

EFFECT OF ALPHA LIPOIC ACID IN TREATMENT OF TYPE 2 DIABETES

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ABSTRACT

Objective: Antioxidant probably can prevent the progression and complications of Type 2 diabetes mellitus (T2DM). Due to effectiveness of alpha lipoic acid (ALA) as an antioxidant, this study was done in T2DM patients to evaluate the effect of ALA on their diabetic status, lipid profile, and oxidative stress (OS) status.

Methods: A total of 35 patients with diabetes were selected randomly who were under insulin treatment mainly and grouped as Group "A." Another age- and sex-matched healthy controls selected grouped as "B." Both groups supplemented with ALA (300 mg/day) for 6 months continuously. All parameters were tested before and after the supplementation.

Results: There was a significant decrease in fasting blood sugar from 161 to 122 mg/dl in Group "A" and from 98 to 90 mg/dl in Group "B." Postprandial blood sugar (PPBS) and glycosylated hemoglobin (HbA1c) levels also significantly decreased from 211 to 158 mg/dl and 8.81% to 7.2%, respectively, in Group "A." PPBS levels significantly decreased from 130 to 124 mg/dl in Group "B," but HbA1c% decreased insignificantly from 5.26% to 5.24% in Group "B." Lipid profile parameters decreased in both groups except triglyceride level, which show insignificant relation in Group "B." OS marker malondialdehyde significantly decreased from 1.967 to 1.592 nm/ml in Group "A" and from 0.613 to 0.472 nm/ml in Group "B." Plasma antioxidant glutathione shows a significant increase in both groups from 2.117 to 2.405 $\mu\text{mol/L}$ in Group "A" and from 2.631 to 2.811 $\mu\text{mol/L}$ in Group "B." Plasma nitric oxide also shows significant increase in both groups from 1.712 to 1.990 $\mu\text{mol/L}$ and from 2.139 to 2.318 $\mu\text{mol/L}$, respectively.

Conclusion: Therefore, ALA is a potent antioxidant and can be used against oxidative injury associate with T2DM.

Keywords: Type 2 diabetes mellitus, Alpha lipoic acid, Oxidative stress markers.

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INTRODUCTION

As a chronic metabolic disorder, diabetes mellitus (DM) characterized by hyperglycemia due to defect in secretion or action of insulin or both, this causes imbalance in carbohydrate and fat metabolism [1]. DM is mainly categorized into Type 1 and Type 2. Type 1 DM (T1DM) is primarily due to autoimmune pancreatic β -cell destruction. Type 2 DM (T2DM) is the frequent form and is due to impaired insulin secretion or insulin resistance [2]. According to the Diabetes Atlas 2011, the incidence of diabetes is increasing and expected to reach from 366 million in 2011 to 552 million by 2030 [3]. Due to diversity of manifestation of disease and its complications, it causes a great human suffering physically, mentally, and even economically, even with the enormous available facilities to control the disorder [4]. In the disease progression, the prolonged exposure to hyperglycemia causes many long-term microvascular or macrovascular complications involving cardiovascular system, excretory system, nervous system causes diabetic cardiomyopathy, diabetic retinopathy, and neuropathy, which are prime cause of disability, morbidity, and premature death in T2DM [5,6].

Oxidative stress (OS) results insulin resistance in T2DM [7]. Hence, number of studies done to know the effect of antioxidant supplementation in T2DM treatment, where some found positive result [8-10], while others found none [11]. Alpha lipoic acid (ALA) a both fat and water soluble antioxidant may help in regenerating other antioxidants and make them active again so often termed as "universal antioxidant." ALA might protect metabolic syndromes such as DM, improving insulin sensitivity and preventing distal sensory-motor diabetic neuropathy [12]. According to Blumenthal study, ALA in their experimental study improved the glycemic condition by acting on the liver [13].

