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STUDY ON EFFECT OF VITAMIN-C AS ADD ON THERAPY WITH ANTIDIABETIC DRUGS IN NEWLY DIAGNOSED TYPE-2 DIABETES MELLITUS PATIENTS

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ABSTRACT

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia, usually associated with oxidative stress. Beside hyperglycemia, oxidative stress also plays a major role in diabetes and its complications such as diabetic neuropathy, nephropathy and retinopathy. Reduction of oxidative stress may have better outcome in diabetic patients. Therefore the present research was designed to study the effect of oral hypoglycemic agents (OHA) and vitamin-C on oxidative stress and lipid profile along with glycemic control. A total of 94 type-II diabetes mellitus patients were taken in open label, prospective study and divided them in to four groups, Group-A (Glimepiride), Group-B (Glimepiride + Vitamin-C), Group-C (Metformin + Voglibose) and Group-D (Metformin+ Voglibose+ Vitamin-C). Glycemic control, lipid profile and oxidative stress were compared before and after 3 months of treatment in all the 4 groups. Data was analyzed By using SPSS Software. At the end of 3 months, significant glycemic control was found in all 4 groups ($p<0.001$) but only Group-B and Group- D showed significant reduction of oxidative stress ($p<0.001$). Marked lipid control was noticed in Group-B, Group-C and Group- D. Supplementation of vitamin-C along with OHA therapy has additional effect on glycemic control and lipid level and being an antioxidant, Vitamin-C reduces the oxidative stress in diabetes mellitus patients.

Keywords: Oral hypoglycemic agents (OHA), Type-II diabetes mellitus, Vitamin-C, Oxidative stress

1. INTRODUCTION

Diabetes mellitus is a multi factorial disorder; affects the metabolism of carbohydrates, proteins and lipids, characterized by hyperglycemia. The rise in blood glucose level is due to either lack of insulin (β-Cell dysfunction) or its action (Insulin resistance). There are various risk factors such as increase in age, obesity, stress, changes in diet and lack of physical activity may responsible for diabetes mellitus [1]. Genetic factors and sedentary lifestyle play a major role in developing Type II-diabetes mellitus and its complications such as nephropathy, neuropathy, and retinopathy which affect the vascular system, kidney, retina and peripheral nerve in chronic cases [2-4].

Globally 415 million people are suffering with diabetes and it is expected to rise to >642 million by 2040. According to Indian statistics, the prevalence of diabetes in India is 8.7 and 69.2 million diabetic cases reported in adult population [5]. Criteria for diagnosis of diabetes mellitus is presence of classical symptoms plus fasting blood sugar (FBS) >126 mg/dl or post prandial blood glucose (PPBS) >200 mg/dl or random blood glucose level >200mg/dl and HbA1C >6.5% [6].

Diabetic complications are mostly associated with oxidative stress and high total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL) and very low density lipoprotein (VLDL) and low high density lipoprotein (HDL-C), so good lipid profile and low oxidative stress can limit the complications and their progress. Currently, there are several antidiabetic agents available but still outcome is poor because such drugs have no marked effect on oxidative stress in

diabetic patients [7]. Hence, development of novel strategies to improve the outcome will be of great benefit.

Diabetic patients will have elevated level of free radicals and low level of antioxidants, including Vitamin C. Vitamin C is a natural antioxidant, play crucial role in prevention of diabetic complications by scavenging of free radicals such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), forestalling the commencement of chain responses that lead to protein glycation [8, 9] and protecting from lipid Peroxidation [8, 10]. Supplementation of vitamin C has been shown marked improvement in glycemic control, lipid profile and reduces cutaneous capillary permeability in Type-II DM [11]. Therefore, the present study was conducted to evaluate the beneficial effects of antioxidant supplementation (vitamin C) along with OHA in patients with type 2 diabetes mellitus.

2. MATERIAL AND METHODS

A prospective, randomized, open label study was carried out in Department of Pharmacology and General Medicine in Rama Medical College, Hospital and Research Centre in 2018 at Kanpur. Study was started after taking approval from institutional ethical committee. Patients were enrolled in the study as per following inclusion and exclusion criteria.

