

# Effects of vitamin C supplementation on the glycemc control and cardiovascular risk in Type II *Diabetes Mellitus*

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**ABSTRACT:** The oral hypoglycaemic agents as well as injectable insulin does not significantly alter the oxidative stress in the diabetes mellitus patients. Being an antioxidant Vitamin C (ascorbic acid) might help in tackling the adversities of reactive oxygen species. A randomized placebo controlled study was carried out with parallel assignment of both the test group and control group of patients. The intervention model included metformin 500mg twice daily and a placebo once daily for control group. Alternatively, Vitamin C chewable tablets were given for the other group along with metformin 500mg twice daily. Our study postulates that there is a significant reduction in the fasting blood glucose, glycosylated haemoglobin levels, troponin T levels and Framingham risk score in participants who received ascorbic acid supplementation along with regular metformin. The supplementation of Vitamin C along with Metformin was well tolerated and did not cause any serious adverse drug reactions. The cheaper cost adjuvant approach with Vitamin C may be beneficial in patients in reducing the cardiovascular risk as well as to maintain an appropriate glycaemic control

**KEYWORDS:** *Diabetes Mellitus*; ascorbic acid; glycemc control; cardiovascular risk.

## 1. INTRODUCTION

Diabetes Mellitus is one of the most important metabolic disorder affecting the mankind characterised not only by hyperglycemia but also by other factors such as insulin resistance by the cells and tissues and marked oxidative stress [1]. There are several research studies that emphasized on the free radical effects in Diabetes Mellitus. The available oral hypoglycaemic agents as well as insulin does not significantly alter the oxidative stress in the diabetic patients. Being an antioxidant Vitamin C might help in tackling these complications by scavenging the reactive oxygen species [2]. Furthermore, Vitamin C may play a significant role in the prevention of non- enzymatic protein glycosylation [3]. Vitamin C enhances the formation of Lipoxin A4, Prostaglandin E1 which are potent antioxidants [4].

The available literature suggests conflicting outcomes in ascorbic acid supplementation in diabetic patients. There are really very few studies that studied the effects of Vitamin C with a fixed drug, for instance metformin, on glycaemic control parameters as well as on the cardiovascular risk parameters in type II diabetes mellitus. However, most studies on this area suggested a randomized study design to effectively analyse these specific outcomes [5,6].

## 2. RESULTS

The scheme of patients included for the study is given in trial profile (Figure 1).

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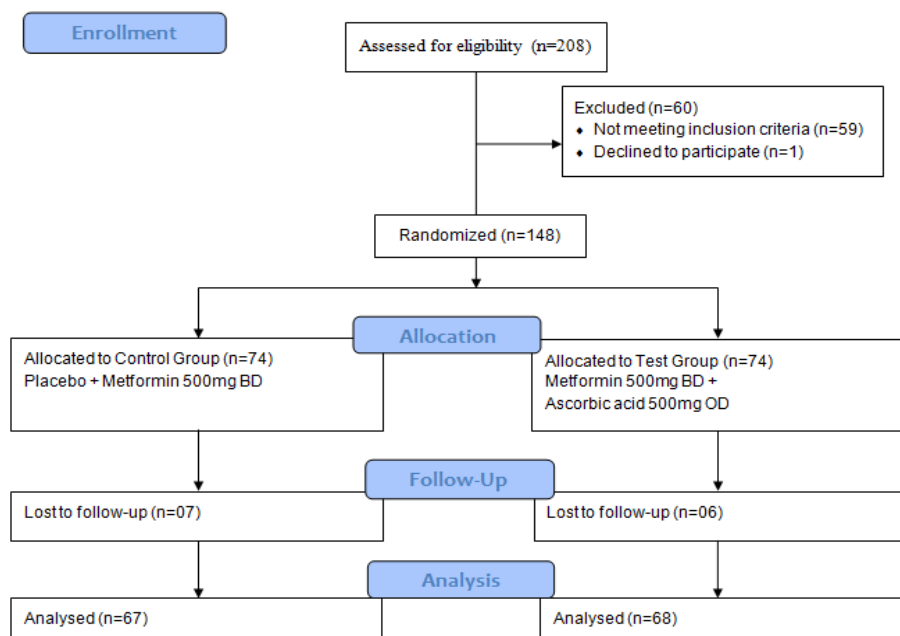


Figure 1. Trial profile.

Table 1. Baseline parameters of study participants.

