Original Research Article

Study of role of vitamin C in type 2 diabetes mellitus patients

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ABSTRACT

Background: Diabetes mellitus (DM) is the most common non-communicable diseases in the present millennium which has become a global public health problem. The treatment of type 2 Diabetes mellitus (T2 DM) often is initiated with monotherapy of oral antidiabetic drugs (OADs), which often do not decrease the plasma sugar levels effectively and consistently that will reduce short term and long-term complications associated with T2 DM. Hence the current study is aimed to determine the effectiveness of vitamin C supplementation with standard OADs on glycemic control.
Methods: This study consisted of 120 T2 DM patients with 80 males and 40 females with a mean age of 50.88 yrs were divided into four groups with equal number of males and females in each group depending upon the OADs they received in solo or with vitamin C for 12 weeks. After the written consent, a detail clinical history, clinical examination, biochemical investigations including fasting plasma sugar (FPS), post prandial plasma sugar (PPS), glycosylated hemoglobin (HBA1c), serum creatinine, serum electrolytes, chest X-ray PA view and standard ECG were done. Repeat FPS, PPS and HBA1c were done after 4, 8 and 12 weeks of study.
Results: After 12 weeks of study FBS, PPS and HBA1c decreased significantly (p<0.01) in study groups (Metformin and tenigliptin with vitamin C) as compared to control groups (OADs without vitamin C). Vitamin C supplementation with OADs found to be effective, well tolerated and devoid of any side effects.
Conclusions: OADs are effective and affordable hypoglycemic agents with vitamin C supplementation.

Keywords: Supplementation, Effective, Affordable, OADs, Vitamin C

INTRODUCTION

Diabetes mellitus (DM) is a common chronic disorder and is one of the leading causes of death worldwide accounting for one death every 6 secs.[1] It is a progressive disorder associated with complications such as metabolic syndrome, cardiovascular disease, nephropathy, stroke, neuropathy, retinopathy and premature deaths, if not managed early and properly in its course.[2]

Nutrients such as vitamin C supplementation play an essential role in the prevention and management of DM and other metabolic disorders. Vitamin C is an essential nutrient and an antioxidant with a similar structure of glucose, is not produced by the humans due to the absence of the enzyme, L-gulonolactone oxidase.[3,4] It is also known as ascorbic acid, a cofactor in multiple enzymatic reactions including collagen synthesis.[5]

Dehydroascorbic acid (DHA, oxidized transportable form of vitamin C) uptake into the cells is accomplished through glucose transporters (GLUTs), GLUT1 and GLUT3, which transport DHA in competition with glucose.[6,7] While hyperglycemia inhibits this cellular uptake of DHA.[8,9]

Hence in a diabetic patient there is deficiency of vitamin C not only due to decreased cellular uptake but also due to

increased urinary losses, and increased metabolic turnover.[10] Consequently deficiency of vitamin C results in the defective formation of collagen and connective tissues and oxidative stress which leads to further disturbed glucose metabolism and enhanced hyperglycemia.[11] Therefore vitamin C supplementation with standard OADs, may have an impact on glycemic control.

Metformin is a biguanide oral anti diabetic drug which inhibits hepatic gluconeogenesis, increases peripheral insulin sensitivity and decreases intestinal glucose absorption.

Teneligliptin, an oral anti diabetic drug is a third-generation class 3 dipeptidyl peptidase (DPP)-4 inhibitor, increases serum insulin levels and decreases serum glucagon levels by increasing the levels of active glucagon like peptide-1 and glucose dependent insulotropic polypeptide through inhibition of DPP-4 enzymatic activity

Hence the current study is focused to determine the effectiveness of vitamin C supplementation in achieving glycemic control in T2 DM and thereby preventing/ reducing short term and long-term complications in a DM patient who is on common oral anti-diabetic drugs such as metformin or teneligliptin, which are affordable and available to all.

