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Diyabetik Polinöropatili Hastalarda Alfa Lipoik Asidin Glisemik Kontrol Üzerine Etkisi

The Effect of Alpha Lipoic Acid on Glycemic Control in Patients with Diabetic Polyneuropathy

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Öz

GİRİŞ ve AMAÇ: Mitokondriyal dehidrojenaz enzimlerindeki kompleksler için doğal bir kofaktör olan alfa-lipoik asidin (ALA), diyabetik periferik nöropati (DPN) semptomlarını iyileştirdiği bildirilmiştir. DPN üzerindeki anti-oksidan etkisinin yanı sıra, mevcut kanıtlar ALA'nın glisemik üzerindeki olumlu etkisini göstermektedir. Biz bu çalışmamızda, DPN hastalarında 600 mg oral ALA'nın glisemik kontrol üzerindeki etkisini değerlendirmeyi amaçladık.

YÖNTEM ve GEREÇLER: Bu çalışmaya 84 diyabetik hasta (55 kadın, 29 erkek) katıldı. Hastalar Nöropati Disabilite Skoru (NDS) ve Nöropati Semptom Skoru (NSS) ile değerlendirilerek DPN varlığına göre iki gruba ayrıldı. 3 ay boyunca DPN grubuna diğer diyabet tedavilerine ek olarak 600 mg/gün ALA başlanırken diyabeti olmayan hastalar mevcut tedavileri ile devam edildi. Tedavi başlangıcı öncesi ve 3 ay sonrası kan glukozu, HbA1c, total kolesterol, trigliserid düzeyleri karşılaştırıldı, NSS ve NDS hesaplandı.

BULGULAR: ALA kullanan DPN grubunda, tedavi öncesi ortalama açlık glikoz seviyeleri 116,65 mg/dl ve 2. kontrolde 116,33 mg/dl (p = 0,837) ve kontrol grubunda 117,55mg/dl ve 119,5mg/dl'dı (p = 0,480). ALA kullanan grupta HbA1c düzeyleri 1. vizitte % 6.16 ve 2. vizitte % 6.26 saptandı (p = 0,283). Kontrol grubunda ise HbA1c seviyeleri başlangıçta% 6,07 ve 2. vizitte % 6,26 idi (p = 0,065).

TARTIŞMA ve SONUÇ: Diyabetik nöropatide oral ALA tedavisinin, açlık plazma glukozu ve Hba1c düzeylerine olumlu etkisi bulunmamaktadır. Klinisyenlerin HbA1c hedeflerine ulaşmak için polifarmasiden kaçınarak randomize klinik çalışmalarla ispatlanmış etkin anti-hiperglisemik ajanları tercih etmesi önerilir.

Anahtar Kelimeler: Alfa lipoik asit, Glisemik kontrol, HbA1c

Abstract

INTRODUCTION: Alpha-lipoic acid (ALA), a natural co-factor for complexes in mitocondrial dehydrogenase enzymes, had reported to improve symptoms of diabetic peripheral neuropathy (DPN). Besides its anti-oxidant effect on DPN, existing evidence suggests the favorable efficacy of ALA on glycemic regulation. We aim to evaluate the effect of 600 mg orally ALA on glycemic control in patients with DPN.

METHODS: 84 diabetic patients (women:55, men:29) participated in this study. The patients were grouped into two according to the presence of DPN evaluated by Neuropathy Disability Score (NDS) and Neuropathy Symptom Score (NSS). DPN diagnosed group received oral 600 mg/daily ALA addition to their diabetes medication whereas non-DPN group preceeded with their current treatment for three months. Blood glucose, HbA1c, total cholesterol, triglycerides levels were compared before and after the treatment. NSS and NDS was performed at the first and second visit.

RESULTS: In ALA treated DPN group, the mean fasting glucose levels before treatment was 116,65 and 116,33 mg/dl end of the treatment(p=0,837) and in the control group 117,55 mg / dl and 119,5, respectively(p=0,480). We also couldn't demonstrate statistical significance in HbA1c levels in ALA treated group as % 6.16 before and %6.26 after treatment(p=0,283). The HbA1c levels were %6,07±0,5 at baseline and second visit %6,26±0,7 in the control(p=0,065) as well.

DISCUSSION AND CONCLUSION: Oral ALA treatment in diabetic neuropathy has no benefical effects on fasting plasma glucose and Hba1c levels. To achieve HbA1c goals, clinicians should focus on approved potent anti-hyperglycemic agents to avoid polypharmacy, over and underprescribing.