However, there are some inconclusive evidences regarding its action in defending the OS level, improving the conditions of insulin deficiency and improvement of lipid profile level in T2DM patients. They are mostly done on animals [14,15]. As the T2DM incidence is increasing rapidly, the present study was undertaken to explore the effect of ALA supplementation on glycemic indexes, lipid profiles, and OS markers in T2DM patients.

METHODS

This was a prospective study including patients who were attending Endocrinology Department (both indoor and outdoor) and their biomolecular investigations were carried in Physiology Department and Biochemistry Department, IMS and SUM Hospital, Bhubaneswar. The institutional ethical committee approval was obtained.

For this study, 35 patients suffering from T2DM were included in Group "A," who were taking insulin as their main treatment. Moreover, 35 healthy participants were taken as controls, who were matched by age and gender, grouped as Group "B." The study protocol was explained to the patients, and their written consent was obtained. All patients were supplemented by ALA capsules (133 mg), 2 capsules/day for 6 months continuously.

- Inclusion criteria were patients with T2DM with fasting blood sugar (FBS) <250 mg/dl. Moreover, patients taking insulin as their main treatment
- Exclusion criteria: Patients with T2DM whose FBS >250 mg/dl; patients with uncontrolled hypertension (blood pressure >140/90 mmHg in spite of antihypertensive drugs); patients with complications of diabetes including nephropathy, retinopathy, and neuropathy; patients with any history of myocardial infarction or cardiac intervention or clinically active cardiovascular diseases; patients

with known renal or hepatic diseases; and pregnant females, unwillingness to participate, or mental incapacity to take the drugs were excluded from the study.

A pro forma was designed to obtain basic demographic information taking data of weight and height. Their body mass index (BMI) was calculated using Quetelet's index by formula $\text{weight}/\text{height}^2$ and expressed in kg/m^2 . Blood samples collected for estimation of FBS, postprandial blood sugar (PPBS), glycosylated hemoglobin (HbA1c), lipid profile, and OS markers. FBS and PPBS were estimated by glucose oxidase method. HbA1c was calculated by cation exchange high-performance liquid chromatography using D-10-Hemoglobin Testing System (Bio-Rad). Lipid profiles were estimated using semi-autoanalyzer, TRANSASIA, ERBA, and CHEM-5-PLUS. OS markers such as malondialdehyde (MDA), glutathione (GSH), and nitric oxide (NO) were measured using spectrophotometer.

Their baseline data and after 6 months supplementation data were compared among both groups. Statistical analysis was performed using Student's paired t-test using SPSS software 20 version, and $p < 0.05$ was considered statistically significant.

RESULTS

As shown in Table 1, there is non-significant difference in age, weight, and height of patients recruited in both groups, so they are matched by all these factors. We recruited 17 females and 18 males in Group A and 16 females and 19 males in Group B. Data are presented as mean \pm standard deviation from mean.

Table 2 shows sugar levels such as FBS, PPBS, and HbA1c values at the initial stage of experiment. In the diabetic group, i.e., Group A has significantly more levels in comparison to Group B, where normal healthy controls were taken as control. As shown in Table 2, low-density lipoprotein (LDL), very LDL (VLDL), triglyceride (TG), and total cholesterol (TCh) levels were more and high-density lipoprotein (HDL) is less in diabetic group, Group A than healthy group, Group B. OS markers such as plasma GSH and NO levels are less and high MDA level in Group A in comparison to Group B.

Effects of administration of ALA on different parameters are shown in Table 3. It shows non-significant change of weight and BMI of both

groups due to ALA effect. Sugar levels such as FBS and PPBS show a significant decrease after ALA supplement. HbA1c values show a significant decrease in Group A but non-significant decrease in Group B after ALA supplementation. Lipid profiles show a significant decrease in both groups due to ALA. OS shows significant decrease as shown by their markers in both groups due to ALA.