METHODS

This is a prospective comparative study of T2 DM patients conducted in the departments of pharmacology and medicine, Mallareddy institute of medical sciences and hospital, Suraram, Hyderabad, TS from 3rd December 2020 to 11th November 2021, after the Institutional Ethical Committee approval. DM was diagnosed as per 2019 American diabetic association (ADA) guide lines.[12] Patients who were smokers, alcoholic, with coronary artery disease (CAD) and chronic kidney disease were excluded from the study.

After a written consent from each patient, a detailed clinical history, clinical examination, biochemical investigations FPS, PPS, glycosylated hemoglobin (HBA1c), serum creatinine, serum electrolytes, chest X-ray PA view and standard electrocardiogram (ECG) were done. The 2 D echocardiogram was done in a few patients with cardiomegaly to rule out ischemic heart disease. Patients were categorized into four groups, each comprising 30 patients (20 males, 10 females).

Study group (Gr) 1: T2 DM patients received metformin (1000 mg BDS) and vitamin C (500 mg BDS) and control group (Gr) 1: T2 DM patients received metformin (1000 mg BDS) only.

Study group (Gr) 2: T2 DM patients received teneligliptin (20 mg/day) and vitamin C (500 mg BDS) and control group (Gr) 2: T2 DM patients received teneligliptin (20 mg/day) only.

Repeat FPS, PPS and HBA1c were done after 4, 8 and 12 weeks of treatment.

Statistical analysis

The data obtained from the study are presented as mean with standard deviation and percentage and results are assessed by using Student's t test; $p < 0.05$ values are considered as statistical significance.

RESULTS

Clinical profile

This study consisted of 120 T2 DM patients with 80 (66.67%) males and 40(33.33%) females with age ranging from 35 to 65 years with a mean of 50.88±7.6 years. Each group consisted of 30 patients with 20 males and 10 females. (Table 1 and Figure 1).
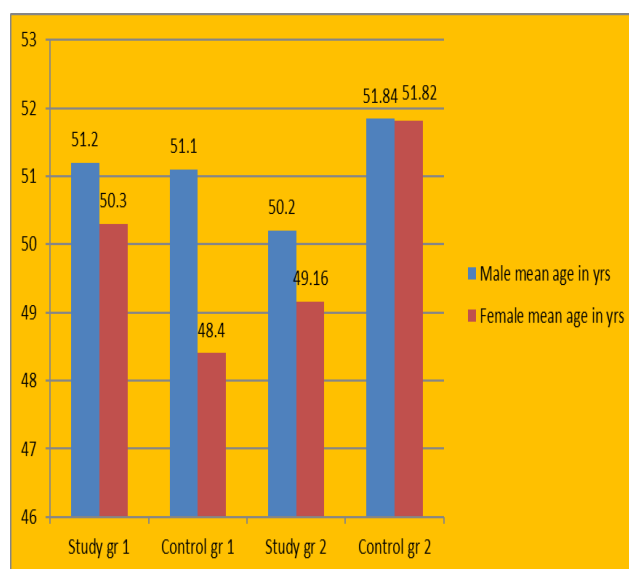
Figure 1: Mean age of male and female patients in years.

The duration of DM in this study ranged from 2 to 10 years with a mean of 4.8±.2.2 years (Table 1).

Routine investigations

The routine biochemical investigations: serum creatinine, and serum electrolytes were within normal limits. 10 patients (8.33%) of the study were subjected to echocardiogram who had cardiomegaly on chest X-ray PA view and left ventricular hypertrophy in standard ECG due to concomitant hypertension, which showed no regional wall motion abnormalities (RWMA) and normal left ventricular systolic function with grade 1 (mild) diastolic dysfunction.

Plasma sugars

Initial

FPS: The initial FPS ranged between 138 to 200 mg/dl with a mean of 180.35±20.2 (Table 2).

PPS: Similarly, the initial PPS ranged between 204 to 300 mg/dl with a mean of 269.38±30.18 (Table 3).

