International Journal of Research in Pharmacology & Pharmacotherapeutics

ISSN Print: 2278-2648 IJRPP |Vol.10 | Issue 3 | Jul - Sep - 2021
ISSN Online: 2278-2656 Journal Home Page: www.ijrpp.com

Research article Open Access

# A comparative study of efficacy and safety of anti-oxidants as an add-on therapy to metformin on non-glycemic parameters in newly diagnosed type 2 diabetes mellitus patients

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## ABSTRACT

**Background**: In diabetes mellitus patients, there is an increased susceptibility to lipid peroxidation which increases the incidence of atherosclerosis and major complication of DM. Antioxidants supplementation defends free radical induced damage and thus decrease further complications.
**Objective:** To evaluate the efficacy and safety of metformin versus metformin with vitamin C and E on non-glycaemic parameters in newly diagnosed type 2 diabetes mellitus.
**Methods**: 60newly diagnosed type 2 diabetes patients were randomized into two groups of 30 in each to receive Metformin (500mg BD) alone in group A versus Metformin (500mg BD) + Vitamin C (500mg OD) + Vitamin E (400mg OD) in group B for 12 weeks. Efficacy was measured by improvement in non-glycaemic parameters (Hb%, Lipid profile) at week 12 from baseline. Safety was assessed by monitoring treatment emergent adverse effects.
**Results**: The baseline characteristics were comparable between the two groups. There is a significant improvement in haemoglobin percentage and significant decrease in lipid levels was observed in group B from baseline to week 12, but the difference was not statistically significant between the two groups ($p>0.05$). No significant adverse effects were noted.
**Conclusion**: Both the groups are effective in improving both haemoglobin percentage and lipid profile in supplementation of vitamins along with Metformin as compared to Metformin alone with no significant adverse effect. Hence, daily consumption of vitamins may be beneficial in decreasing lipids in patients with T2DM and thus reducing the risk of complications.

**Keywords:** Diabetes mellitus; Oxidative stress; Metformin; Vitamin C; Vitamin E.

## INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterised by hyperglycaemia due to insulin deficiency and/or insulin resistance.[1] According to International Diabetic Federation atlas 2017, 425 million people with DM globally and 69.2 million in India.[2]

Metformin lowers blood glucose by decreasing production of hepatic glucose and increasing peripheral glucose uptake. Hence, it is one of the most common oral anti-diabetic agents used to treat type 2 DM and is currently accepted as the first-line treatment for this condition.[3]

The gradual decrease in anti-oxidant defence mechanism and raise in free radical's potential is related to diabetes mellitus with oxidative stress. Oxidative stress is defined as insufficient removal and/or excess formation of reactive oxygen species and reactive nitrogen species which are highly reactive molecules.[4]

Anti-oxidants are chemical or biological agents such as Vitamin E and Vitamin C which effectively scavenges the free radicals in cell membranes, thereby preventing lipid peroxidation and also terminating the free radical induced peroxidation of lipid membrane.[6]

High levels of oxidative stress caused by hyperglycaemia are the main cause of increased requirements of vitamin C in type 2 DM. Plasma vitamin C concentrations have been inversely correlated to glycosylated haemoglobin and fasting and postprandial blood glucose and oxidative stress Three-month supplementation of vitamins C and E decreased hypertension, blood glucose while increasing superoxide dismutase and glutathione levels. In addition, vitamin C has been shown to reduce blood glucose, plasma cholesterol and triglycerides in type 2 DM patients.[7]

In type 2 DM patients there is a decrease in concentration of vitamin E as well. High concentrations of α-tocopherol have been associated with decreased risk of diabetes in the general population. Inhibiting the oxidation of PUFAs in RBC membrane, thus reducing the fragility of erythrocytes and preventing the oxidative stress-induced premature erythrocyte lysis during various types of haemolytic anaemia. Enhancing erythropoiesis in experimental animals and some of the anaemic human subjects, thereby improving blood haemoglobin and haematocrit levels in these individuals.[6]

However, there has been limited clinical data regarding efficacy of anti-oxidant property of vitamin C and E on non-glycaemic parameters in type 2 DM. Thus, more studies are needed before it is recommended as a routine treatment for diabetic patients.

