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To Study The Efficacy Of A Combination Of Metformin And Vit-C In Patients Of Type-2 Diabetes Mellitus

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ABSTRACT

Background: Diabetes mellitus (DM) is a complex metabolic disorder characterized by persistent hyperglycemia, resulting from either insufficient insulin production, insulin resistance, or a combination of both. The accumulation of free radicals significantly contributes to the advancement of diabetes and its associated complications.

Aim: This study aims to evaluate the effectiveness of a combination of metformin and vitamin C in patients diagnosed with type 2 DM.

Materials and Methods: The study involved 120 patients diagnosed with type 2 DM, who underwent a thorough medical history review, clinical examination, and biochemical assessments, including HbA1c, fasting plasma glucose (FPG), postprandial plasma glucose (PPG), total antioxidant capacity (TAC), and superoxide dismutase 2 (SOD2). Participants were subsequently divided into two groups, with 60 individuals in each. Group A received metformin at a dosage of 500 mg twice daily. In comparison, Group B was administered metformin at 1000 mg along with 1000 mg of vitamin C daily, divided into two doses, for three months. FPG and PPG were measured weekly over the three months, and HbA1c, TAC, and SOD2 levels were assessed at the end of the study. Data analysis was performed using SPSS software version 26.0.

Results: After three months of treatment, both groups exhibited a significant decrease in FPG, PPG, and HbA1c levels ($p<0.05$). However, TAC and SOD2 levels showed a substantial increase in Group B ($p<0.05$).

Conclusion: Both treatment groups experienced a notable reduction in blood glucose levels; however, patients receiving vitamin C in combination with metformin demonstrated a significant increase in TAC and SOD2 levels, indicating a reduction in oxidative stress. Therefore, the addition of vitamin C to antidiabetic therapy may help mitigate oxidative stress-related complications associated with diabetes mellitus.

Keywords: Diabetes Mellitus, Vitamin C, Metformin, Total Antioxidant Capacity

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by high levels of sugar in the blood, which is caused by a lack of insulin, its action, or both. Chronic hyperglycemia can cause damage or dysfunction in various organs, including the kidneys, heart, eyes, and blood vessels, ultimately

leading to increased rates of morbidity and mortality.[1] Common manifestations of type 2 diabetes mellitus (T2DM) include frequent urination, excessive thirst, increased hunger, fatigue, and unintended weight loss.[2] In the 21st century, T2DM has emerged as a significant public health concern. In 2021, approximately 536.6 million individuals were diagnosed with diabetes worldwide, and projections indicate this number could escalate to 783.2 million by 2045.[3] In India, the prevalence of diabetes mellitus stands at 8.7%, impacting around 69.2 million people, with expectations of growth to 109 million by 2035.[4, 5]

Oxidative stress arises from an imbalance between the production and elimination of highly reactive molecules, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS). These molecules are significant contributors to the onset and progression of type 2 diabetes mellitus.[6,7] Superoxide dismutase 2 (SOD2), an essential enzyme within the SOD family, plays a vital role in neutralizing free radicals and is also known as manganese superoxide dismutase (Mn-SOD). The SOD2 gene is situated on chromosome 6q25, where an Ala16Val polymorphism has been identified in exon 2. This alteration changes the normal GCT sequence to GTT. The Ala16Val (rs4880) polymorphism is the most extensively researched variant of the SOD2 gene and holds functional importance. This single nucleotide polymorphism (SNP) results in the substitution of the amino acid Alanine (Ala) at position 16 with Valine (Val). The presence of the Valine ('T' allele) variant leads to the production of unstable mRNA, which diminishes the enzyme's transport into the mitochondrial matrix and subsequently hinders its antioxidant capabilities, thereby increasing oxidative stress.[8, 9]

In addition to superoxide dismutase (SOD), the body contains various antioxidant enzymes, including glutathione, catalase (XAT), and glutathione peroxidase (GPx). These enzymes function synergistically to maintain cellular redox balance by neutralizing detrimental reactive oxygen species (ROS) and reactive nitrogen species (RNS).[10, 11] A decline in superoxide dismutase levels correlates with an increase in oxidative stress, which can result in inadequate glycemic control among diabetic patients. Therefore, the current study aims to investigate the potential advantages of vitamin C supplementation for diabetic patients who are undergoing treatment with antidiabetic medications.