S.No	Characteristics	Control (n=67)	Trial (n=68)	P value
01	Age in yrs (mean±SEM)	41.6±8.2	48.2±7.2	0.5231
02	Male (n=84)	47	37	0.6612
03	Duration of Diabetes in yrs (mean±SEM)	3.2±0.9	3.5±0.5	0.7715
04	Family History (n=67)	35	32	0.7214
05	BMI (mean±SEM)	24.3±0.5	23.2±0.9	0.2886
06	HTN (n=36)	20	16	0.6241
07	Dyslipidemia (n=0)	0	0	1.0000
08	Bronchial Asthma (n=2)	1	1	1.0000
09	Sr.Vitamin C Levels mg/dL(mean±SEM)	0.54±0.16	0.49±0.13	0.8090

BMI-Body Mass Index, HTN - Hypertension

All values are Mean±SEM unless otherwise mentioned. \*p<0.05 is considered significant

Table 1 includes the baseline parameters of the selected participants in the study. It could be seen that there is no significant difference between both the groups during the initial screening.

Table 2. Fasting blood glucose levels.

Fasting Blood Glucose Levels (mg/dL)	0 <sup>th</sup> Month	3 <sup>rd</sup> Month	6 <sup>th</sup> Month	9 <sup>th</sup> Month
Control (n=67)	182.2±4.1	175.1±7.6	167.4±6.2	159.3±5.1
Trial (n=68)	187.3±4.2	169.2±3.7*	157.7±3.0*	144.6±5.4*

All values are Mean±SEM.\*p<0.05 is considered significant.

On performing the analysis of variance followed by a post-hoc analyses, it was found out that trial arm had a significant reduction in the fasting blood glucose levels ( $p=0.0032$ ).

**Table 3.** HbA<sub>1</sub>C levels.

HbA <sub>1</sub> C levels (%)	0 <sup>th</sup> Month	3 <sup>rd</sup> Month	6 <sup>th</sup> Month	9 <sup>th</sup> Month
Control (n=67)	9.7±0.2	9.4±0.6	8.9±1.2	8.3±1.1
Trial (n=68)	9.6±0.3	8.4±0.7*	7.7±0.3*	6.9±0.4*

All values are Mean±SEM.\* $p<0.05$  is considered significant.

On performing the analysis of variance followed by a post-hoc analyses, it was found out that trial arm had a significant reduction in the HbA<sub>1</sub>C levels ( $p=0.0083$ ).

**Table 4.** Troponin T levels.

Troponin T levels (ng/L)	0 <sup>th</sup> Month	3 <sup>rd</sup> Month	6 <sup>th</sup> Month	9 <sup>th</sup> Month
Control (n=67)	12.2±2.1	12.1±1.6	12.7±1.5	12.3±1.1
Trial (n=68)	12.3±1.2	11.2±1.7*	9.7±1.0*	8.6±0.4*

All values are Mean±SEM.\* $p<0.05$  is considered significant.

On performing the analysis of variance, it was found out that trial arm had a significant reduction in the Troponin T levels ( $p=0.0495$ ).

**Table 5.** Framingham risk assessment score.

Framingham Risk Score	0 <sup>th</sup> Month	3 <sup>rd</sup> Month	6 <sup>th</sup> Month	9 <sup>th</sup> Month
Control (n=67)	17.7±1.2	17.4±0.9	16.9±1.1	16.3±2.1
Trial (n=68)	19.6±1.3	16.4±1.7	15.7±1.3*	13.9±2.4*

All values are Mean±SEM.\* $p<0.05$  is considered significant.

Table 5 indicates Framingham risk assessment that is a Canadian risk assessment scale for predicting the cardiovascular risk. On performing the analysis of variance, it was found out that trial arm had a significant reduction in the Framingham Risk assessment ( $p=0.0312$ ).

**Table 6.** Serum vitamin C levels.

Serum Vitamin C (mg/dL)	0 <sup>th</sup> Month	3 <sup>rd</sup> Month	6 <sup>th</sup> Month	9 <sup>th</sup> Month
Control (n=67)	0.54±0.16	0.51±0.19	0.59±0.25	0.53±0.16
Trial (n=68)	0.49±0.13	0.74±0.11*	0.87±0.16*	1.01±0.23*

All values are Mean±SEM.\* $p<0.05$  is considered significant.

On performing the analysis of variance, it was found out that trial arm had a significant reduction in the Serum Vitamin C levels ( $p=0.0002$ ). Not a single case of hypervitaminosis reported during the entire Study.

### 3. DISCUSSION

Our study postulates that there is a significant reduction in the fasting blood glucose, glycosylated haemoglobin levels, troponin T levels and Framingham risk score in participants who received ascorbic acid supplementation along with regular metformin. Although we had lost few patients to follow up, we were able to achieve a target sample size throughout the course of the study. The significant reduction in fasting blood glucose levels (Table 2) agrees with the report published by Girgis C *et al* 2015 [7]. Similarly Kostisawat J *et al* had reported that Vitamin C might help in reduction of glycated haemoglobin levels in Diabetes patients [8]. In our study, the glycated haemoglobin levels of the trial participants significantly reduced from the 3rd Month evaluation. Our results contradicts with the results published by McSorley PT *et al* is significantly reducing Troponin T levels [9]. Framingham risk score is significantly reduced predominantly due to reduction in systolic blood pressure, which is an integral parameter in assessing Framingham Risk score. This results correlates with the study published by Mason SA *et al* [10].