Keywords: Alpha lipoic acid, Glycemic control, HbA1c

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is the most common microvascular complication of diabetes with a prevalance of variable results up to 50% according to previous studies (1, 2). DPN is defined as symmetrical, peripheral nerve dysfunction in diabetics characterized by symptoms and signs that reduce quality of life and increase mortality and morbidity (3). Vascular dysfunction, oxidative stress and impaired glucose metabolism are key points in

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development of diabetic neuropathy. Chronic hyperglycemia is the major cause of the metabolic reactions of DPN; impaired glucose control causes over production of reactive oxygen species (ROS), mitocondrial dysfunction, inflamation and increases oxidative stress that plays an important role on the nerve dysfunction (4,5).

Although tight glycemic control by anti-hyperglycemic agents might not delay the progression of DPN. Therefore, various biochemical mechanisms and indirect pathways involving the pathogenesis required further therapies.

Alpha-lipoic acid (ALA), a natural anti-oxidant and co-factor for complexes in mitocondrial dehydrogenase enzymes, had reported to improve symptoms of DPN (6).

In addition to its anti-oxidant effect on DPN, existing evidence suggests the favorable efficacy of ALA on glycemic regulation and insulin sensitivity (7, 8). Although aforementioned studies on antidiabetic and anti-lipidemic effects of ALA, the outcomes of fasting and postprandial glucose levels remain still controversial (9,10). Furthermore, ALA might inhibit the progression of diabetes and preserve beta-cell function (11, 12).

Herein, we aimed to investigate the effect of alpha lipoic acid on glycemic control in DM2 patients with DPN.

METHODS

Study design and duration

This cross-sectional study is conducted at the Department of Fatih Sultan Mehmet Hospital Diabetes Center from May 2014 to November 2014.

Patient Population

The patients with type 2 DM were evaluated according to the individualized HbA1c goals (accompanying diseases and age) and the patients at target HbA1c levels were selected. All patients were older than 18, had a diagnosis of T2DM for ≥one year from the recruitment day, arterial blood pressure lower than 140-90 mmHg, and LDL cholesterol lower than 100 mg / dl. None of the participants received diabetic neuropathy treatment in at least 3 months. All patients were assessed for DPN by using Neuropathy Disability Score and Neuropathy Symptom Score. The patients diagnosed as having cancer, pregnancy or lactation and other causes of neuropathy incluing vitamin B12 deficiency, hypothyroidism, metabolic disorders, neuropathy due to renal failure, vasculitis, chronic alcholism and/or receiving any form of insulin and insulin secretagogues (sulfanilides and meglitinides) were excluded. The participants were divided into two group according to diagnosis of DPN. The study protocol was approved by our local Ethical Committee. Written informed consent was obtained from all participants.

At baseline visit, DPN-diagnosed group, were prescribed 600 mg ALA preparations once a day prior to breakfast time for three months without any change in their current medical treatment. At the second visit, all groups were evaluted for anthropometric, laboratory measurements and neuropathy scores. The non-DPN group were followed as their present medications.

Anthropometric and Laboratory Measurements

All participants were questioned about medical history and related diseases. Two visits were scheduled. At each visit, before physical examination, height and weight were measured, and body mass index (BMI) was calculated. Waist circumference (WC) was measured in the midpoint between iliac crest and lowest rib. Systolic and diastolic blood pressure was measured twice, and mean values were considered.

After a 10-12 h fasting venous blood samples were collected for fasting serum glucose, glycated hemoglobin (HbA1c), lipid profile. Plasma glucose levels were measured using glucose oxidase method. HbA1c were measured using a high-pressure liquid chromatography by Trinity Biotech Premier.

Diabetic Neuropathy Assessment

We used both Neuropathy Disability Score (NDS) and Neuropathy Symptom Score (NSS to assess the patients for DPN. NSS is a questionare using numerical evaluation of muscular weakness, sensory symptoms, pain localization and autonomic symptoms. In each column maximum score can be given only once. A score ≥ 1 is considered as PNP (13).

A well-trained, experienced physician could evaluate muscle weakness, reflex and sensory abnormalities with NDS, NDS consists of cranial nerves, muscle weakness, reflexes and sensorial examination. Total examination score ≥2 is considered as DPN (13).

NSS and NDS was performed at both baseline and second visit in patients with DPN under ALA treatment. All collected data were analysed using SPSS software. P value < 0.05 was considered as statistically significant.