2.1. Inclusion criteria

- Newly diagnosed type-II diabetes mellitus patients.
- Patients with age group of 30-50 years from both sexes.
- Who are willing to give informed concern

2.2. Exclusion criteria

- Smokers/alcoholics/Pregnant & lactating women's.
- Type-I Diabetes mellitus patients.
- Patients with Psychiatry, Liver, Kidney, Cardiac problems and also chronic infections like TB, leprosy, recent trauma, surgery.
- Hypersensitivity to vit-C and any of the study drugs.
- Unwilling to participate and give informed concern or mental incapacity to take the drugs.

A total of 94 newly diagnosed type-II diabetes mellitus patients satisfying inclusion/exclusion criteria were enrolled for the study. At the beginning of study demographic data along with patient past medical history was taken and followed by basic investigations for glycemic control (HbA1c, FBS and PPBS) lipid profile (TC, TG, HDL, LDL and VLDL) and oxidative stress (using TAC and MDA as parameters) were done. Based on the treatment plan, patients were divided in to 4 groups and treated them for 3 months as follows

Group-A: (n=32) patients were given Glimepiride (4mg/day)

Group-B: (n=30) patients received glimepiride (4 mg/day) + vitamin-C (1000mg/day)

Group-C: (n=20) patients were given Metformin (1000 mg/day) + voglibose (0.4 mg/day)

Group-D: (n=12) patients treated with Metformin (1000 mg/day) + voglibose (0.4 mg/day) + vitamin-C (1000 mg/day).

This study had 6 follow-up's which were scheduled after every 15 days. At every follow-up general medical condition was assessed and investigations for glycemic control (FBS and PPBS) were done. Similarly lipid profile and oxidative stress was assessed along with glycemic control after commencement of the study for each subject.

2.3. Determination of Biochemical parameters

Estimation of blood Glucose was done by glucose oxidase and Peroxidase enzymatic method [12], HbA1c was estimated by Ion exchange resin method [13]. Malondialdehyde (MDA) was estimated as thiobarbituric acid reactive substances (TBARS), Total antioxidant capacity was analyzed by ferric reducing ability of plasma (FRAP) and TC by Modified Roeschlau's Method [14], TG by Tinder Method [15], HDL by Phosphotungstic acid Method [16], LDL by Friedewald formula [17].

2.4. Statistical Analysis

Data was analyzed using Paired' test and results were expressed as mean ± standard deviation (SPSS 20 software).

3. RESULTS

In group-A after 3 months of treatment, there was a significant reduction of FBS PPBS, HbA1c (p=0.000) and no significant reduction of TC (p=0.527), TG (p=0.558), LDL (p=0.372), VLDL (p=0.271) and TAC (p=0.060) observed. Similarly elevation of HDL (p=0.085) and MDA (p=0.075) was observed but which is also not significant (Table 1).

After 3 months of treatment with glimepiride+ vitamin C(Group-B), there was a significant reduction of FBS, PPBS, HbA1c(p=0.000), MDA, TC, TG, LDL-C,

VLDL($p<0.05$) and significant elevation of TAC and HDL-C ($p<0.05$)observed (Table 2).

There was a significant reduction of FBS, PPBS, HbA1c ($p=0.001$), TC, TG, LDL, VLDL ($p<0.05$) and elevation of HDL ($p<0.05$) seen in group-C patients who were treated with Metformin + voglibose. Similarly reduction of TAC ($p=0.185$) and elevation of MDA ($p=0.073$) was seen but which is not statistically significant (Table 3).

In group-D after 3 month of treatment, there was a significant reduction of FBS, PPBS, HbA1c, TC, TG, LDL ($p=0.001$), MDA, VLDL ($p<0.05$) and significant elevation of HDL ($p=0.001$) and TAC ($p<0.05$) observed (Table-4).

Table 1: Comparison of 3 months findings with baseline values in group-A

Variables	Baseline	3 months	Mean difference	p-Value
HbA1c (%)	6.8±0.1	6.3±0.3	0.42±0.42	0.001***
FBS (Mg/dl)	147± 10.3	131.4± 7.41	15.58±5.7	0.001***
PPBS (Mg/dl)	231.6±16.8	210.5±14	21.08±9.4	0.001***
TAC (mmol/l)	0.84±0.1	0.78±0.14	0.06±0.28	0.060
MDA (mmol/l)	4.13±0.45	4.37±0.63	0.20±0.64	0.075
TC(Mg/dl)	172.9±23.77	167.9±33.77	4.97±46.68	0.527
TG(Mg/dl)	170.1±21.1	162.7±25.24	7.41±39.68	0.558
HDL(Mg/dl)	40.7±9.59	45.19±9.4	4.47±15.12	0.085
LDL(Mg/dl)	98.66±28.13	90.99±35.81	7.67 ± 50.92	0.372
VLDL(Mg/dl)	34.02±4.21	32.54±5.0	1.47±7.92	0.271