DISCUSSION

As shown in Table 1, all patients were matched by age and gender; also by their height, weight, and BMI. The basal values of sugar levels show higher values in Group A, who were diabetics. Due to worsening of hyperglycemia condition overtime, progressive decrease in beta-cell function occurs [16]. This demands added medications such as insulin and other oral hypoglycemic drugs to control this blood sugar level [17]. However, as there is multifactorial pathogenesis to develop different complications in T2DM, monotherapy appears insufficient to deal with T2DM [18,19].

ALA has antioxidant properties, can enhance glucose uptake in T2DM, and also can prevent β -cell destruction in T1DM [20-24]. Results from this study indicate that oral ALA supplementation caused significant reduction in plasma FBS and PPBS levels in both groups. HbA1c level was significantly decreased in Group A, whereas a non-significant lowering of HbA1c level was seen in Group B. These data are in agreement with studies of Mazzone *et al.*, 1984 [25]; Packer *et al.*, 2001 [26]; Maritim *et al.*, 2003 [27]; and Kandeil *et al.*, 2011 [28]. Glucose uptake is increased due to ALA as it increases glucose transporter translocation to cell membranes [29,30]. According to Sasvari and Nyakas, 2003 [31] and Bitar *et al.*, 2004 [32], ALA activates the pathway of insulin signaling, causes phosphorylation of insulin receptors, and on myocytes and adipocytes, it exerts insulin-like actions [28,33].

Lipid profile levels show increased LDL, VLDL, TGs, and TCh levels in diabetic group, Group A in comparison to Group B. These results supported by other studies such as Monnier *et al.*, 1995 [34]; Abdel-Azim *et al.*, 2002 [35]; Mazzone *et al.*, 1984 [25]; Sheela and Augusti, 1992 [36]; and Sobenin *et al.*, 1994 [37] studies. The abnormally high concentration of serum lipid profiles in T2DM is mainly a result of increased mobilization of free fatty acids from peripheral depots as insulin inhibits hormone-sensitive lipase, while glucagon and catecholamine enhance lipolysis [38,39].

Table 3 shows a significant lowering of LDL, VLDL, TG, and TCh levels and significant increase in HDL, the good cholesterol level after ALA treatment. These findings are in accordance with Kocak *et al.*, 2000 [40]; Song *et al.*, 2005 [41]; and Lee *et al.*, 2005 [42]. Researchers reveal that ALA activates catabolism of cholesterol into simpler components for the eventual synthesis of steroid hormones [43].

As shown in Table 2, OS markers such as GSH and NO levels, which combat the OS, are at lower level in Group A than Group B. Similarly, MDA a product of lipid peroxidation is significantly more in Group A than Group B. In patients with diabetes, there is increased production of AGEs [28] and due to overgeneration of reactive oxygen species (ROS), causing an imbalance and produces OS [44]. GSH is a tripeptide present in all cells in micromolar concentrations has great antioxidative property [45,46]. Low levels of GSH in T2DM patients in our study are in accordance with findings of other studies [47-51].

β -oxidation of fatty acids initiated by increased activity of enzyme fatty acyl coenzyme A oxidase due to hypoinsulinemia results lipid peroxidation [52]. The products of lipid peroxidation such as MDA are harmful to most of body cells and are associated different disease conditions such as brain damage, micro- and macrovascular complications [53].

ALA has amphiphilic nature and reduces ROS in cell membrane as well as at their mitochondrial source level [53-56]. Inside cells and tissues, ALA is reduced to dihydrolipoic acid that is even more potent antioxidant.

Table 1: Demographic data of both groups

Parameters	Group A (n=35)	Group B (n=35)
Age (years)	51.08 \pm 13.085	48.60 \pm 12.23
Weight (kg)	60.914 \pm 9.546	62.400 \pm 6.869
Height (cm)	158.685 \pm 6.430	159.514 \pm 6.045
BMI (kg/m^2)	24.046 \pm 2.263	24.505 \pm 2.111