ALA treatment

In DPN group, 600 mg/daily ALA was added to the current diabetes treatment for 3 months whereas non-DPN group were followed up with their actual medication.

RESULTS

A total of 84 diabetic patients (women:55, men:29) were included in this study. Table 1 demonstrates the baseline demographic and anthropometric characteristics in detailed. No significant differences between the groups were observed with respect to age, gender, height, weight, BMI, waist circumference, blood pressure, and pulse.

Table 1*. Charactarestics and parameters of patients in DPN and non-DPN groups*

	DPN group (n:46)	Non-DPN group (n:38)	P
Age (years)	56,2 ±7,3	54,86 ±8,3	0,433
Female/Male	35 /11	24/14	0,197
Height	162,4 ±8,7	162,2 ±9,3	0,938
Weight	82,03 ±12,8	80,9±12,6	0,701
BMI kg/m2	31,1 ±4,7	30,8 ±5,4	0,823
waist circumference(cm)	102,9 ±10,5	102,1 ±12,08	0,775
Systolic BP-sitting mm Hg	130,8±16,8	131,0±15,8	0,963
Systolic-BPstanding mm Hg	131,1±15,1	129,8±13,8	0,687
DiastolicBPsitting mm Hg	80,0±9,3	78,4±7,7	0,429
DiastolicBP-standing mmHg	83,8±9,7	80,8±6,9	0,125
Pulse (per minute)	80,1±7,0	81,9±8,2	0,294
Fasting glucose(mg/dl)	116,6±21,1	117,5±18,3	0,837
HbA1c (%)	6,16± 0,6	6,07±0,5	0,441

In ALA-treated DPN group, the mean fasting glucose levels before treatment were 116,65 (± 21) and 116,33 mg/dl(p=0,837) end of the treatment; whereas in the control group 117,5 and 119,5 mg/dl (p= 0,480) respectively. A non-significant increase was observed in HbA1c in Group ALA treated group (% 6.16 before and %6.26 after treatment, p=0,283), as demonstrated in table 2.

Similarly, in non- DPN group HbA1c showed a non significant statistical increase in HbA1c as 6,07±0,5 at baseline and 6,26±0,7 at the end (p= 0,065), in table 3. The effect of ALA on lipid profile showed no significant changes in triglycerides levels (p= 0,173). Total cholesterol, LDL-cholesterol and HDL-cholesterol levels did not improve after ALA treatment.

The changes in neuropathy clinical scores using NSS in before and after treatment ALA treated group resulted in similar scores 1,50 ±0,63 and 1,58±0,54; p= 0,632, respectively. No significant difference was found with respect to reflexes,

motor and sensorial examination regarding NDS (p=0.543).

Table 2. *Changes in characteristics before and after 600 mg ALA treatment daily in DPN-group*

Parameters	DPN group (n:46)		P
	Baseline	End of 3 months	
Fasting glucose(mg/dl)	116,6±21,1	116,33±19,2	0,837
HbAc (%)	6,16± 0,55	6,26±0,58	0,283
BUN(mg/dl)	14,51±5,45	13,24±3,68	0,149
Creatine(mg/dl)	0,77±5,12	0,79±0,12	0,479
Total cholesterol, mg/dl	202,43±31,45	207,92±38,21	0,916
Triglycerides, mg/dl	173,36±81,69	171,82±81,45	0,073
HDL-cholesterol, mg/dl	44,69±11,16	44,72±10,18	0,218
LDL-cholesterol, mg/dl	123,40±27,38	128,39±30,88	0,981
NSS	1,50 ±0,63	1,58±0,54	0,632
NDS	2,62±0,62	2,25±0,45	0,543

Table 3*. Changes in characteristics baseline and end of 3 months in non-DPN group.*

Parameters	Non-DPN group(n:38)		P
	Baseline	End of 3 months	
Fasting glucose(mg/dl)	117,5±18,3	119,5±20,6	0,480
HbAc (%)	6,07±0,5	6,26±0,7	0,065
BUN(mg/dl)	12,86±2,87	13,78±4,70	0,643
Creatine(mg/dl)	0,75±0,12	0,79±0,12	0,937
Total cholesterol, mg/dl	201,67±32,74	202,37±34,87	0,509
Triglycerides, mg/dl	144,72±52,58	142,54±53,95	0,268
HDL-cholesterol, mg/dl	52,38±8,79	45,94± 8,95	0,079
LDL-cholesterol, mg/dl	123,25±29,51	126,90±28,14	0,826

DISCUSSION

The aim of this study was to evalute the effects of oral ALA on glycemic regulation in patients with diabetic neuropathy. Oral ALA treatment didn't cause any significant difference in glucose and HbA1c levels. Furthermore, no significant improvement in NDS and NSS was observed at baseline and final visit in ALA-treated neuropathy group. No beneficial respond to ALA was noted on lipid parameters. Given these outcomes, this study presented herein that oral ALA treatment resulted no benefical effect on fasting plasma glucose, HbA1c levels and lipid parameters.

