Original Article

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Vitamin E, Its Beneficial Role in Diabetes Mellitus (DM) and Its Complications

Biochemistry Section

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ABSTRACT

Introduction: Studies have shown that diabetes is accompanied by an increased oxidative damage to all the bimolecular. Enhanced oxidative stress contributes to the development of the diabetic complications. The key lipid soluble chain breaking antioxidant,-tocopherol, is known to be deficient in diabetes. Human intervention studies have indicated the role of vitamin E in improving the endothelial function, the retinal blood flow and the renal dysfunction. The aim of the study was to find the role of vitamin E in preventing the development and the progression of the diabetic complications.

Methodology: Both type I and II DM patients with and without complications were included in this study. They were divided separately into the test (which received insulin/oral hypoglycemic and vitamin E) and the control groups (which received only insulin/oral hypoglycemic drugs). The Fasting Blood Sugar(FBS), Post-prandial Blood Sugar(PPBS) and the Total Cholesterol(TC) were estimated and the Blood Pressure (BP) was noted at 0(beginning),12,18 and 24 months. Cardiovascular disease, retinopathy, nephropathy and foot ulcer development and progression were monitored. The data was analyzed by the Z test for the means and for the proportions.

Results: It was evident from the analysis of the data that the PPBS, TC and the Diastolic Blood Pressure (DBP) declined gradually and significantly in the test groups. This was a beneficial development for the diabetic patients. The patients who were on the vitamin E supplementation had a delayed development and a slow progression of the complications.

Conclusion: Vitamin E supplementation has an important role in delaying the onset of the diabetic complications as well as for slowing down the progression of the complications.

Key Words: Diabetes mellitus, Antioxidant, Diabetic complications

INTRODUCTION

Diabetes is accompanied by severe oxidative stress (especially lipid per oxidation) which is caused by increased oxygen free radical production. Toxic oxygen free radicals have been implicated in the pathogenesis of Diabetes mellitus, and its micro and macro vascular complications [1]. An imbalance which results from an increased production and/or the reduced scavenging of these free radicals leads to a metabolic state of oxidative stress, which consequently leads to tissue damage. Auto glycosylation reactions, alterations in the sorbitol pathway and hyperglycemia have been proposed as some of the mechanisms which are responsible for this increased oxidative stress [1].

The damage which is done to the bimolecular by the reactive oxygen species (oxidative damage) is kept in check by a complex network of antioxidant defense and repair systems which are synthesized within the human body [2]. In addition, certain antioxidants are obtained from the diet [2,3]. One of the best characterized of these is vitamin E, a fat-soluble vitamin that helps in preventing damage to the lipids by the oxygen free radicals [4]. When highly-reactive species attack the lipids within the membranes or the lipoproteins, they set off the chain reaction of lipid per oxidation [2]. Vitamin E halts this chain reaction, e.g. it acts as a chain breaking inhibitor of lipid per oxidation [3].

Antioxidants have shown a beneficial role in the prevention of the diabetic complications. Diabetes forms a good model of the chronic oxidative damage and it is a particularly suitable disease for antioxidant supplementation [4]. It was found that there was a significant correlation between the increased blood sugar levels and the depletion of the antioxidants. This depletion was a major risk factor for the development of the complications and antioxidant supplementation (vitamin E,C) could decrease this risk [5].

But, only a few studies have shown the impact of the antioxidant therapy in diabetic patients, in developing countries like India [4]. Keeping these facts in mind, the present study was undertaken to evaluate the role of antioxidant supplementation along with the standard ant diabetic therapy in the prevention of diabetic complications.

AIMS AND OBJECTIVES

1. To evaluate the role of the vitamin E therapy in preventing the development of complications in diabetic patients (primary prophylaxis).

2. To evaluate the role of the vitamin E supplementation in controlling the progression of the complications in diabetic patients (secondary intervention).

MATERIALS AND METHODS

This was a prospective clinical study. Diabetic patients of either sex, who were above the age of 45 years, with or without diabetic complications, who received regular treatment, were included in the study. Smokers, tobacco chewers and people who suffered from any acute or chronic illnesses were excluded from the study.

The institutional ethical committee approval was sought and an informed consent was obtained from the patients.

The recruited patients were broadly categorized into two groups, the primary and the secondary prevention groups. In the primary prevention group, 64 type I and 64 type II patients with 1-2 years of duration of the disease were included. The group which involved the type I patients was further divided into the test and the control groups, which consisted of the patients who received insulin and the vit E supplementation and the patients who received only insulin respectively. Similarly, the type II patients were further divided into the test and the control groups which consisted of those who received oral hypoglycemic and the vit E supplementation and those who were on oral hypoglycemic only respectively.

