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THE EFFECT OF SHORT TERM ALPHA LIPOIC ACID ADMINISTRATION ON ADIPONECTIN AND BODY WEIGHT IN TYPE 2 DIABETES MELLITUS PATIENTS

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Abstract

Background. Alpha lipoic acid (ALA) acts as essential co-factor for mitochondrion respiratory enzymes. It has an increasing importance in diabetic neuropathy treatment. Its positive effects on weight gain and metabolic parameters have also been discussed. In this study, we aimed to search for the effect of ALA on weight, appetite, adiponectin and metabolic parameters in type 2 diabetes mellitus patients.

Methods. This study is designed as a randomised, double-blind, placebo controlled, prospective study. 23 type 2 diabetes mellitus patients with peripheral neuropathy (6 normal weight, 17 obese) and 21 normal weight control group were included in the study. Patients were given 600mg/day oral ALA for 6 weeks, added to their routine therapy. Body mass index (BMI), adiponectin, fasting plasma glucose, HbA1C, lipid parameters and CRP levels were tested before and after ALA treatment. Results were evaluated using SPSS 15.0 for Windows.

Results. Adiponectin levels were statistically significantly lower and CRP levels were higher in diabetes group when compared to control group. Although ALA treatment caused a slight weight loss, it was not statistically significant. Appetite scores were decreased in the diabetes group but it did not cause statistically significant weight loss. There was no significant change in metabolic parameters or adiponectin after the treatment.

Conclusions. 600mg/dL ALA treatment for 6 weeks did not favor for metabolic parameters in type 2 diabetes patients. This result might be due to the dose or the duration of the treatment, genetic predisposition or dietery habits. Trial of higher doses for long terms might be needed for recovery.

Key words: alpha lipoic acid, adiponectin, type 2 diabetes mellitus.

INTRODUCTION

Type 2 diabetes mellitus (DM) is a disease including metabolic abnormalities like glucose and lipid profile abnormalities, insulin resistance and obesity. These metabolic abnormalities are well-known risk factors for micro and macrovascular complications. Alpha -lipoic acid (ALA) is a natural substance that exists in some food and is synthesized in the body. It exists in large amounts in plant and animal tissues that have dense mitochondrial complexes. It is a cofactor in mitochondrial dehydrogenases reactions and an important anti-oxidant. There are recent studies about its usage to prevent the micro and macrovascular damage caused by free oxygen radicals. It is used in diabetic neuropathy (1), atherosclerosis (2) and hypertriglyceridemia (3) because of its anti-oxidant activity. A LA supplementation in DM is shown to favour for hyperglycaemia and dyslipidaemia (4) and weight loss by reduced hunger and increased energy expenditure due to hypothalamic AMPK activity decrease (5). It is renoprotective and improves glycaemia in diabetic rats (6). Oral administration is shown to improve insulin sensitivity in type 2 DM (7).

Abnormal adipokine excretion in DM contributes to insulin resistance, obesity and other metabolic disturbances. Adiponectin which is secreted from subcutaneous and visceral fat tissue is the most important adipokine in metabolic arrangement. It has lipid lowering, anti-inflammatory and insulin sensitizer effect (3). Its amount in circulation decreases with weight gain and increases with weight loss (8). Its concentration is higher in hunger and decreases in satiety (9). Adiponectin is shown to increase at early stages of obesity while small adipocytes are active, and decrease in long-term obesity and type 2 DM when adipocytes become hypertrophic (10). Among insulin sensitizer drugs, glitazones increase adiponectin levels whereas metformin has no effect on it. Adiponectin directly causes weight loss by increasing thermogenesis more than decreasing appetite or food intake (11-14). There is a relationship between hypoadiponectinemia and type 2 DM development (15). Adiponectin increases insulin

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sensitivity, and also decreases non-esterified fatty acid excretion, increases fatty acid oxidation and decreases glucose production by inhibiting gluconeogenesis in the liver (16, 17).

We designed this study to investigate the effect of ALA on neuropathy symptoms, weight management, adipokine levels and metabolic parameters in type 2 DM patients when given at routine doses and for a short treatment period.

PATIENTS AND METHODS

Twenty-three type 2 DM patients (20 female, 3 male) who were diagnosed with diabetic neuropathy (DN) using electromyography (EMG) and who still had neuropathy symptoms (pain, loss of sensation, paresthesia) and 21 healthy people (20 female, 1 male) as control group were randomly selected from outpatient clinic and included in our study. Patients with accompanying diseases other than DM and using drugs related to these diseases were excluded from the study.