Table 2: Baseline sugar levels, lipid profile levels of both groups

Parameters	Group A (n=35)	Group B (n=35)
FBS (mg/dl)	161.31 \pm 15.94*	98.05 \pm 12.59*
PPBS (mg/dl)	211.37 \pm 22.30*	130.02 \pm 12.87*
HbA1c (%)	8.81 \pm 1.07*	5.26 \pm 0.42*
TCh (mg/dl)	223.34 \pm 25.77*	147.22 \pm 14.*83
TG (mg/dl)	175.57 \pm 29.83*	128.22 \pm 20.48*
HDL (mg/dl)	36.60 \pm 4.50*	39.34 \pm 3.21*
LDL (mg/dl)	161.85 \pm 19.60*	107.17 \pm 10.9*9
VLDL (mg/dl)	36.88 \pm 6.77*	28.80 \pm 4.22*
MDA (nm/ml)	1.967 \pm 0.581*	0.613 \pm 0.368*
GSH ($\mu\text{mol}/\text{L}$)	2.117 \pm 0.749*	2.631 \pm 0.495*
NO ($\mu\text{mol}/\text{L}$)	1.712 \pm 0.427*	2.139 \pm 0.536*

* $p < 0.05$: Significant. FBS: Fasting blood sugar, PPBS: Postprandial blood sugar, HbA1c: Glycosylated hemoglobin, TCh: Total cholesterol, TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, MDA: Malondialdehyde, GSH: Glutathione, NO: Nitric oxide

Table 3: Comparative analysis of changes in parameters before and after the supplementation of ALA in both groups

Parameters	Groups (n=35)	Basal values	Values after supplement
Weight (kg)	Group A	60.914±9.546	61.085±9.262
	Group B	62.400±6.869	62.428±6.431
BMI (kg/mt ²)	Group A	24.046±6.869	24.122±2.190
	Group B	24.505±2.111	24.515±1.858
FBS (mg/dl)	Group A	161.314±15.940*	122.428±16.705*
	Group B	98.057±12.597*	90.657±10.389*
PPBS (mg/dl)	Group A	211.371±22.305*	158.571±21.003*
	Group B	130.028±12.871*	124.200±9.103*
HbA1c (%)	Group A	8.817±1.073*	7.200±0.737*
	Group B	5.262±0.422	5.242±0.398
LDL (mg/dl)	Group A	152.685±25.986*	128.725±24.566*
	Group B	82.240±14.506*	73.337±16.700*
HDL (mg/dl)	Group A	36.600±4.506*	39.628±4.366*
	Group B	39.342±3.217*	42.000±2.754*
VLDL (mg/dl)	Group A	35.114±5.967*	32.617±5.577*
	Group B	25.645±4.097	24.948±3.485
TG (mg/dl)	Group A	175.571±29.836*	162.342±27.355*
	Group B	128.228±20.488	124.742±17.426
TCh (mg/dl)	Group A	223.342±25.772*	200.971±24.266*
	Group B	147.228±14.830*	140.285±16.851*
MDA (nm/ml)	Group A	1.967±0.581*	1.592±0.562*
	Group B	0.613±0.368*	0.472±0.315*
GSH (µmol/L)	Group A	2.117±0.749*	2.405±0.714*
	Group B	2.631±0.495*	2.811±0.491*
NO (µmol/L)	Group A	1.712±0.427*	1.990±0.426*
	Group B	2.139±0.536*	2.318±0.522*

*p<0.05: Significant. FBS: Fasting blood sugar, PPBS: Postprandial blood sugar, HbA1c: Glycosylated hemoglobin, TCh: Total cholesterol, TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, MDA: Malondialdehyde, GSH: Glutathione, NO: Nitric oxide, BMI: Body mass index, ALA: Alpha lipoic acid

Our results show after ALA supplementation OS levels were reduced, which support other studies [57-60].

CONCLUSION

Results obtained in our study indicate that the ALA can be used as an antioxidant in T2DM treatment along with the antidiabetic therapy to reduce different consequences as a result DM itself. ALA may be used to manage OS and dyslipidemic conditions developed due to hyperglycemic conditions in DM.

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