These patients were followed up for 12, 18 and 24 months. If any complications developed, they were analyzed.

THE STUDY DESIGN

At the beginning of the study, the history of the patients was taken in detail. General physical examinations and systemic examinations were carried out. The routine blood parameters like FBS, PPBS, urea, creatinine, lipid profile and hemoglobin were estimated. A routine urine examination was done. Ophthalmoscope examination of both the fungi was done.

The advice regarding the medications and the dietary modifications was given.

The patients were followed up once a month. The history regarding the complications was taken. The routine investigations were done. Fundoscopic examinations were done. The ECG was recorded.

The secondary intervention group contained 90 types I and type II patients each who had 5-7 years of disease duration with complications. Both the type I and II patients were divided into the test and the control groups. The test group consisted of those who were on insulin/oral hypoglycemic plus vit E and the control group consisted of those who were on insulin/oral hypoglycemic only. The history taking, the examination, the investigations, etc were done as they were done in the primary prevention group. Additional investigations like LDH, CPK, SGOT and SGPT were done. The complications like cardiovascular diseases, nephropathy retinopathy, foot ulcer, etc were graded.

METHODOLOGY

FBS and PPBS were estimated by the glucose oxides peroxides method [6] by using an auto analyzer.

Total Cholesterol (TC) was estimated by the CHOD-PAP method by using a human diagnostic manual kit. The enzymatic method of Allain et al., was adopted [7].

STATISTICAL ANALYSIS

The data was analyzed by the Z test for the difference between the two means. The observations for the complications were analyzed by the Z test for the difference between the two proportions. The statistically significant data has been shown in the [Table/Fig-1 to 7].

RESULTS

- There was a statistically significant ($p<0.05$) decrease in the post-prandial blood sugar, total cholesterol and the diastolic blood pressure in the test group (type I DM) at 24 months as compared to those in the control group [Table/Fig-1].
- There was a statistically significant decrease in the post-prandial blood sugar, total cholesterol and the diastolic blood pressure in the test group (type II DM) at 24 months as compared to those in the control group. The decrease in the FBS and the SBP in the test group was observed at 24 months , but it was statistically insignificant [Table/Fig-2].
- The number of patients who developed cardiovascular complications and diabetic retinopathy in the test group was significantly low as compared to that in the controls. The other complication was less in the test group than in the control group. This was statistically insignificant [Table/Fig-3].
- There was a gradual and a significant decrease in the postprandial blood sugar, total cholesterol and the diastolic blood pressure in the test group (type I) at 24 months as compared to those in the control group [Table/Fig-4].
- There was a statistically significant change in the postprandial blood sugar and a decrease in the total cholesterol and the diastolic blood pressure in the test group(type II) at 24 months as compared to those in the control group [Table/Fig-5].

Variables	Control(n=32) Mean±SD				Test(n=32) Mean±SD			
	0 baseline	12months	18months	24months	0 baseline	12months	18months	24months
FBS (mg%)	101.4± 13.35	103± 13.21	105.4± 10.15	107±11.12	102.8±14.92	104±13.6	104.5±12.15	105±12.32
PPBS mg%)	180.2 ±8.69	182.7± 8.25	184.5±27.22	186±16.45	180±7.99	181±12.84	179±24.50	178±14.73*
TC (mg%)	202.5± 10.14	200.2± 8.88	201±±8.41	202±7.36	205±13.22	202.8±14.54	199.5±14.84	195.2±16.57*
SBP (mmHg)	124.6± 8.94	125.4± 10.51	124.4±7.78	125±7.38	124.4±11	124±9.55	123±7.05	122±7.88
DBP (mmHg)	83.6± 6.36	85± 7.99	85.5±8.73	87±9.84	83.2±9.65	83±8.31	83.8±8.52	82.4±8.15*

[Table/Fig-1]: Metabolic profile and blood pressure of type I DMpatients without complications (PrimaryPrevention)

Variables	Control(n=32) Mean±SD				Test(n=32) Mean±SD			
	0 baseline	12months	18months	24months	0 baseline	12months	18months	24months
FBS (mg%)	106.3±13.3	107±13.85	107.8±15.61	108.2±14.05	106.1±16.51	105±15.12	103.8±15.92	102±16
PPBS mg%)	181.7±6.76	182.8±7	183.5±8.29	183±8.49	181±8.83	181±9.45	185±7.55	178.2±7.58*
TC (mg%)	206.45±8.19	208.05±8.08	208.95±7.65	210±7.68	207.65±10.67	205.85±12.34	205±11.43	204±11.18*
SBP (mmHg)	123.2±8.50	124±8.89	124.5±9.15	124±8.12	123±10.20	123±9.20	122±8.78	121.5±8.54
DBP (mmHg)	82.1±5.02	83.3±4.69	83.8±3.78	84±3.65	83.8±7.51	81.7±7.51	81.1±7.55	80.9±6.67*