Thirteen of the DM patients were on oral anti-diabetic drug (OAD) (metformin, sulfonilurea, glitazone combined or solo), 4 were on insulin, 6 were on OAD+insulin. No drug or dietary changes were advised. All patients' weight (kg) and height (cm) were measured and body mass index (BMI) (kg/m^2) was calculated at the beginning. Blood samples from antecubital vein at sitting position, after 10-hour-fasting, were obtained from all patients and fasting plasma glucose, HbA1C, LDL-chol (low density lipoprotein cholesterol), HDL-chol (high density lipoprotein cholesterol), triglyceride (TG), sCRP (sensitive C-reactive protein) and adiponectin levels were measured. 600mg/d oral ALA 30 minutes prior to meals were started to all patients. After 6 weeks of treatment, all measurements were repeated.

Statistical method

Statistical analysis was performed using SPSS 15.0 for Windows program. Descriptive statistics were reported as number and percentage for categorical variables and as mean and standard deviation for numerical variables. When the numerical variables were distributed normally, in comparison with more than 2 independent groups one-way Anova, if those groups were not distributed normally, Kruskal-Wallis tests were performed. In non-parametric tests, subgroup analyses were performed with Mann Whitney U test and commented with Bonferroni correction. The ratios of categorical variables between groups were tested with chi square test. When parametric test criteria could not be achieved, the associations of numerical variables were investigated with Spearman correlation analysis. The discriminating factors were tested with linear regression analysis. The statistical alpha significance level was regarded as $p<0.05$.

RESULTS

Clinical and laboratory features of patients are summarized in Table 1.

Table 1. Clinical and laboratory features of groups

	Patient		Control	
	n	%	n	%
Gender Female	20	87.0	20	95.5
Male	3	13.0	1	4.5
BMI Normal weight	6	26.1		
Overweight	7	30.4		
Obese	9	39.1		
Morbidly obese	1	4.3		
	Mean±STD	Median	Mean±STD	Median
Age (year)	56.1±6.6	56	36.3±7.5	35
Glucose (mg/dL)	154.5±55.2	133	85.9±10.1	84
HBA1c (%)	7.5±1.5	6.95	5.5±0.6	5.5
T-chol (mg/dL)	222.4±59.3	217	176.6±29.9	178
Triglyceride (mg/dL)	192.6±146.9	142	86.6±45.9	82
HDL-chol (mg/dL)	46.2±12.5	45	54.3±13.1	55
LDL-chol (mg/dL)	142.9±48.4	138.8	105.0±27.4	103.2
CRP (mg/L)	7.6±9.8	5.5	4.3±10.4	0.8
Insulin(u/dL)	9.2±4.4	9.8	5.4±2.6	4.8
Adiponectin (ng/mL)	9.3±2.7	9.6	11.6±3.4	12.0

(BMI: Body mass index, CRP: C reactive protein, chol: cholesterol).

As a result of random inclusion of patients, who were seen in out-patient clinic, consecutively to the study, the majority of patients were female as a coincidence and results referred particularly to women.

Eighteen patients (78%) of 23 DN patients declared different degrees of regression for their DN symptoms (pain, loss of sensation, paresthesia).

Mean age and biochemical parameters other than HDL were statistically significantly higher and mean HDL level was lower, in patient group than in control group. There was statistically significant difference only for mean glucose, total cholesterol and LDL cholesterol levels in different BMI groups in patient group (p=0.043 p=0.035 p=0.022). Glucose level was significantly lower in obese group than overweight group (p=0.017). Total cholesterol in obese group and LDL in obese and overweight group was statistically significantly higher when compared to normal group (p=0.017 p=0.048 p=0.036 p=0.033).

There was no significant change in laboratory parameters of patient group after 6 weeks when compared to beginning values (Table 3).

There was no correlation in percentage changes in measured laboratory parameters (Table 4).

Table 2. Demographic features and P values of groups according to BMI

	Normal weight		Overweight		Obese – Morbidly obese	
	Mean±STD	Median	Mean±STD	Median	Mean±STD	Median
Age (year)	58.0±6.1	57.5	54.0±6.6	56	56.5±7.1	56.5
Glucose (mg/dL)	162.8±42.0	163.5	180.3±63.7	139	131.4±51.2	113.5
HBA1c	7.4±1.2	7.45	7.9±1.8	7.5	7.2±1.6	6.2
T-chol (mg/dL)	170.3±40.9	168	242.6±42.7	243	239.5±63.2	225.5
Triglyceride (mg/dL)	133.5±48.8	127	233.3±150.6	08	199.6±180.7	129
HDL-chol (mg/dL)	45.5±18.7	41.5	43.0±8.7	39	48.9±11.0	50.5
LDL-chol (mg/dL)	98.1±28.7	98.9	161.1±44.1	165.8	157.2±46.5	158
CRP (mg/L)	5.5±3.1	5.95	11.4±17.0	6.1	6.1±4.6	4.66
Insulin(u/dL)	10.3±6.8	7.6	9.5±3.2	10.29	8.4±3.5	8.6
Adiponectin (ng/mL)	10.9±1.0	10.81	9.9±2.4	11.0	8.0±3.2	7.8

(BMI: Body mass index, CRP: C reactive protein, chol: cholesterol, STD: standard deviation).

