with vitamin C alone and with vitamin E substantially alleviated the serum levels of FBS, HbA1C, TG, cholesterol, HDL, and LDL (1). Their findings correlate moderately with ours, except for LDL and cholesterol. This discordance could be justified by the difference in the administered dosage of vitamin C (500 mg twice in a study by Hamed et al. and 250 mg four times a day in ours). In addition, our experiment's double-blind study design and higher sample size cannot be disregarded.

Multiple enzymatic reactions, including collagen synthesis, require vitamin C. Because humans lack a digestive enzyme that catalyzes the last step in ascorbic acid synthesis, vitamin C is essential to our health (14). Due to its reducing properties, vitamin C can act as an antioxidant during free radical-mediated oxidation processes. Patients with diabetes should be advised about healthy eating and vitamin C dietary sources, such as fresh fruits and vegetables, even though diabetes is not traditionally considered a risk factor for vitamin C deficiency (15). Vitamin C is recommended in the diet at 45 mg per day for adults. It has been suggested that diabetics may have an increased need for vitamin C and an increased risk of deficiency due to increased cellular uptake and turnover of vitamin C (16). Our study is in complete agreement with the clinical trial conducted by Dakhale et al., who found that vitamin C outperformed the placebo in reducing FBS, HbA1C, and post-meal blood glucose (4). Furthermore, Afkhami-Ardekani et al. reported improvement in FBS, TG, LDL, HbA1c, and serum insulin after consuming 1000 mg of vitamin C for six weeks. Interestingly, no significant alteration of

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mentioned parameters was found with the dose of 500 mg (17). Forghani et al. reported significantly reduced levels of HbA1c in T2DM patients who consumed 1000 mg of vitamin C (250 mg four times daily) after six weeks. The rise in FBS levels was unremarkable (6). Further studies are required to determine the effective dose of vitamin C on these parameters.

Our findings were not consistent with thestudy by Darvish Moghaddam et al. (5). Darvish Moghaddam et al. reported that administrating 1 g of vitamin C for three months yields no significant change in FBS and HbA1c levels in a study including 53 DM patients. They concluded that weight reduction significantly minimizes HbA1c and FBS in patients with T2DM, and vitamin C administration was ineffective in controlling the complications of DM. It could be argued that smaller sample size, non-blinded study design, and statistically discrete study group characteristics could affect their inference's reliability (5).

It is plausible that a number of limitations could have influenced the obtained results. The first is the lack of complete surveillance of patients' diets. The variation in patients' daily diet and compliance with their treatment creates an inevitable uncertainty in the results. The second limitation is the short duration of treatment. Some serum components, such as cholesterol, could be affected in prolonged treatments.

Conclusions

This paper outlined the possible beneficial effects of adding vitamin C supplements to the existing treatments and diets prescribed for DM patients. Vitamin C may assist in better control, as well as hinder disease progression and the manifestation of complications in diabetic patients.

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Conflict of Interest

The authors declare no conflict of interest.

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