[Table/Fig-2]: Metabolic profile and blood pressure of type II diabetic patients without complications (Primary Prevention)

Complications	Type I DM Control(n=32) No of patients (%)	Type I DM Test(n=32) No of patients (%)	Type II DM Control(n=32) No of patients (%)	Type II DM Test(n=32) No of patients (%)
Cardiovascular complications	16 (50)	8 (25)*	15 (46.88)	7 (21.88) *
Diabetic retinopathy	12(37.5)	5 (15.63) *	13 (40.63)	6 (18.8) *
Diabetic nephropathy	12 (37.5)	8 (25)	11 (34.38)	7 (21.88)
Diabetic foot ulcer	9 (28.13)	5 (15.63)	10 (31.25)	6 (18.8)

[Table/Fig-3]: Effect of vitamin E on prevention of complications at 24 months (primary prevention)

Variables	Control(n=45) Mean±SD				Test(n=45) Mean±SD			
	0 baseline	12months	18months	24months	0 baseline	12months	18months	24months
FBS (mg%)	106.7±22.49	102.6±11.54	107.1±13.2	112.1±14.2	107.5±14.30	103±14.6	105±11.91	109.3±12.85
PPBS mg%)	183±8.34	183.8±7.6	184.2±8.14	185.5±7.39	183.9±8.31	182.4±7.4	182±6.9	182±5.64*
TC (mg%)	206.4±8.09	206±7.54	207±7.53	208±8.86	206.8±10.07	205.8±9.1	205±8.68	204.5±4.33*
SBP (mmHg)	124.5±8.25	124.2±7.66	125.4±7.99	125.5±6.97	125±9.70	124.5±9.77	124±8.48	123.5±6.54
DBP (mmHg)	84±4.49	85.2±6.83	86±8.13	86.8±7.61	84.8±10.28	85±9.32	84.4±7.01	83.8±6.39*

[Table/Fig-4]: Metabolic profile and blood pressure of type I DM with complications (secondary prevention)

Variables	Control(n=45) Mean±SD				Test(n=45) Mean±SD			
	0 baseline	12months	18months	24months	0 baseline	12months	18months	24months
FBS (mg%)	111.2±7.78	110±5.91	110±5.91	108.5±5.5	111.6±13.58	107.5±12.95	107±12.8	106±17.96
PPBS mg%)	178.7±6.7	180±5.6	183±7.02	184.5±6.56	180.1±8.26	181.8±8.87	182±8.30	181.2±8.14*
TC (mg%)	209.8±9.69	210.7±10	212±±10.68	212.8±10.34	211±13.01	211.8±14.4	209.0±9.98	208±12.04*
SBP (mmHg)	124.6±6.58	125.4±8	126±7.3	126.4±6.21	125.2±6.9	124.3±6.7	123.8±7.35	123.4±7.28
DBP (mmHg)	80.4±5.75	81±5.46	82.3±5.68	82.8±5.58	81.2±7.59	81.8±7.38	80.9±6.89	80±6.70*

[Table/Fig-5]: Metabolic profile and blood pressure of type II DM with complications (secondary prevention)

Complications	Type I DM Control(n=45) No of patients (%)	Type I DM Test(n=45) No of patients (%)	Type II DM Control(n=45) No of patients (%)	Type II DM Test(n=45) No of patients (%)
Cardiovascular complications	16 (50)	9 (28.13)	16 (50)	8 (25) *
Diabetic retinopathy	5(15.63)	10 (31.25)	6 (18.8)	10 (31.25)
Diabetic nephropathy	6 (18.8)	9(28.13)	6 (18.8)	10 (31.25)
Diabetic foot ulcer	4 (12.5)	8 (25)	5 (15.63)	9 (28.13)

[Table/Fig-6]: Effect of vitamin E on controlling the progression of complications at 18 months(secondary prevention)

Complications	Type I DM Control(n=45) No of patients (%)	Type I DM Test(n=45) No of patients (%)	Type II DM Control(n=45) No of patients (%)	Type II DM Test(n=45) No of patients (%)
Cardiovascular complications	21 (65.63)	13(40.63)*	23(71.88)	15(46.88)*
Diabetic retinopathy	6(18.8)	13(40.63)*	7(21.88)	15(46.88)*
Diabetic nephropathy	8 (25)	13(40.63)	7(21.88)	14 (43.8)
Diabetic foot ulcer	6 (18.8)	13(40.63)*	7(21.88)	16 (50) *

[Table/Fig-7]: Effect of vitamin E on controlling the progression of complications at 24 months(secondary prevention)

- The number of patients who developed cardiovascular complications in the test group (type II) was less than that in the controls. An improvement was seen in more patients in both the test groups as compared to that in the controls in other complications [Table/Fig-6].
- A significantly less number of patients had cardiovascular complications in the test group (both type I and II) as compared to that in the controls. More number of patients in the test groups showed improvement in the other complications as compared to that in the controls [Table/Fig-7].