HBA1c: So also, the initial HBA1c in this study ranged between 7.4-9.6% with a mean of 8.5±0.9 (Table 4).

The mean FPS, PPS and HBA1c were slightly higher in females as compared to males in all groups.

After 4 weeks of study

FPS: The mean FPS decreased by 10.5 mg/dl (5.84%) in study Gr 1 as compared to 7.1 mg/dl (3.95%) in control Gr 1. Similarly, the mean FPS decreased by 10.6 mg/dl (5.89%) in study Gr 2 as compared to 7.4 mg/dl (4.12%) in control Gr 2 (Table 5).

PPS: The mean PPS decreased by 16.3 mg/dl (6.09%) in study Gr 1 as compared to 10.7 mg/dl (3.97%) in control Gr 1. So, also the mean PPS decreased by 22 mg/dl (8.11%) in study Gr 2 as compared to 12.1 mg/dl (4.49%) in control Gr 2 (Table 6). The decrease of PPS was significant in both study groups with vitamin C.

HBA1c: Mean HBA1c decreased by 0.4% (4.71%) in study Gr 1 as compare to 0.3% (3.57%) in control Gr 1. Similarly, mean HBA1c decreased by 0.5% (5.81%) study Gr 2 compared to 0.3% (3.53%) in control Gr 2 (Table 7).

After 8 weeks of study

FPS: The mean FPS decreased by 18.4 mg/dl (10.24%) in study Gr 1 as compared to 14.1 mg/dl (7.85%) in control Gr 1. Similarly, the mean FPS decreased by 19.9 mg/dl (11.05%) in study Gr 2 as compared to 14.4 mg/dl (8.01%) in control Gr 2 (Table 5). The decrease of mean FPS was statistically significant in all groups, while FPS<126 mg/dl occurred in 6 (20%) and 7 (23.33%) patients of study Gr 1 and study Gr 2 respectively.

PPS: The mean PPS decreased by 30 mg/dl (11.21%) in study Gr 1 as compared to 22.1 mg/dl (8.21%) in control Gr 1. So, also the mean PPS decreased by 35.5 mg/dl (13.09%) in study Gr 2 as compared to 25 mg/dl (9.3%) in control Gr 2 (Table 6). The decrease of mean PPS was statistically significant in all groups, while PPS<200 mg/dl was achieved in 8 (26.67%) and 9 (30%) in study groups 1 and 2 respectively as compared to 4 (13.33%) and 5 (16.67%) in control groups 1 and 2 respectively.

HBA1c: The mean HBA1c decreased by 0.9% (9.41%) in study Gr 1 as compare to 0.6% (7.14%) in control Gr 1. Similarly, the mean HBA1c decreased by 1.0% (11.63%) in study Gr 2 as compared to 0.6% (7.06%) in control Gr 2 (Table 7). The decrease of mean HBA1c was statistically significant in all groups of patients. However, HBA1c <6.5% of HBA1c occurred in 6 (20%) and 7 (23.33%) patients in study groups 1 and 2 respectively as compared to 2 (6.67%) and 3 (10%) in control groups 1 and 2 respectively.

After 12 weeks of study

FPS: The mean FPS decreased by 22.2 mg/dl (12.35%) in study Gr 1 as compared to 16.1 mg/dl (8.96%) in control Gr1.Similarly the mean FPS decreased by 28 mg/dl (15.55%) in study Gr 2 as compared to 17.3 mg/dl (9.62%) in control Gr 2 (Table 5). The decrease of mean FPS was statistically significant in all groups. The FPS <126 mg/dl occurred in 9 (30%) and 11 (36.67%) patients of study groups 1 and 2 respectively while it occurred in 4 (13.33%) and 5 (16.67%) patients of control groups 1 and 2 respectively.