Subgroup analysis

		T-chol(mg/dL)	LDL-chol(mg/dL)	Glucose(mg/dL)
		p	p	
Normal weight	overweight	0.056	0.036	0.668
	obese	0.048	0.033	0.103
Overweight	obese	0.992	0.981	0.017

(chol: cholesterol).

Table 3. Comparison of parameters of diabetic patients before and after ALA treatment

		N	Mean±STD	p
Glucose (mg/dL)	B	23	154.5±55.2	0.101
	A		137.0±30.8	
HbA1c	B	18	7.5±1.6	0.824
	A		7.6±1.5	
T-chol(mg/dL)	B	20	218.5±62.5	0.658
	A		210.2±47.1	
Triglyceride (mg/dL)	B	16	216.0±170.7	0.301
	A		180.4±66.0	
HDL-chol (mg/dL)	B	22	46.7±12.5	0.273
	A		44.3±10.0	
LDL-chol (mg/dL)	B	23	143.0±48.4	0.102
	A		132.4±38.7	
CRP (mg/L)	B	23	7.6±9.8	0.784
	A		7.9±7.7	
Insulin (u/dL)	B	22	9.0±4.3	0.072
	A		15.0±18.0	
Adiponectin (ng/mL)	B	21	9.3±2.9	0.569
	A		9.7±2.7	

(Before: B After: A) (ALA: Alpha lipoic acid CRP: C reactive protein, chol: cholesterol STD: standard deviation).

DISCUSSION

There are a limited number of studies about usage of ALA as a therapeutic agent in DNP symptoms in type 2 DM and the results are conflicting. Our study showed that in type 2 DM, administration of 600 mg/day of ALA treatment for a short period of time as 6 weeks did not favor for body weight, adiponectin, lipid, fasting blood glucose or insulin levels. But adiponectin level was significantly lower in type 2 DM patients compared to control group (p=0.019) (18-20).

Experimental studies showed that ALA had hypolipidemic effect and also favoured for weight loss and glucose homeostasis, but human studies did not always correlate with these findings and the favouring effect was found to be dose related (21-23).

In a study done by Koh *et al.* in obese type 2 diabetic patients, treatment of 1200 mg/d and 1800 mg/d ALA for 20 weeks was found to be non-effective on fasting blood glucose, HbA1c, cholesterol and triglyceride levels. In 1200mg/d group, there was no significant body weight change compared to placebo, but a slight decrease in 1800mg/d group. It has been reported that ALA can only be used as anti-obesity drug at high doses (24).

In another study, non-diabetic, PCOS and normal weight patients were given 600 mgx2/d ALA for 6 weeks and a decrease in triglyceride levels and increase in insulin sensitivity was found. But there was no significant change in LDL-chol, HDL-chol, CRP or oxidative stress factors (25).

Okanovic *et al.* found positive effect of 600mg/d ALA use for 20 weeks on weight loss and triglyceride levels, but no effect on cholesterol or fasting blood glucose (18). Different doses of ALA (300, 600, 900, 1200mg/d) were used in type 2 DM patients for 6 months in a study and there was a dose-dependent decrease in HbA1c and fasting blood glucose but there was no favor for lipids (19). Timmers *et al.* conducted a similar study on rats and showed that after LA supplementation, there was no significant change in fasting blood glucose, but a decrease in insulin levels and they related this result to ALA's anorectic effect which led to weight loss (20).

Maximum tolerable of ALA dose is not specified in literature but the usual dose is accepted as 600mg /d and, at this dosage, the side effects are kept at minimum and studies support this finding. We used the same dosage in our study but there was no significant weight loss. This could be related to a short period of treatment time, genetic predisposition or dietary habits.

Different results were also obtained from experimental studies. Yi and Maeda showed that plasma cholesterol level was decreased in streptozotocin-induced diabetic rats after addition of 1.65gr/kg ALA to diet for 20 weeks. Weight loss and improvement in glucose metabolism due to slight beta-cell recovery accompanied these findings (21). Thiranavukkarasu *et al.* showed that intraperitoneal 35mg/kg/d and 70mg/kg/d ALA decreased serum cholesterol and TG levels (22). Ford *et al.* showed that 300mg/kg/d ALA decreased TG level in streptozotocin-induced diabetic rats (23). Despite all the data from these studies, the mechanism of lipid lowering effect of ALA is still unclear.