## OBJECTIVES

To evaluate the efficacy and safety of metformin versus metformin with vitamin C and E on non-glycaemic parameters in newly diagnosed type 2 diabetes mellitus.

## METHODOLOGY

A Randomized, Prospective, Comparative study conducted between November 2016 to May 2018 in the out-patient department of Medicine, Victoria & Bowring hospitals, attached to Bangalore Medical College & Research Institute, Bengaluru. Patients willing to give written informed consent, aged 18-60 years of either sex, newly diagnosed type 2 DM (as per ADA guidelines of 2016) were included in the study.

Patients with Type-1 Diabetes Mellitus, Cardiac disease**,** Liver disease, Renal disease, Malignancy, haematological disorders, patients with diabetic ketoacidosis, complication of diabetes, patients on lipid lowering drugs or who received vitamin C and E or any other antioxidant over last three months, Smokers and alcohol patients, allergic to study medication and pregnant and lactating mothers were excluded from the study.

After obtaining institutional ethics committee clearance and written informed consent, the out-patients in the department of medicine fulfilling the inclusion and exclusion criteria were enrolled in the study.60 study subjects will be randomly assigned into two groups of 30 patients in each group and randomized in a 1:1 ratio using computer random sequence generator (www.randomization.com) to receive either Tablet Metformin 500 mg (BD) (n=30) orally with food in Group A and Tablet Metformin 500mg (BD) with food and Capsule vitamin E 400mg (OD) and Tablet Vitamin C 500mg (OD) (n=30) orally after breakfast in Group B.

Demographic data, medical history, co-morbid conditions, physical examination, vital signs, relevant laboratory investigations were done at baseline, at the end of 4, 8 and 12 weeks, drug prescription by the treating physician was recorded in the study proforma. Relevant laboratory investigations were done at baseline, at the end of 4, 8 and 12 weeks. Concomitant medications that are necessary were given at the discretion of the physician and were recorded.

Efficacy was assessed by improvement of Hb% and lipid profile parameters at week 4, 8 and 12 from baseline. Safety was assessed by monitoring treatment emergent adverse effects. Adverse events were recorded and graded according to severity. Medication compliance was assessed with the help of

a medication compliance card and patient were said to be compliant if he takes 80% of medication.

### Statistical Analysis

Data was collected and continuous variables were expressed as Mean±Standard Deviation (parametric data). The continuous data in this study was analysed using repeated measure ANOVA (analysis of variance) for intragroup comparison and unpaired 't' test (parametric data) for intergroup comparison. Categorical data was expressed as percentages/proportions and was analysed using chi-square test. P value < 0.05 was considered statistically significant. Statistical analyses were performed using Vassar Stats software.

## RESULTS

Sixty-six patients were screened for inclusion in the study of whom 60 patients who met the inclusion and exclusion criteria and gave written informed consent to participate in the study were enrolled in the study. Patients were randomised either to the Metformin arm (Group A) or Metformin+ Vitamin C + Vitamin E arm (Group B) with 30 patients in each of the arms for a duration of 12 weeks. Table 1 represents the demographic profile of the patients included in the study. Both the treatment groups were matched with respect to baseline demographic characteristics.