PPS: The mean PPS decreased by 35.2 mg/dl (13.16%) in study Gr 1 as compared to 25.2 mg/dl (9.36%) in control Gr 1. So, also the mean PPS decreased by 44.0 mg/dl (16.22%) in study Gr 2 as compared to 28 mg/dl (10.39%) in control Gr 2 (Table 6). PPS<200 mg/dl was achieved in 10 (33.33%) and 11 (36.67%) in study groups 1 and 2 respectively as compared to 5 (16.66%) and 6 (20%) in control groups 1 and 2 respectively. The decrease of mean PPS was statistically significant in all groups of patients.

HBA1c: The mean HBA1c decreased by 1.4% (16.47%) in study Gr 1 as compare to 1.0% (11.90%) in control Gr 1. Similarly, the mean HBA1c decreased by 1.5% (17.44%) in study Gr 2 as compared to 1.0% (11.76%) in control Gr 2 (Table 7). The decrease of mean HBA1c was statistically significant in all groups of patients. HBA1c<6.5% occurred in 8 (26.67%) and 9 (30%) patients in study groups 1 and 2 respectively as compared to 3 (10%) and 4 (13.33%) in control groups 1 and 2 respectively.

Table 1: Age and duration of DM in type 2 diabetic patients.

Parameters		Control group 1 (Metformin)	Study group 1 (Metformin and vit C)	Control group 2 (Tenegliptin)	Study group 2 (Tenegliptin and vit C)
Age (years)	Range	35-63	35-64	35-65	38-62
	Mean	49.75 ±7.7	50.57±8.1	51.83±8.3	49.68±6.1
DM duration (years)	Range	2-9	2-9	2-8	2-10
	Mean	4.2±1.3	4.7±1.8	4.4±1.5	4.3±1.6

Table 2: Fasting plasma sugar and oral antidiabetic drugs.

Blood sugar FPS (mg/dl)		Control group 1 (Metformin)	Study group 1 (Metformin and vit C)	Control group 2 (Teneligliptin)	Study group 2 (Teneligliptin and vit C)
Initial	Range	140-200	138-200	142-200	142-199
	Mean	179.6±20.1	179.7±22.2	179.8±21.2	180.1±19.3
After 4 weeks	Range	134-193	134-194	136-192	133-167
	Mean	172.5±21.2	169.2±21.3	172.4±20.1	169.5±19.2
After 8 weeks	Range	128-184	120-176	130-184	121-165
	Mean	165.5±22.2	161.3±20.1	165.4±21.2	160.2±18.4
After 12 weeks	Range	125-180	125-172	124-178	119-157
	Mean	163.5±23.4	157.5±25.3	162.5±23.4	152.1±22.2

Table 3: Post prandial plasma sugar and oral antidiabetic drugs.

Blood sugar PPS (mg/dl)		Control group 1 (Metformin)	Study group 1 (Metformin and vit C)	Control group 2 (Teneligliptin)	Study group 2 (Teneligliptin and vit C)
Initial	Range	210-300	204-285	213-300	214-295
	Mean	269.3±33.4	267.5±25.3	269.5±31.5	271.2±30.5
After 4 weeks	Range	201-294	191-267	200-282	195-274
	Mean	258.6±32.3	251.2±25.4	257.4±32.3	249.2±29.6
After 8 weeks	Range	193-281	181-253	193-273	185-259
	Mean	247.2±31.5	237.5±21.2	244.5±30.5	235.7±25.3
After 12 weeks	Range	189-275	177-247	187-264	174-244
	Mean	244.1±32.2	232.3±20.1	241.5±29.6	227.2±23.4

Table 4: Glycosylated hemoglobin and oral antidiabetic drugs.