DISCUSSION

In the present study [Table/Fig-1,2,4 & 5], the fasting blood sugar levels were found to be increased in both the test and the control group of the type I patients over 24 months (105 ±12.32 mg/dl and 107 ±11.12 mg/dl respectively). But this was not statistically significant. In the type II DM, there was a gradual decline in the FBS levels over 24 months, which was statistically insignificant.

The PPBS levels were decreased in the vit E supplemented patients of the type I DM patients over 24 months (181 ±12.84mg/dl after 12 months, 179 ±24.50 mg/dl after 18 months and 178 ±14.736 mg/dl after 24 months) and also in the type II DM patients (181±9.45 mg/dl after 12 months,180 ±7.556mg/dl after 18 months and 178.2±7.58mg/dl after 24 months). This decline was statistically significant only at the end of 24 months.

The Total Cholesterol (TC) in the controls increased gradually over 24 months in the type II diabetics (210±7.689mg/dl).The type I vitamin E supplemented patients of the primary prevention group had a decrease in the TC at the end of 24 months (195.2±16.577 mg/dl).When this was compared with that of the control group, it was found to be significant. Similarly, the type II vit E treated patients showed a statistically significant change in the TC levels at the end of 24 months (204±11.184mg/dl).This was in accordance with the findings of the studies which were done by Kuznetsov NS et al., [8] and Raheja BS [9].

The systolic BP in the control group showed a slight rise towards the end of 24 months (124±8.124mmHg) in type II DM. In the test group, there was a gradual decrease in the SBP over 24 months (121.5±8.545mmHg). However, it was insignificant.

The DBP in the test group declined after 24 months (82.4±8.15 in type I and 80.9±6.67 mmHg in type II), which was statistically significant. The findings of our study were in accordance with those of the studies which were done by Jain S et al., [10].

The improvement in all the biochemical parameters and the BP, which was seen in the test group, can be attributed to the vitamin E supplementation, as both the groups were comparable and as the compliance was uniform. As the variables which were compared were laboratory parameters, an observer bias was not present.

A statistically significant decrease in the PPBS,TTC and the DBP which was observed at the end of 24 months ,implied that a long term vitamin E supplementation was necessary for the beneficial effect to take place.

[Table/Fig-3,6 & 7] show that the vitamin E supplemented diabetics had a lesser incidence (a 25% lower risk) of the cardiovascular complications after 24 months. This suggested that a long term vit E supplementation was beneficial for the cardiovascular complications. This was in accordance with the findings of the Cambridge Heart Antioxidant Study [11] and of Meir JS [12].

The Cambridge Heart Antioxidant Study showed that and tocopherol treatment significantly reduced the risk of cardiovascular death and nonfatal myocardial infarction after 1 year of the treatment [11].

An improvement was observed in the retinopathy in the test group, as well as the number of patients who developed the retinopathy was also less in the test group. This was similar to the findings of a study which was done by Narang APS et al., [13].

Even though some improvement was noticed in the nephropathy in the test group, it was statistically not significant. A significant improvement was noted in the foot ulcers of the test group patients at the end of 24 months, which implied that a long term supplementation of the antioxidants was beneficial.

Jialal et al., [14,15] concluded that the type II diabetic patients who were supplemented with tocopherol had a decrease in both the lipid per oxidation and the free radical production by the circulating monocytes. It also decreased the markers of inflammation, which included the C-reactive protein [16], IL-1 and IL-6 [14,15]. In another study, the tocopherol treatment which was given for four months was found to improve the retinal blood flow and the renal dysfunction in patients with type 1 diabetes, without changing the glycated hemoglobin levels [17].

This explained the beneficial role of vitamin E in delaying the onset as well as the progression of the complications.

CONCLUSION

It can be concluded from the present study, that the vitamin E therapy in DM prevents the development of late complications like retinopathy, foot ulcers and cardiovascular complications after 24 months. A long term antioxidant therapy is beneficial, as it slows down the progression of the complications.

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