*Highly significant P<0.001***; Significant P<0.05***

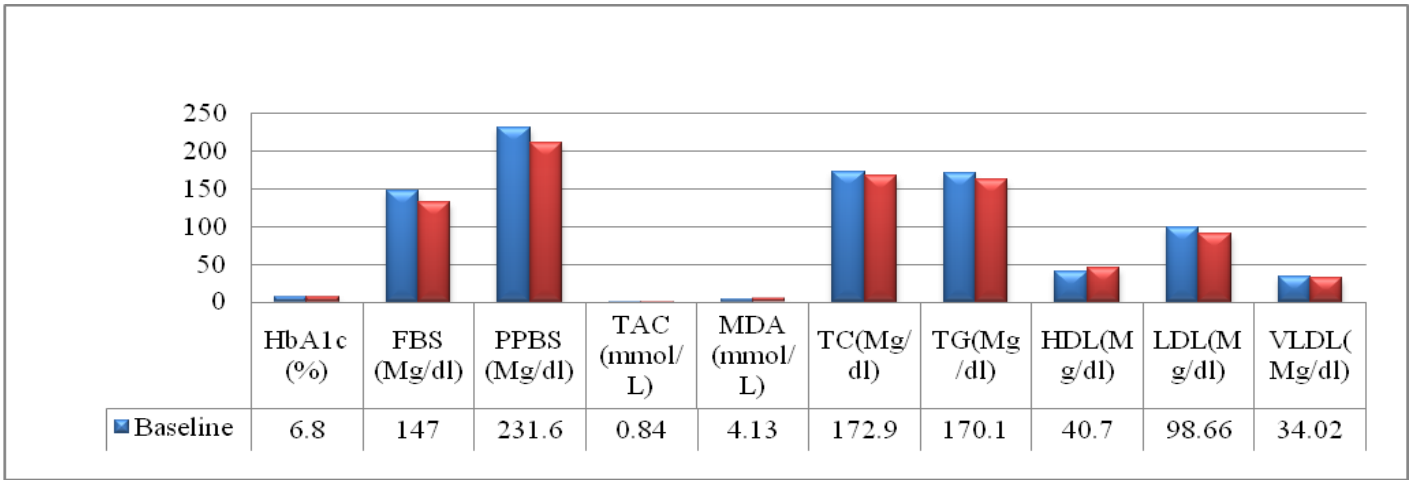


Fig. 1: Baseline Vs 3 months values in group-A

Table 2: Comparison of 3 months findings with baseline values in group-B

Variables	Baseline	3 months	Mean difference	p-value
HbA1c (%)	7.2±0.16	6.5±0.2	0.6± 0.2	0.001***
FBS (Mg/dl)	152.9±9.26	132.3±5.26	20.6±9.13	0.001***
PPBS (Mg/dl)	244.2±12.01	215.5±9.79	28.7±12.9	0.001***
TAC (mmol/l)	0.71±0.09	0.82±0.18	0.1±0.1	0.013**
MDA (mmol/l)	4.50±0.57	4.09±0.59	0.4±0.66	0.002**
TC(Mg/dl)	181.1±17.88	170.3±25.56	10.53±21.06	0.010**
TG(Mg/dl)	170.8±8.5	157.6±23.89	13.2±21.07	0.002**
HDL(Mg/dl)	41.43±7.86	49.37±10.86	6.1±13.36	0.003**
LDL(Mg/dl)	105.2±20.48	93.38±23.65	11.84±23.71	0.011**
VLDL(Mg/dl)	34.7±4.24	29.8±5.61	4.66±7.73	0.003**