Multiple pathways such as oxidation of glucose, Polyol pathway, non-enzymatic Glycosylation of proteins may contribute to the increased release of free radical [11-13]. The effects of such reactive oxygen species may be overcome by administering the patients with an antioxidant such as ascorbic acid. It was clearly evident from the initial screening that most of the diabetic patients had vitamin C deficiency. Hence, they are in a dire necessity to receive ascorbic acid. The improvement in the Serum Vitamin C status of trial group has been observed from the 3rd month itself. The Vitamin C status gradually increased in the normal range between 0.6mg/dL and 1.2mg/dL during this period. Thus forth, there is no case of hypervitaminosis being reported (Fig 5). This may probably due to the water soluble nature of vitamin C [14]. The supplementation of vitamin C would have reduced the ameliorating cardiovascular risk in diabetic patients. The significant improvement in the glycaemic control status maybe correlated with antioxidant effects on beta cells [15]. Hence other antioxidant micronutrients such as vitamin E could also be beneficial. Furthermore, an evaluative study on the pharmacokinetic interaction between metformin and vitamin C could help us understand the basis of this outcome [16].

No serious Adverse Drug Reaction (ADR) is reported in the study. All the patients were closely monitored by a team of general physicians, endocrinologist, dietician and other health care workers throughout the study. The limitation of this study is the small sample size which could be analysed and improved in the future studies.

### 4. CONCLUSION

The supplementation of ascorbic acid along with metformin was well tolerated and improved the glycemic status significantly. Also, the cardiovascular risk significantly reduced in the patients who received ascorbic acid supplementation. Furthermore, it did not cause any serious Adverse Drug Reaction. The cheaper cost adjuvant approach with vitamin C may be beneficial for adequate glycemic control and cardiovascular risk reduction in diabetic patients. However we recommend for a large scale study in the near future.

### 5. MATERIALS AND METHODS

#### 5.1. Study design

A randomized placebo-controlled study was carried out in the general medicine department of a tertiary care teaching hospital with parallel assignment of both the test group and control group of patients. Per-protocol analysis was followed in the selection of the patients. Randomized permuted blocks method was used in randomly allocating the patients. This allocation sequence was derived from an online randomization generator [17]. The primary endpoint is the safety and efficacy analysis.

#### 5.2. Patient selection

Initially 208 patients were interested to take part in our study. We allocated patients only if they suitably qualify the Inclusion and Exclusion criteria. All the patients above 18 years of age who are diagnosed with type II diabetes mellitus and taking metformin alone were included. Patients having fasting blood glucose level in the range of 126 to 250 mg/dL and HbA1C in the range of 7.0-9.9% were included.

Individuals unable to give informed consent, those with a medical history of significant gastrointestinal disease e.g. inflammatory bowel disease, those who had undergone a previous bowel resection, individuals taking diabetes medication other than metformin were excluded from the study. Routine investigations like electrocardiogram, serum electrolytes, blood urea, creatinine and liver function tests were performed to

exclude active medical problems in all patients. The study was approved by the Institutional Ethics Committee VISTAS-SPS/IEC/2018/I/07. Informed consent has been obtained from all the participants of the study.

### 5.3. Sample size and treatment arms

Sample size was derived based on the previous literature and population size of 500 (Prevalence rate at the study site in the previous year), the sample size was estimated to be atleast 139. The intervention model included metformin 500mg twice daily and a placebo once daily for control group. Alternatively, ascorbic acid 500mg chewable tablets were given for the other group along with metformin 500mg twice daily. All the participating patients were advised on their usual diet plans limiting the consumption of Vitamin C rich foods. Each patient was counselled by a dietician on the diet to be followed. Initially, all the patients were evaluated for parameters such as serum vitamin C levels, Fasting Blood Glucose levels, HbA1C, troponin T, lipid profile, etc. The same parameters was repeated every 3 months until the 9<sup>th</sup> month end. Necessary auto-analysers were used for evaluation of each of these parameters. The medication adherence was evaluated using the traditional pill count method.

### 5.4. Statistical analysis

All parametric data expressed in mean  $\pm$  SEM (Standard Error of Mean). The Efficacy analysis would be carried out with the help of Analysis of Variance with a 95% level of significance. 'P' Value less than 0.05 is considered significant. All statistical analysis were performed using Graph Pad prism software.

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**Conflict of interest statement:** The authors declared no conflict of interest.

**Ethics committee approval:** The study was approved by the Institutional Ethics Committee VISTAS-SPS/IEC/2018/I/07. Informed consent has been obtained from all the participants of the study.

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