Diabetic peripheral neuropathy is one of the most common chronic complications associated with prolonged diabetes, and together with increasing the incidence of diabetes. Apart from the treatment strategies focusing on prevention, and reversal of DPN especially by strict glycemic control; there are a limited number of drugs that target pathogenesis, such as ALA. ALA could also provide additional benefit in most patients as pathogenesis-targeted treatment (14).

Evidence to date, have suggested that ALA has a hypoglycemic action and actives the AMPK complex in hypotalamus and peripheral tissues. Activation of AMPK stimulates glucose uptake because of increase of the glucose transporter-4 (GLUT 4) in plasma and muscles. Furthermore, this transportation impresses, similar to insülin, by increasing glucose uptake, and improves glucose levels (15,16). Lee et al. defined the insulin-stimulated glucose uptake associated with the improvement of insulin sensitivity and secondary to activation of AMPK (17).

Porasuphatana et al. documented a reduction on dose dependant manner in fasting glucose and HbA1c levels in a randomized trial with ALA at four different doses (300, 600, 900 and 1200 mg / day) versus placebo over a period of six months (18). Morakinyo et al. diabetic rats reported lower glucose levels but no significant effect on insulin in ALA-treated, streptozotocin-induced diabetic rats (19). They also underlined a reduction in LDL-cholesterol, TG and an increase in HDL.

Similar to these trials, Ansaar et al. showed a reduction in fasting plasma glucose levels with oral ALA 300 mg twice daily (10).

Although these findings suggest the glucose lowering effect of ALA, particularly on fasting glucose, other studies held opposite views. Agathos et all. examined the effect of ALA on painful diabetic neuropathy 600 mg/daily and

found no difference in fasting plasma glucose, total cholesterol, LDL-C, high-density lipoprotein cholesterol, HbA1c, BMI, arterial blood pressure between baseline and final visit (20). However, there are also trials showing no significant reduction in fasting glucose levels (8, 10).

In our study, there were no significant reduction in fasting blood glucose and Hba1c levels. This result can be attributed to patient's good glycemic control and hba1c levels. Therefore, the duration of the study (12 weeks) and oral formulation of ALA instead of intravenous form might be one of the reasons. It should also be kept in mind that NDS and NSS of the patients participated in the study were at mild degrees and even if ALA is a pathogenesis-based effect, treatment response could be delayed or extened. ALA has shown to have a rapid clearance and no accumulation in the tissues (21). The lack of insulin sensitivity is other limitation of the current study.

In addition to these results, the hypoglycemia related ALA may be due to insulin autoimmune syndrome (IAS) a rare condition attributed to the sulfydryl group of the drug. In individuals especially in Asia with genetic variations were reported to have hypoglycemic episodes linked with oral ALA products (22). IAS is characterized by spontaneous hypoglycemia, excessive serum insulin levels and insulin autoantibodies and resolves with discontinuation of ALA. None of the study group were on insulin and insulin secretogog medication and we did not detected any hypoglicemic event.

CONCLUSION

Our study suggests that oral ALA treatment in diabetic neuropathy has no benefical effects on fasting plasma glucose and Hba1c levels. Management of hyperglycemia in diabetes accompanied by microvascular and macrovascular complications required more medications. Although anti-oxidant ALA is one of the options for the treatment-based pathogenetic mechanisms of diabetic neuropathy, evidence from randomized trails have been limited. Consequently, ALA should be placed out of the glucose lowering treatment to achieve HbA1c goals, and the clinicians should consider the risk of polypharmacy, over and underprescribing and avoid unnecessary medications in the treatment regimen.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Committee Approval:

Ethics committee approval was received for this study from the Ethics Committee of Fatih Sultan Mehmet Education and Research Hospital (13.03.2014 Desicion No: 2014/29)

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