Alpha lipoic acid lowers fatty acid synthase and SREBP-1c (Sterol regulatory element-binding

Table 4. Correlation coefficients (rho) between parameters and P values (p) after ALA treatment

Difference%		Glucose	HbA1c	T.chol	TG	HDL	LDL	CRP	Insulin
HbA1c	rho	0.428							
	p	0.076							
T. chol	rho	0.332	-0.088						
	p	0.152	0.745						
TG	rho	0.115	-0.165	0.512					
	p	0.672	0.573	0.043					
HDL	rho	0.374	0.321	0.484	-0.147				
	p	0.086	0.209	0.036	0.587				
LDL	rho	0.330	-0.154	0.877	0.418	0.436			
	p	0.124	0.542	<0.001	0.107	0.042			
CRP	rho	0.234	0.267	-0.161	0.271	-0.220	-0.063		
	p	0.282	0.284	0.498	0.311	0.326	0.774		
Insulin	rho	-0.154	-0.397	0.265	0.082	0.277	0.012	0.119	
	p	0.493	0.115	0.273	0.771	0.225	0.958	0.597	
Adiponectin	rho	0.077	-0.194	-0.092	0.104	0.126	0.153	0.397	0.014
	p	0.741	0.471	0.717	0.713	0.586	0.507	0.074	0.955

proteins) mRNA level, regulates lipogenic enzyme genes and these might have a part in hypolipidemic effect (26, 27). It also inhibits hypothalamic AMPK (adenosine monophosphate-activated protein kinase) activity and induces FFA(free fatty acid) oxidation resulting in decrease in lipid accumulation and weight loss. ALA also increases glucose transport and fatty acid beta oxidation in muscle tissue by AMPK activation (28). But those mechanisms cannot be defined as specific lipid lowering effects of ALA.

The pathogenesis of type 2 DM is accepted as impaired insulin secretion or insulin resistance in peripheral tissues. One of the ways to improve DM is glucose transport into cells via glucose transporters in peripheral tissues. Metformin is a GLUT-4(Glucose transporter type 4) protein enhancing agent. ALA is also reported to activate GLUT-4 in the muscle and fat tissue (29, 30). In studies, the additive effect of metformin for glucose homeostasis should also be considered (19, 25). In our study, there were no dietary or treatment changes, so this effect was not excluded.

Although oral bioavailability of ALA is high, parenteral short term studies did also show positive results. Zhang *et al.* found improvement in insulin sensitivity, lipid and adiponectin levels in obese patients with 600mg/d PE ALA for 2 weeks (31). Similarly, Kamenova *et al.* showed insulin sensitivity improvement with oral administration of ALA, but no improvement in body weight or lipid levels (32). The improvement in glucose and insulin levels is considered to be related to weight loss and positive effect on hypothalamic AMPK (32).

Adiponectin is an insulin sensitizing adipokine (33). Insulin sensitizer agents (e.g. pioglitazone, metformin and omega-3 fatty acids) increase adiponectin levels (34, 35). Adiponectin secretion is related to weight gain and visceral fat tissue. In obesity, its circulating amount is decreased whereas it is increased when weight loss is achieved (36). Adiponectin directly causes weight loss by enhancing thermogenesis (12). In our study, similarly, we found a significant decrease in adiponectin levels in DM patients compared to control group. CRP levels were also significantly high in DM group.

There are conflicting results in literature about ALA supplementation, adiponectin levels and weight loss. Cheng *et al.* showed suppression in adiponectin increase in ovariectomized rats after 7 weeks of 200mg/kg ALA treatment, but there was a decrease in appetite and amount of fat tissue which was thought to be a result of AMPK activation (37).

Cummings *et al.* reported that 80mg/kg/d ALA had no effect on adiponectin level or weight loss in type 2 DM rats on fructose diet (38). On the contrary, Hontoria *et al.* reported a weight loss in obese rats with addition of ALA to their diet, adiponectin gene expression was upregulated in white adipose tissue and there was an increase in adiponectin levels (39). Houng and Ide (27) showed increase in adiponectin levels in rats with addition of 1-5g/kg ALA to their diets for 21 days. In our study, in type 2 DM patients, 600mg/day ALA addition to treatment caused appetite loss tendency but there was no significant weight loss after 6 weeks. Adiponectin is an adipokine related directly to visceral fat tissue and lack of significant changes of its level could be related to lack of weight loss. This result in adiponectin levels did not differ for the obese or the normal weight. The conflicting results of different studies show that further clinical investigation is needed.

In conclusion, ALA has an important place in DNP treatment but more long term studies with higher doses of ALA are needed to show its positive effect on blood glucose and lipid levels and basal metabolism. Also, additive effect of the oral agents used in DM treatment, dietary habits and genetic predisposition should be considered as contributors to metabolic improvement seen in those patients.

Conflict of interest

The authors declare that they have no conflict of interest.

Key messages

ALA is an important agent of DNP.

Long term studies are needed to prove that usage of ALA at high doses, for longer periods might have positive impact on blood glucose and lipid levels and basal metabolism. Adiponectin is still a key component of obesity and metabolic state.

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