MATERIAL AND METHODS

A research study was carried out involving individuals diagnosed with type 2 diabetes at Narayana Medical College and Hospital in Nellore, Andhra Pradesh. Before initiating the project, approval was taken from the institutional ethics committee. The study took place from January 2024 to June 2024, within the Biochemistry Department, in collaboration with the General Medicine Department. Participants were chosen based on established inclusion and exclusion criteria.

Inclusion criteria

- Type-2 DM patients
- Patients in the age group of 30 to 60 years from both sexes
- Participants who were willing to give their written informed concern.

Exclusion criteria

- Type-1 Diabetes mellitus patients
- Smokers, alcoholics/ pregnant/ lactating women
- Patients with other chronic illnesses like kidney, liver, cardiac problems, TB, leprosy, recent trauma, surgery, and psychiatric problems
- Patients who are allergic to vitamin C
- Patients who are receiving antioxidants like vitamins A, E and C

In this study, a total of 120 patients diagnosed with type 2 diabetes mellitus (type-2 DM) were enrolled after obtaining informed consent, along with collecting sociodemographic data and medical histories for each participant. Subsequently, 5 ml of venous blood was drawn from a peripheral vein using Di sodium EDTA vacutainers to assess various blood glucose parameters, including HbA1c (measured by the Exchange Resin Method), fasting blood sugar (FBS), postprandial blood sugar (PPBS) (using the GOD & POD method), SOD2 (determined by the Xanthine method, an enzymatic approach), and total antioxidant capacity (TAC) (assessed via the Ferric Reducing Ability of Plasma Method, or FRAP). Based on the treatment regimen, the patients were categorized into two groups: Group A and Group B, with 60 patients in each group. Patients in Group A received metformin 500 mg twice daily, while those in Group B were administered metformin 1000 mg along with vitamin C 1000 mg, both in two divided doses over three months. The study included six visits, scheduled every 15 days, during which each patient was evaluated for their overall medical condition, and glycemic control investigations (FBS and PPBS) were conducted. After three months of treatment, the levels of HbA1c, TAC, and SOD2 were measured and compared to baseline values alongside the blood glucose parameters.

Statistical Analysis: The collected data was input into Excel and subsequently analyzed using the paired test and unpaired test through SPSS software version 26.0. p-value of less than 0.05 was deemed statistically significant.

RESULTS

The present study involved 120 patients with type 2 diabetes mellitus, 66 participants (55%) were male, while 54 (45%) were female. The majority of the participants were aged between 41 and 50 years (n=76), followed by 26 patients in the 31 to 40 age group and 18 patients in the 51 to 60 age group.**Table-1**

After a three-month treatment period with metformin, group A exhibited a significant decrease in mean fasting plasma glucose, postprandial plasma glucose, HbA1c, as well as total antioxidant capacity (TAC) and superoxide dismutase 2 (SOD2) levels ($p<0.05$). **Table 2** In contrast, patients in group B, who received metformin in combination with vitamin C, also showed a significant reduction in mean fasting plasma glucose, postprandial plasma glucose, and HbA1c levels, while TAC and SOD2 levels increased significantly. **Table-3**

When comparison was done between the groups, no significant differences were noted in mean fasting plasma glucose, postprandial plasma glucose, and HbA1c levels at both baseline and after three months of treatment. However, the mean reductions in these parameters were greater in the patients who received vitamin C along with metformin (group B). A significant difference was observed in mean TAC and SOD2 levels at the three-month mark between the groups ($p<0.05$), although no such difference was present at baseline. **Table-4**

Table 1: Age and gender-wise distribution of patients

Variables		**n= 120**
Age	31 to 40 years	26(21.66%)
	41 to 50 years	76(63.33%)
	51 to 60 years	18(15%)
Gender	Male	66 were (55%)
	Female	54 were (45%)

Table 2: Level of blood glucose, TAC, and SOD2 in Group a

Variables	Baseline	3month	Mean difference	P value
FPG(mg/dl)	151± 10.3	131.4± 7.41	19.6 ±5.7	0.001
PPPG(mg/dl)	239.6±16.8	210.5±14	29.1±9.4	0.003
HbA1c (%)	6.9±0.1	6.3±0.3	0.6±0.42	0.005
TAC(mmol/l)	0.84±0.1	0.78±0.14	0.06±0.28	0.001
(SOD2(U/ml))	128.2± 6.85	119.3±5.31	8.9± 2.96	0.002