**Table 1: Baseline characteristics**

| Parameters | | Group A Tablet Metformin 500 mg/day n=30(%) | Group B Tablet Metformin 500mg/day + Tablet Vitamin C 500mg/day + Capsule Vitamin E 400mg/day n=30(%) | *p* value |
|---|---|---|---|---|
| **Age in years** | 18 – 40 | 4(14) | 9(30) | 0.20† |
| | 41 –60 | 26(86) | 21(70) | |
| **Gender** | Male | 15(50) | 12(40) | 0.60* |
| | Female | 15(50) | 18(60) | |
| **Family history of DM** | Present | 20(67) | 17(57) | 0.59* |
| | Absent | 10(33) | 13(43) | |
| **Weight in kg** | 50 – 60 | 5(17) | 5(17) | 0.39† |
| | 61 – 70 | 10(33) | 16(53) | |
| | 71 – 80 | 12(40) | 8(27) | |
| | 81 – 90 | 3(10) | 1(3) | |
| **Hypertension associated with T2DM** | Present | 20(67) | 13(43) | 0.11* |
| | Absent | 10(33) | 17(57) | |

**† Data analysed using Fisher Exact Test, *Data analysed using Chi-square, *p*<0.05 is considered statistically significant, T2DM-Type 2 diabetes mellitus**

The age range of patients with diabetes mellitus was between 18 to 60 years. The mean age was 48.33±5.80 years in Group A and 46.43±7.74 years in the Group B ($p$ = 0.20). 86% and 70% of patients belonged to be age group of 41 – 60 in group A and group B respectively.

Both the study groups were gender matched. There were 50% male and 50% female patients in the group A and 40% male and 60% female patients in the group B ($p$=0.60). There were 67% of patients had family history of diabetes mellitus in the group A and 57% of the patient had family history of DM in the group B($p$=0.59). In the group A, 67% of patients had history of hypertension and in the group B, 43% of patients had history of hypertension associated with newly diagnosed type 2 diabetes mellitus patients. Table 2 shows baseline non-glycaemic parameters at baseline in both group A and group B, both the groups were comparable with respect to non-glycaemic parameters at baseline.

**Table 2: Baseline Non-Glycaemic Parameters**

| PARAMETERS | GROUP A (Mean±SD) mg/dl | GROUP B (Mean±SD) mg/dl | p VALUE |
|---|---|---|---|
| HAEMOGLOBIN (%) | 12.40±2.5 | 12.68±1.87 | 0.62* |
| TOTAL CHOLESTEROL | 154.3±29.31 | 145.5±28.87 | 0.24* |
| LDL | 91.53±24.89 | 84.76±24.0 | 0.28* |
| HDL | 35.73±8.91 | 36.56±8.05 | 0.70* |
| TRIGLYCERIDES | 134.93±52.14 | 122.06±34.26 | 0.26* |
| VLDL | 26.76±10.53 | 24.23±6.82 | 0.27* |

***Data analysed by unpaired t test, (p<0.05 is considered statistically significant)**

Mean Hb% in Group A was 12.40±2.50 at baseline and12.46±2.51 at week 12, and Group B was 12.68±1.87 at baseline and 12.76±1.92 at week 12. Group B shows effective improvement in Haemoglobin percentage from baseline to week 12 (p = 0.003) which was statistically significant when compared to group A. Mean Hb% between groups at 12 weeks was not statistically significant (p =0.59). **Figure 1** shows mean haemoglobin percentage from baseline to week 12 in both the groups.