*Highly significant P<0.001***; Significant P<0.05***

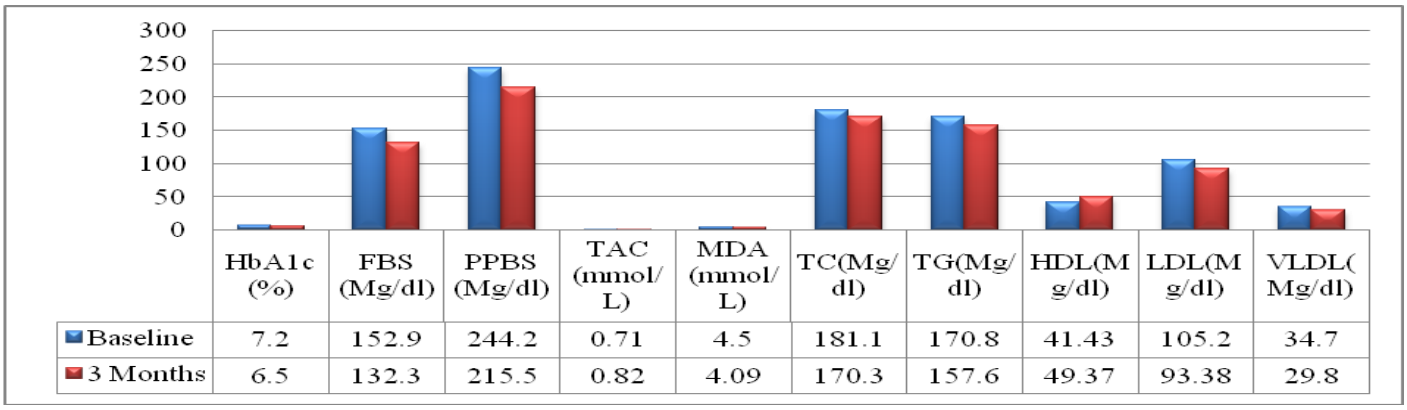


Fig. 2: Baseline Vs 3 months values in group-B

Table 3: Comparison of 3 months findings with baseline values in group-C

Variables	Baseline	3 Months	Mean Difference	p-value
HbA1c (%)	8.13±0.29	7.24±0.25	0.88±0.12	0.001***
FBS (Mg/dl)	161.6±11.7	138.6±8.31	23±7.218	0.001***
PPBS (Mg/dl)	258.3±14.4	226.6±7.03	31.75±9.08	0.001***
TAC (mmol/l)	0.77±0.18	0.73±0.09	0.03±0.11	0.185
MDA (mmol/l)	5.27±0.84	5.66±0.97	0.39±0.92	0.073
TC(Mg /dl)	181.1±20.17	167±30.33	14.15±19.92	0.005**
TG(Mg/dl)	157.8±13.93	148.2±17.25	9.5±12.98	0.004**
HDL(Mg/dl)	39.45±4.67	45.2±7.53	5.75±7.77	0.004**
LDL(Mg/dl)	110.5±19.16	99.56± 28.8	10.96±18.39	0.015**
VLDL(Mg/dl)	30±6.82	25.7±3.24	4.30±7.8	0.023**