P<0.05 statistically significant**

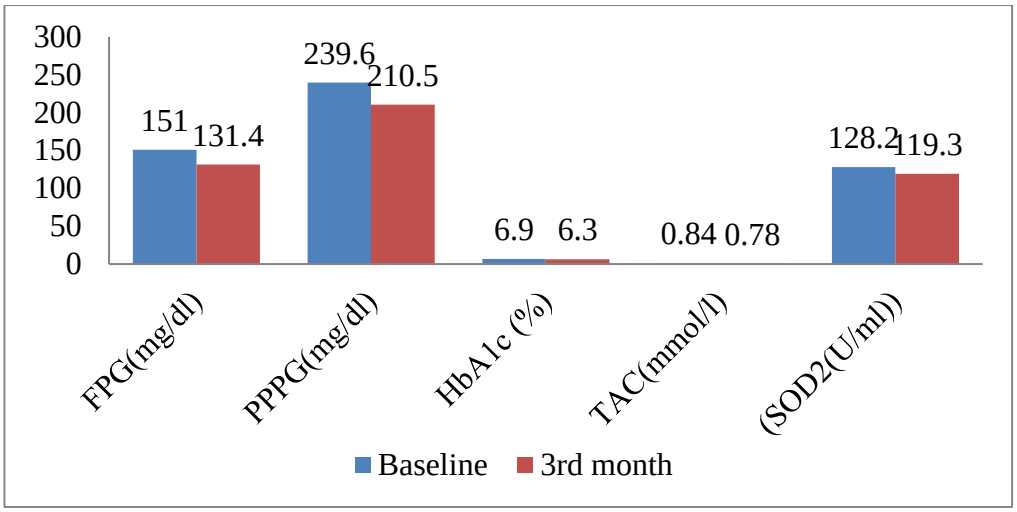

Figure 1: Graphical representation of blood glucose, SOD2, and TAC level in Group-A

Table 3: Level of blood glucose, TAC and SOD2 in group B

Variables	Baseline	3month	Mean difference	P value
FPG(mg/dl)	152.9±9.26	125.3±5.26	27.6±9.13	0.001
PPPG(mg/dl)	244.2±15.01	205.5±9.79	38.7±5.22	0.002
HbA1c (%)	7.2±0.36	6.4±0.21	0.8±0.15	0.004
TAC(mmol/l)	0.68±0.12	0.98±0.26	0.3±0.28	0.003
(SOD2(U/ml)	129.6± 5.61	143.1±3.52	13.5± 2.09	0.001

P<0.05 statistically significant**

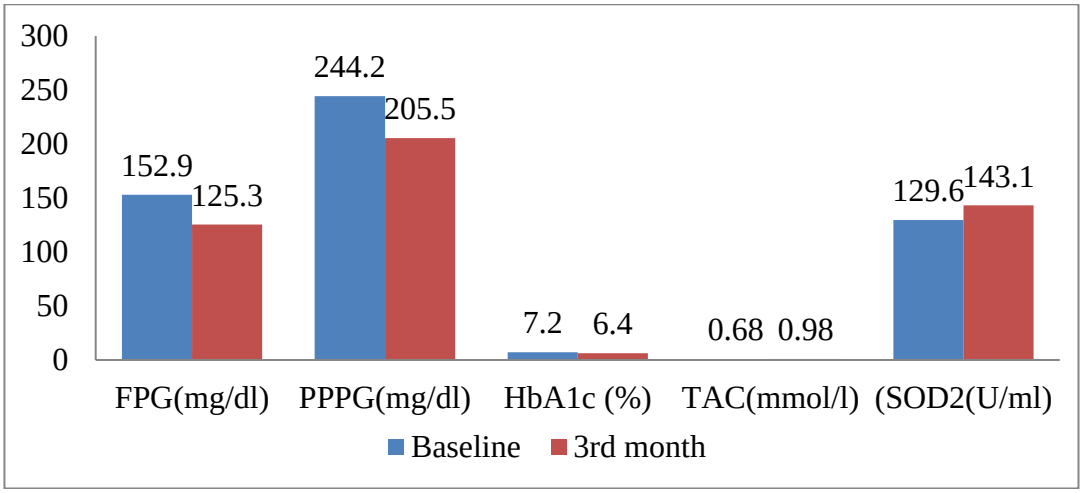

Figure-2: Graphical representation of blood glucose, SOD2, and TAC level in Group-B