Blood sugar HBA1c (%)		Control group 1 (Metformin)	Study group 1 (Metformin and vit C)	Control group 2 (Teneligliptin)	Study group 2 (Teneligliptin and vit C)
Initial	Range	7.4-9.6	7.7-9.6	7.6-9.6	7.6-9.6
	Mean	8.4±0.7	8.5±0.9	8.5±0.9	8.6±1.0
After 4 weeks	Range	7.1-9.2	7.3-8.9	7.3-9.0	7.1-9.0
	Mean	8.1±0.8	8.1±0.8	8.2±0.8	8.1±0.9
After 8 weeks	Range	6.9-8.8	6.8-8.5	7.0-8.7	6.7-8.4
	Mean	7.8±0.9	7.7±0.7	7.9±0.8	7.6±0.7
After 12weeks	Range	6.5-8.0	6.4-7.9	6.5-8.4	6.3-7.6
	Mean	7.4±0.6	7.1±0.5	7.5±0.2	7.1±0.4

Table 5: Effects of oral antidiabetic drugs on fasting plasma sugar.

Blood sugar Parameter: FPS (mg/dl)	Control group 1 (Metformin)	Study group 1 (Metformin and vit C)	Control group 2 (Teneligliptin)	Study group 2 (Teneligliptin and vit C)
Initial mean	179.6	179.7	179.8	180.1
After 4 wks	172.5	169.2	172.4	169.5
% of ↓	-7.1; 3.95%	-10.5; 5.84%	-7.4; 4.12%	-10.6; 5.89%
After 8 wks	165.5	161.3	165.4	160.2
% of ↓	-14.1; 7.85%, (p<0.05)	-18.4; 10.24%, (p<0.01)	-14.4; 8.01%, (p<0.05)	-19.9; 11.05%, (p<0.01)
After 12 wks	163.5	157.5	162.5	152.1
% of ↓	-16.1; 8.96%, (p<0.05)	-22.2;12.35%, (p<0.01)	-17.3; 9.62%, (p<0.05)	-28.0; 15.55%, (p<0.01)

Table 6: Effects of oral antidiabetic drugs on postprandial plasma sugar.

Blood sugar parameter: PPS (mg/dl)	Control group 1 (Metformin)	Study group 1 (Metformin and vit C)	Control group 2 (Tenegliptin)	Study group 2 (Tenegliptin and vit C)
Initial mean	269.3	267.5	269.5	271.2
After 4 wks	258.6	251.2	257.4	249.2
% of ↓	-10.7; 3.97%	-16.3; 6.09%, (p<0.05)	-12.1; 4.49%	-22; 8.11%, (p<0.05)
After 8 wks	247.2	237.5	244.5	235.7
% of ↓	-22.1; 8.21%, (p<0.05)	-30; 11.21%, (p<0.01)	-25; 9.3%, (p<0.05)	-35.5; 13.09%, (p<0.01)
After 12 wks	244.1	232.3	241.5	227.2
% of ↓	-25.2; 9.36%, (p<0.05)	-35.2; 13.16%, (p<0.01)	-28; 10.39%, (p<0.01)	-44; 16.22%, (p<0.001)

Table 7: Effects of oral antidiabetic drugs on HBA1c.

Blood sugar parameter: HBA1c (%)	Control group 1 (Metformin)	Study group 1 (Metformin and vit C)	Control group 2 (Tenegliptin)	Study group 2 (Tenegliptin and vit C)
Initial mean	8.4	8.5	8.5	8.6
After 4 wks	8.1	8.1	8.2	8.1
% of ↓	-0.3; 3.57%	-0.4; 4.71%	-0.3; 3.53%	-0.5; 5.81%
After 8 wks	7.8	7.7	7.9	7.6
% of ↓	-0.6;7.14%, (p<0.05)	-0.9; 9.41%, (p<0.05)	-0.6;7.06%, (p<0.05)	-1.0; 11.63%, (p<0.01)
After 12 wks	7.4	7.1	7.5	7.1
% of ↓	-1.0; 11.90%, (p<0.01)	-1.4; 16.47%, (p<0.001)	-1.0; 11.76%, (p<0.01)	-1.5; 17.44%, (p<0.001)

DISCUSSION

In this study mean FPS, mean PPS and mean HBA1c decreased significantly in study groups of metformin and tenegliptin with vitamin C without any side effects as compared to control groups. FPS <126 mg/dl after 12 weeks occurred in 30% and 36.67% patients of study groups with metformin and vitamin C and tenegliptin with vitamin C respectively.