*Highly significant P<0.001***; Significant P<0.05***

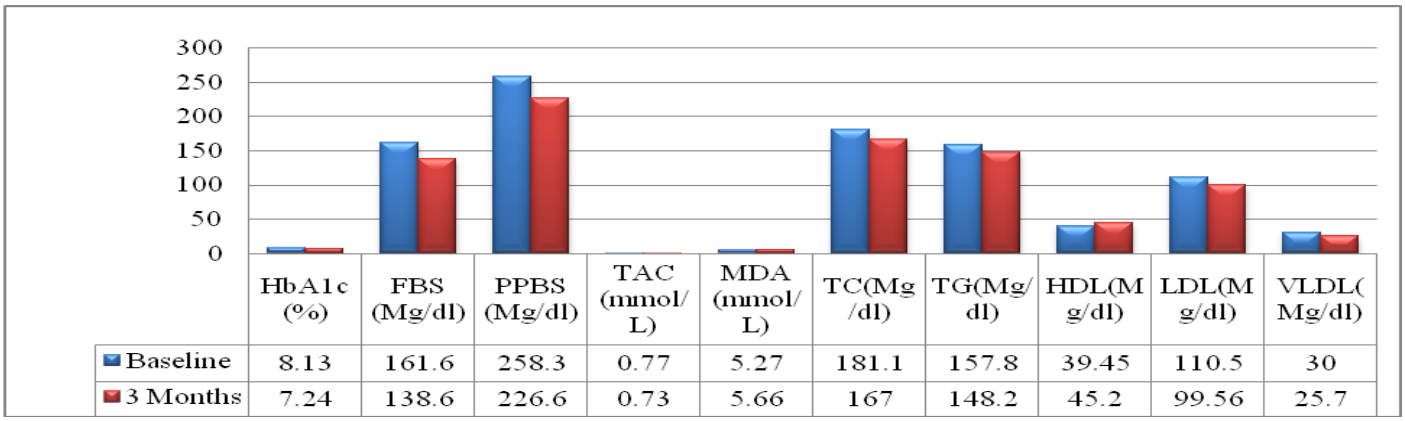
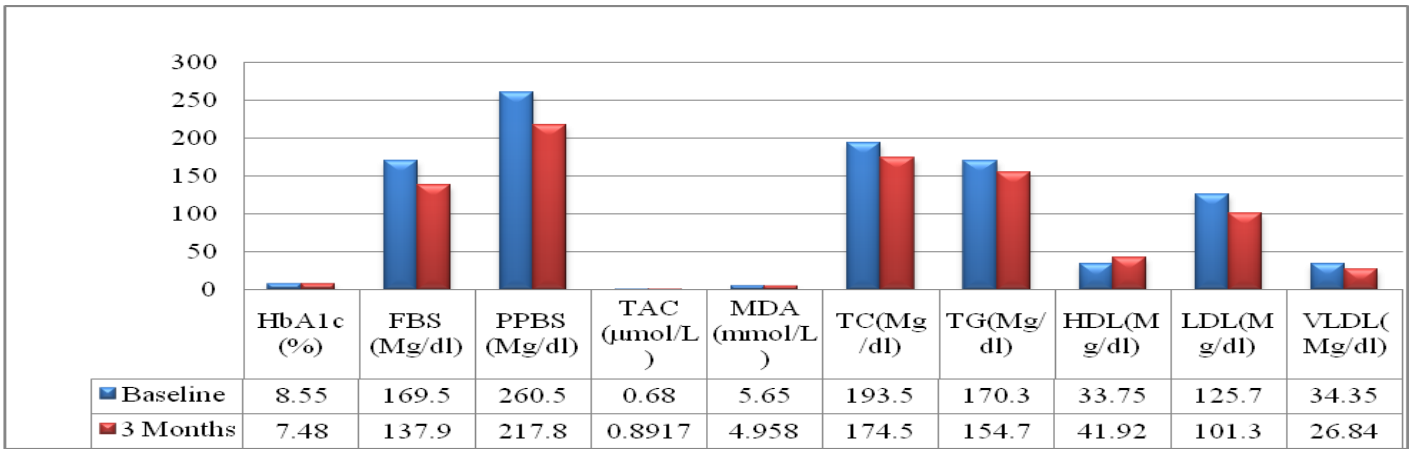


Fig. 3: Baseline Vs 3 months values in group-C

Table 4: Comparison of 3 months findings with baseline values in group-D

Variables	Baseline	3 Months	Mean Difference	p-value
HbA1c (%)	8.55±0.40	7.48±0.39	1.06±0.14	0.001***
FBS (Mg/dl)	169.5±8.59	137.9±4.81	31.58±7.48	0.001***
PPBS (Mg/dl)	260.5±12.57	217.8±11.54	42.75±15.97	0.001***
TAC (mmol/l)	0.68±0.12	0.89±0.26	0.20±0.28	0.029**
MDA (mmol/l)	5.65±0.78	4.95±0.87	0.7±0.93	0.025**
TC(Mg /dl)	193.5±16.62	174.5±15.33	19±14.56	0.001***
TG(Mg/dl)	170.3±13.38	154.7±16.52	15.67±4.90	0.001***
HDL(Mg/dl)	33.75±4.13	41.92±7.75	8.16±5.96	0.001***
LDL(Mg/dl)	125.7±17.36	101.3±15.43	24.35±19.92	0.001***
VLDL(Mg/dl)	34.35± 2.47	26.84 ± 5.81	7.50 ± 7.17	0.004**

*Highly significant P<0.001***; Significant P<0.05***



	HbA1c (%)	FBS (Mg/dl)	PPBS (Mg/dl)	TAC (µmol/L)	MDA (mmol/L)	TC(Mg/dl)	TG(Mg/dl)	HDL(Mg/dl)	LDL(Mg/dl)	VLDL(Mg/dl)
Baseline	8.55	169.5	260.5	0.68	5.65	193.5	170.3	33.75	125.7	34.35
3 Months	7.48	137.9	217.8	0.8917	4.958	174.5	154.7	41.92	101.3	26.84