Table-4: Level of blood glucose, TAC and SOD2 in both group A & B

Variables		Group-A Mean±SD	Group-B Mean±SD	Mean difference	P value
FPG (mg/dl)	Baseline	151± 10.3	152.9±9.26	1.9± 1.04	0.081
	3 month	131.4± 7.41	125.3±5.26	6.1±2.15	0.074
PPPG (Mg/dl)	Base line	239.6±16.8	244.2±15.01	4.6±1.79	0.061
	3 month	210.5±14	205.5±9.79	5±4.21	0.085
HbA1c (%)	Baseline	6.9±0.1	7.2±0.36	0.3±0.26	0.061
	3 month	6.3±0.3	6.4±0.21	0.1±0.09	0.074
TAC (mmol/l)	Base line	0.84±0.1	0.68±0.12	0.16±0.02	0.213
	3 month	0.78±0.14	0.98±0.26	0.2±0.12	0.05**
SOD2 (U/ml)	Baseline	128.2± 6.85	129.6± 5.61	1.4±1.24	0.061
	3 month	119.3±5.31	143.1±3.52	23.8±1.79	0.002**

P<0.05 statistically significant**

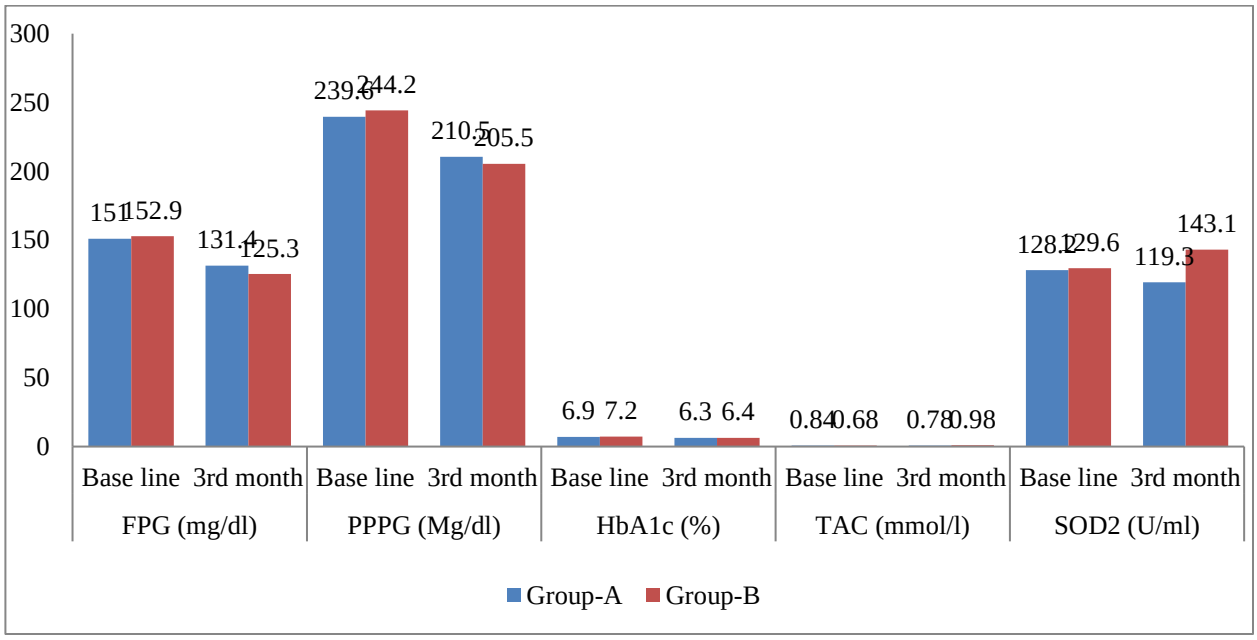

Figure-3: Graphical representation of blood glucose, SOD2 and TAC level in Group-A&B

DISCUSSION

This study aimed to evaluate the beneficial effects of vitamin C as an adjunct therapy along with antidiabetic medications in patients with type 2 diabetes mellitus. While various classes of antidiabetic drugs are currently available, their primary function is to manage blood glucose levels. Oxidative stress is recognized as a contributing factor to diabetic complications, which encompass both microvascular and macrovascular. The supplementation of antioxidants may mitigate or avert complications associated with oxidative stress. Therefore, in this study, diabetic patients received vitamin C (an antioxidant) along with antidiabetic medication to assess its beneficial impact on glycemic control and oxidative stress levels.