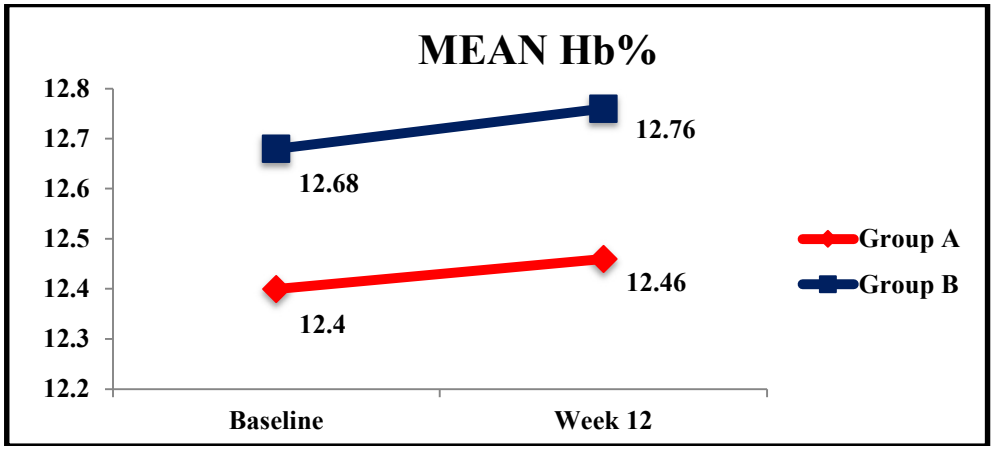


**Figure 1: Mean reduction of Haemoglobin% from baseline to week 12in both the groups**

**Table 3** represents mean lipid profile from baseline to week 12 in both group A and group B. Mean total cholesterol in group A was 154.3±29.31and 154.6±29.32at baseline and week 12 and group B was 145.5±28.87 and 140.43±26.87 at baseline and week 12 respectively, which shows effective reduction of mean plasma cholesterol from baseline to week 12 (p = 0.002) which was statistically significant. Mean reduction of LDL levels (p = 0.01) in group B, triglyceride levels (p = 0.0007) in group B and VLDL levels (p = 0.0005) in group B was statistically significant. Mean HDL level shows effective improvement in both group A and group B from baseline to week 12 (p = 0.01) and (p = 0.02) respectively.

**Table 3: Mean lipid profile from baseline to week 12in both the groups**

| Parameters | Groups | Baseline (Mean±SD) mg/dl | Week 12 (Mean±SD) mg/dl | p value |
|---|---|---|---|---|
| **Total cholesterol** | **Group A** | 154.3±29.31 | 154.6±29.32 | 0.90 |
| | **Group B** | 145.5±28.87 | 140.43±26.87 | 0.002† |
| **LDL cholesterol** | **Group A** | 91.53±24.82 | 90.83±23.44 | 0.70 |
| | **Group B** | 84.76±24.0 | 81.2±22.06 | 0.01† |
| **HDL cholesterol** | **Group A** | 35.73±8.91 | 36.83±8.34 | 0.01† |
| | **Group B** | 36.56±8.05 | 37.6±6.51 | 0.02† |

| | | | | |
|---|---|---|---|---|
| **Triglycerides** | **Group A** | 134.93±52.14 | 137.9±48.38 | 0.47 |
| | **Group B** | 122.06±34.26 | 110.36±34.57 | 0.0007† |
| **VLDL cholesterol** | **Group A** | 26.76±10.53 | 27.8±9.69 | 0.22 |
| | **Group B** | 24.23±6.82 | 21.9±6.91 | 0.0005† |

**Data analysed by unpaired t test, † p<0.05 is considered statistically significant**

**Figure 2** shows mean lipid levels after treatment in group A and group B at 12 weeks. Mean triglycerides level in both group A and group B was 137.9±48.38 and 110.36±34.47 at week 12 respectively (p=0.01) and mean VLDL level was 27.8±9.69 and 21.9±6.91 at week 12 in group A and group B respectively (p=0.008). There is an effective reduction of Triglycerides and VLDL cholesterol in both the groups after 3 months treatment which was statistically significant (p<0.05).