Fig. 4: Baseline Vs 3 months values in group-D

4. DISCUSSION

The present study aimed at studying the beneficial effect of vitamin-C after adding with oral hypoglycemic agents in type-II diabetes mellitus patients. Among 94 newly diagnosed type-II diabetes mellitus patients there are 54.2% males and 45.7% females. 48.9% of study population belongs to age group 41 to 50, followed by 37.2% and 15.95% of patients belongs to age group 30 to 40 and 51 to 60 years respectively. There was a significant reduction in HbA1c ($P<0.001$), FBS ($P<0.001$) PPBS($P<0.001$) level seen in all 4 groups but mean reduction in HbA1c, PBS and PPBS level was high in Group-B(HbA1c; 0.6±0.2 , FBS; 20.6±9.13 and PPBS;28.7±12.9)and Group-D(HbA1c; 1.06± 0.14, FBS; 31.58±7.48 and PPBS; 42.75±15.97) as compared to group-A (HbA1c; 0.42±0.42, FBS; 15.58±5.7 and PPBS; 21.08±9.4) and group-C(Hb A1c; 0.88±0.1268 , FBS; 23±7.21 and PPBS; 31.75± 9.08) respectively. In a study diabetic patients were treated with glimepiride and they had shown significant glycemic control [18]. The combination of Sulfonylureas with Vitamin-C showed significant reduction of FBS and PPBS [19]**.** Significant reduction of HbA1c, FBS and PPBS was seen in patients who were treated with metformin and voglibose [20].

Most of the antihyperglycemic agents also have lipid lowering effect along with their hypoglycemic effect, but this effect is variable. In present study significant control on lipid level was noticed in all groups except group-A ($P>0.05$), but the mean reduction of TC, TG, HDL, LDL, VLDL level was high in group-D (TC; 19±14.56, TG; 15.67±4.90, HDL; 8.16±5.96, LDL; 24.35±19.92, VLDL; 7.50±7.17) and group-B(TC; 10.53±21.06, TG;13.2±21.07, HDL;6.1±13.36, LDL ;11.84±23.71,VLDL; 4.66±7.73) as compared to group-C (TC; 14.15±19.92, TG; 9.5±12.98, HDL; 5.75±7.77, LDL; 10.96±18.39, VLDL; 4.30±7.8), but mean reduction of total cholesterol level was more in group-C (Metformin+ voglibose) than group-B (glimepiride+ vitamin-C). Another similar study had shown significant reduction of TC, TG, LDL, and VLDL and elevation of HDL in diabetic patients after treatment with glimepiride alone but such findings not supporting present study [21]**.** In our study we found a significant control on lipid profile in patients treated with Sulfonylureas + vitamin C, similar results were mentioned in another study [19]. Metformin+ voglibose (group-C) combination showed a significant reduction of TC, TG, LDL and VLDL and elevation of HDL level, these findings are in line with the previous studies [22]**.** Supplementation of Vitamin C reduces the insulin resistance by improving endothelial function and lowering oxidative stress [19]**.** Present study showed that there is a significant reduction of MDA and elevation of TAC level in group-B and group-D treated with OHA and vitamin C supplementation($P<0.05$), but Group-A and group-C had not shown significant difference in MDA and TAC level($p>0.05$). High mean reduction in MDA (0.7±0.93) and marked elevation of TAC (0.20±0.28) level was observed in Group-D as compared with group-B (MDA; 0.4±0.66, TAC; 0.1±0.1). So supplementation of vitamin-C along with antidiabetic drugs has been proved to be more effective in control of blood glucose, oxidative stress and lipid level.

5. CONCLUSSION

Based on the results of our study we conclude that supplementation of vitamin-C along with OHA therapy has additional effect on glycemic control and lipid level

and being an antioxidant, Vitamin-C reduces the oxidative stress in diabetes mellitus patients. Treatment aim in Type-II diabetes mellitus cases is not only to control blood glucose level but also diabetic complication, unfortunately the aim is not fulfilled with currently available antidiabetic agents. Hence there is a need of novel strategies to achieve good glycemic control and prevent diabetic complications and their progression.

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Conflicts of interest

There are no conflicts of interest.

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