In the current study, 55% of the participants were male (n=66), while the remaining 45% comprised female individuals (n=54).**Table 1** Previous studies have indicated that the prevalence of diabetes mellitus is slightly higher in males compared to females, which aligns with the findings of this study.[12, 13] The majority of participants fell within the age range of 41 to 50 years (n=76), followed by 26 and 18 individuals in the age groups of 31 to 40 and 51 to 60 years, respectively, results are in line with previous study.[14] A notable decrease in mean fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), and HbA1c levels were observed in the group of patients treated solely

with metformin, consistent with another study.[15] However, a similar investigation reported no significant glycemic control in patients receiving 1000 mg/day of metformin alone.[16]

In the present study, in patients who were treated with metformin+ vitamin C (group B), a significant reduction in mean fasting plasma glucose, postprandial plasma glucose, and HbA1c levels were observed, whereas TAC and SOD2 levels were elevated significantly. **Figure 1** An elevation of TAC and SOD2 levels indicates the reduction of oxidative stress, but this was not noticed in patients who were treated with metformin alone. A previous study mentioned that a significant glycemic control was observed in patients who received metformin+ vitamin C when compared to patients who were treated with metformin + placebo; these results support the present study.[17]

In the current study, patients administered metformin along with vitamin C (group B) exhibited a notable decrease in mean fasting plasma glucose, postprandial plasma glucose, and HbA1c levels. Concurrently, there was a significant increase in the levels of total antioxidant capacity (TAC) and superoxide dismutase 2 (SOD2).**Figure 2** The rise in TAC and SOD2 levels suggests a reduction in oxidative stress, which was not observed in patients receiving metformin alone. Previous research has indicated that patients treated with metformin and vitamin C demonstrated great glycemic control, similar results were observed in the present study.[17] Another study also mentioned that supplementation of vitamin C along with antidiabetic drugs has reduced oxidative stress.[18] A previous study also stated that supplementation of antioxidants like vitamin C and E had reduced glycemic levels and increased antioxidant enzymes such as SOD and glutathione (GSH).[19]

Upon conducting a comparison between the groups, no significant differences were observed in the mean levels of fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), and HbA1c at both the baseline and after three months of treatment. However, patients in group B, who received vitamin C in combination with metformin, exhibited a greater mean reduction in FPG, PPPG, and HbA1c levels. A significant difference was noted in the mean levels of total antioxidant capacity (TAC) and superoxide dismutase 2 (SOD2) in the 3rd month between the groups ($p<0.05$), although no such difference was present at baseline. This suggests that the addition of vitamin C may have contributed to a reduction in oxidative stress. **Figure 3** It is important to note that glucose and vitamin C share structural similarities, leading to competition for cellular entry. Insulin plays a crucial role in facilitating the transport of these substances across cell membranes. In diabetic conditions, as glucose levels rise, the cellular uptake of vitamin C diminishes. In instances of hyperglycemia, vitamin C serves as an antioxidant, mitigating end-organ damage by inhibiting the intracellular accumulation of sorbitol and decreasing protein glycosylation.[20]

CONCLUSION

The study findings indicate that the supplementation of vitamin C with metformin in diabetic patients results in effective glycemic control and diminishes oxidative stress by increasing the activity of the antioxidant enzyme SOD2, which acts as a free radical scavenger. Therefore, the addition of vitamin C to antidiabetic medications may also help in preventing complications related to oxidative stress in diabetes.

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- **Data collection**: Dr. Nishitha Ganugapeta[1], Dr. Dr. Sai Sravan Kumar R[5]
- **Statistical analysis & results interpretation of results:** Dr. Sreekanth Gaddam[3], Dr. Arun Devaraju[2], Dr. Dr. Sai Sravan Kumar R[5]
- **Draft manuscript preparation**: Dr. Sreekanth Gaddam[3], Dr. Srihitha Gaddam[4]

All authors reviewed the results and approved the final version of manuscript.

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