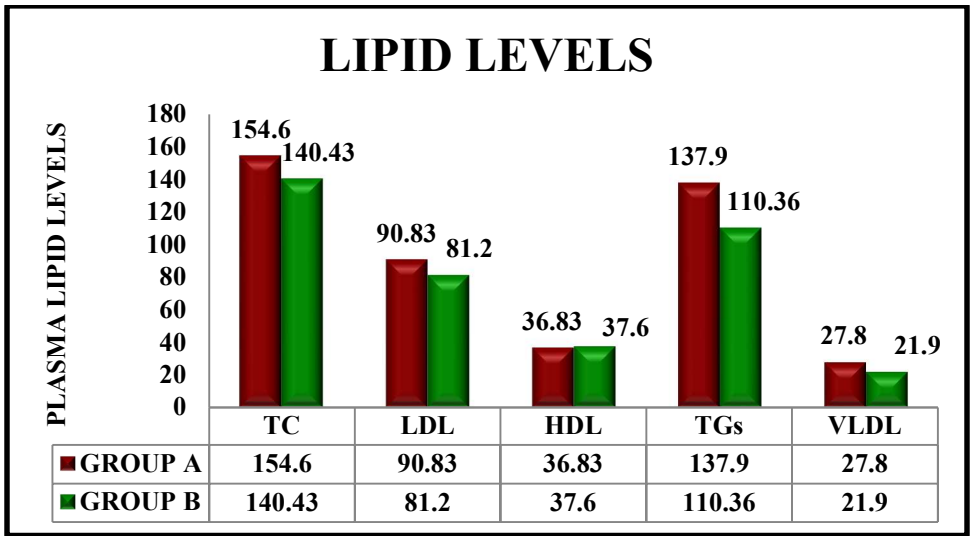


**Figure 2: Mean lipid levels between groups at week 12**

The treatment was well tolerated in both the groups. The adverse effects encountered were mild to moderate in nature; no serious adverse events were noted. None of the adverse effect warranted discontinuation of study medication. **Figure 3** shows the various adverse effects encountered in both the groups.

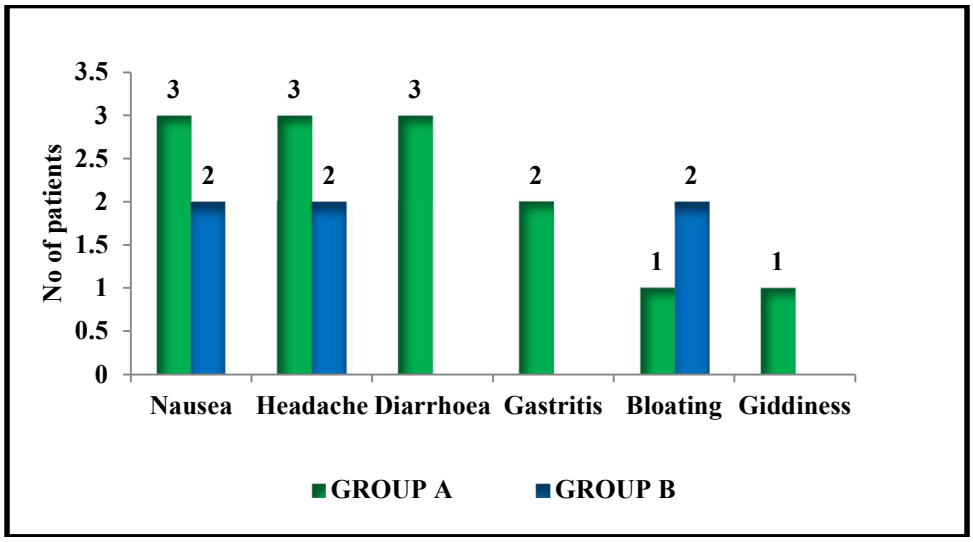


**Figure 3: Adverse effects**

## DISCUSSION

The present study was designed to compare the efficacy and safety of metformin alone versus supplementation of vitamin C and vitamin E along with metformin on haemoglobin percentage (Hb%) and lipid profile among newly diagnosed type 2 diabetic patients in tertiary care hospital. Based on the experimental protocol, the participants were divided into two groups, the first group (Group A) treated with tablet Metformin 500mg BD without any vitamin supplementation (n=30). The second group (Group B) was treated with tablet Metformin 500mg BD supplemented with tablet vitamin C 500mg OD and capsule vitamin E 400mg OD (n=30). Both the groups were followed up monthly for three months.