Similarly, after 12 weeks PPS <200 mg/dl was achieved in 33.33% and 36.67%, in study groups with metformin and vitamin C and tenegliptin with vitamin C respectively.

Mean HBA1c decreased by 16.47-17.44% in patients who received vitamin C along with OADs and HBA1c<6.5% occurred in 26.67% and 30% patients in study groups of metformin with vitamin C and tenegliptin with vitamin C respectively.

Similarly, Eriksson et al reported that Ascorbic acid improved glycemic control, lowering both FPS and HBA1c.[13] So, also Sargent et al in their prospective population-based study from 1995 to 1998 in Norfolk, UK found an inverse association between plasma vitamin C and HBA1c, and recommended dietary measures to increase plasma vitamin C as an important health strategy for reducing the prevalence of DM.[14]

Our study results are also in agreement with previously published data showing betterment in glycemic control with vitamin C supplementation in STZ-rats by Sridulyakul et al and decreased of HBA1c and blood glucose in type 2 diabetic patients supplemented with vitamin C by Ardekani et al.[15,16]

Dakhale et al also found addition of 500 mg twice daily vitamin C supplementation to standard therapy in 70 patients treated with metformin for T2 DM for 12 weeks, lower HBA1c, fasting and post-meal blood glucose levels when compared to the placebo group.[17]

So, also Bhatt et al in their study on 62 T2 diabetic patients for 3months found that vitamin C supplementation significantly decreased the total cholesterol and LDL cholesterol besides also decreased HBA1c and fasting blood sugar though not statistically significant.[18]

A meta-analysis of 5 RCTs by Tabatabaei-Malazy et al found a significant effect on FBS, and non-significant effect on HBA1c from a single intake of ascorbic acid versus placebo.[19]

Similarly, a meta-analysis by AW Ashor et al noted administration of vitamin C for more than 30 days in T2 DM patients significantly reduced FPS as compared to

postprandial insulin concentration and advocated supplementation of vitamin C in T2 DM patients.[20]

The beneficial effects of supplementation of vitamin C in T2 DM are (1) due to its free radical-scavenging antioxidants effect and (2) vitamin C-mediated increase in insulin action mainly due to its improvement in nonoxidative glucose metabolism.[21]

The study of effect of vitamin C in T2 DM patients who are also managed with OADs and insulin/or Insulin only were not included in this study as there were not enough patients due to COVID-19 pandemic, besides most of these patients ideally require inpatient management for better follow up and conclusion. A larger number of patients and inclusion of T2 DM patients who are managed with insulin/ insulin and OADs in this study could have given wider implications and recommendations for supplementation of vitamin C in the management of DM

CONCLUSION

DM is the most common non-communicable diseases in the present millennium which has become a global public health problem and a leading cause of death worldwide. DM is also a chronic and progressive disorder associated with complications and premature deaths, if not managed early and properly in its course. Supplementation of vitamin C, an essential nutrient and an antioxidant, with a similar structure of glucose play an essential role in the prevention and management of DM. In a diabetic patient there is deficiency of vitamin C not only due to decreased cellular uptake but also due to increased urinary losses, and increased metabolic turnover. Hence in this study, supplementation of vitamin C with metformin and teneligliptin was well tolerated and devoid of any side effects; besides its cheaper cost and improvement in FPS, PPS, and HBA1c, make it attractive therapeutic adjuvant in the treatment of type 2 DM; and may provide a simple means of preventing and ameliorating the complications of diabetes mellitus.

ACKNOWLEDGEMENTS

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