Our findings suggest that there is no significant difference in non-glycaemic parameters in between the groups by the end of the study. There is no significant difference in the adverse effect profile in both the groups.

Haemoglobin percentage was improved from 12.40±2.50 to 12.46±2.51 g/dl in group A and it was improved from12.68±1.87 to 12.76±1.92 g/dl in group B from baseline to week 12 respectively, which is statistically significant only in group B. But there was no effective improvement in haemoglobin percentage between group A and group B at week 12 (p= 0.59). Results of our study suggest that supplementation of Vitamin E and Vitamin C along with metformin significantly improves the haemoglobin percentage. The total cholesterol levels changed from 154.3±29.31 to154.6±29.32 mg/dl in group A and it was reduced from 145.5±28.87 to 140.43±26.8 mg/dl in group B from baseline to week 12 respectively, statistically significant reduction seen only in group B.

LDL cholesterol reduced from 91.53±24.82 to 90.83±23.44 in group A, reduced from 84.76±24.0 to 81.2±22.06 in group B from baseline to week 12 respectively. Statistically significant reduction seen only in group B from baseline to week 12. HDL cholesterol increased from 35.73±8.91 to 36.83±8.34 in group A, increased from 36.56±8.05 to 37.6±6.51in group B from baseline to week 12, statistically significant improvement seen in both the groups at week 12. Triglycerides levels changed from 134.93±52.14 to 137.9±48.38 in group A and it is reduced from 122.06±34.26 to 110.36±34.57 in group B from baseline to week 12 respectively, statistically significant reduction seen only in group B.

VLDL cholesterol levels changed from 26.76±10.53 to 27.8±9.69 in group A, and it is reduced from 24.23±6.82 to 21.9±6.91 in group B from baseline to week 12 respectively, statistically highly significant reduction seen only in group B. In a study conducted by Ali Abd El-Aal et al. [8] in 2018 with T2DM patients and 10 in each group of aged between 40-60 years, one group treated with metformin alone and another group treated with vitamin C (500mg BD) and vitamin E (400mg BD) along with metformin (500mg BD) for three months. Among non-glycaemic parameters, TC reduced 215.90±12.98 to 187.71±7.45 mg/dl, TG decreased from 236.80±24.10 to 182.00±22.01 mg/dl, VLDL-C from 47.35±4.82 to 36.39±4.39 mg/dl, and HDL-C improved from 38.14±1.43 to 43.90±1.53 mg/dl, which is similar to our study results.

Another study conducted by Amin T Hamed et al.[9] in 2015, a non-randomized prospective controlled trail in T2DM patients and 20 patients in each group, one group treated with metformin alone and another group treated with Vitamin C (1000mg OD) and Vitamin E (800mg OD) along with Metformin for three months. Among non-glycaemic parameters their results are as follows, TC reduced from 233.84±22.84 to 200.10±27.26 mg/dl, TG from 241.00±68.70 to 183.94±40.67, LDL-cholesterol from 147.84±29.02 to 123.26±29.16 from baseline to week 12 respectively, HDL-cholesterol increased from 37.89±2.28 to 39.94±5.27 from baseline to week 12 in vitamin E and C supplemented group, which is similar to our study results.

In another study done by Syed Wasif Gillani et al.[10]in 2017, on combined effect of metformin with Vitamin C 500mg/day versus metformin with placebo in newly diagnosed type 2 DM patients and followed up for 12 months. They got significant reduction of TC, LDL-C, TG and improvement in HDL-C found in vitamin C supplemented group which could be due to long term administration (48 weeks), these results are matching with our group B results.

A study by Jayesh K Bhatt et al. [11] in 2012, included 65 T2DM patients of aged between 30-70 years, with minimum of 6 months ongoing oral hypoglycaemic agents' treatment (Metformin and/or Glibenclamide). Patients in the intervention group received Vitamin C (500 mg OD) along with oral hypoglycaemic agents, patients in control group received only oral hypoglycaemic agents for a period of 3 months. The result shows that significant changes in the group supplemented with vitamin C with respect to total cholesterol and LDL cholesterol which is similar to our study results but there is no statistically significant decrease in triglyceride level and there is no statistically significant increase in HDL-C in same group. these results could be due to inclusion of patients suffering from T2DM of ≥3year of duration without treatment.

A study by Rafighi Z et al. [12]in 2011, conducted on T2DM patients in Iran. One group received OHA

with placebo and another group received oral hypoglycaemic agents with vitamin C+E supplementation (266.7 mg + 300IU each three times a day). They found highly statistically significant results with respect to TC, TG, LDL and HDL; this is almost similar to our study results and even we got statistically significant results with non-glycaemic parameters, for them getting highly statistically significant results could be due to higher dose of vitamin C and E administered.

In a study done by V R Kathore et al.[7] included 50 T2DM patients who were on oral hypoglycaemic drugs with mean duration of DM 1 to 8 years and to all 50 patients they supplemented only vitamin C (500mg BD) for 12 weeks. Among non-glycaemic parameters, TC reduced from 217.32±29.41 to 158.53±25.47 mg/dl, TG reduced from 234.66±55.41 to 163.17±34.32 mg/dl, LDL-C from 133.14±33.65 to 83.71±13.54 mg/dl and HDL-C increased from 37.25±4.3 to 42.19±3.6 mg/dl from baseline to week 12 respectively. Results of this study matches with our study results.

A study done by Nath RK et al. [13] (2013), included 46 T2DM patients who were already on treatment, to them they supplemented only vitamin C (1000mg OD) for 8 weeks. TC reduced from 198.28±38.10 mg/dl to 178.72±31.20 mg/dl, TG from 210.02±65.1 mg/dl to 186.56±54.00 mg/dl, LDL reduced from132.90±36.4 mg/dl to 121.65±26.76 mg/dl matching with our study, HDL increased from 41.72±120 to 43.35±11.60 mg/dl which is not statistically significant but in our study we got statistically significant results.

Study done by Ardekani et al. [14] (2007), included 84 T2DM patients who were already on treatment, they were supplemented with only vitamin C, group A (n=41) received vitamin C (500 mg OD) and group B (n=43) received vitamin C (1000mg OD) for six weeks. They got significant reduction in TG, LDL and significant increase in HDL-C in group B and there is no significant reduction in above mentioned parameters in group A, this could be due to short duration of supplementation of vitamin C. In our study we got significant reduction in non-glycaemic parameters in supplemented group, this could be due to additional supplementation of vitamin E along with vitamin C in our study.

Mild adverse effects were seen in both the groups, i.e., nausea, headache, diarrhoea, gastritis, bloating, giddiness and it is not statistically significant. Both the drugs were well tolerated by the patients. 43% of patients in the group A and 20% of the patients in the group B were experienced adverse effects.

In the group A, the adverse effects were nausea (10%), headache (10%), diarrhoea (10%), gastritis (6%), and bloating (3%). In the group B, the adverse effects were nausea (6%), headache (6%), and bloating (6%). The occurrence of adverse effects was not statistically significant between the groups ($p$=0.09) although the incidence of overall adverse effects was greater in group A.

Supplementation of antioxidants to newly diagnosed type-2DM patients might improve endogenous antioxidant capacity due to reducing lipid profile and they may play a role in preventing complications in Type 2 diabetes. Since vitamin E and C are exogenous antioxidants that are not associated with toxicity at recommended dosage, supplementing these vitamins along with regular antidiabetic drugs should be considered.

## CONCLUSION

Both the groups are effective in improving both haemoglobin percentage and lipid profile in supplementation of vitamins along with Metformin as compared to Metformin alone with no significant adverse effect. Hence, daily consumption of vitamins may be beneficial in decreasing lipids in patients with T2DM and thus reducing the risk of complications.

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