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The Effect of Alpha Lipoic Acid (Thioctacid HR®) on Endothelial Function in Diabetic and Hypertensive Patients

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ABSTRACT

Background and Objectives : α-Lipoic acid (ALA) is known to improve endothelial function in patients with diabetes. However, the effect of ALA on endothelial function in hypertensive patients is unknown. The aim of this study was to investigate whether ALA improves endothelial function in diabetic and hypertensive patients. **Subjects and Methods :** This study included 40 patients who were treated with ALA (Group I: 20 diabetic patients, 54.9±10.2 years, Group II: 20 hypertensive patients, 56.5±9.0 years). ALA was administered in 600 mg/day doses during the first four weeks, and 1,200 mg/day doses during the second four weeks. Clinical characteristics and endothelial function were assessed at baseline, 4 weeks and 8 weeks after ALA administration. Evaluation of patients included: assessment of the brachial artery for flow mediated vasodilation (FMD) and the inflammatory marker (high sensitive CRP: hsCRP). **Results :** Clinical characteristics (body mass index, total cholesterol/HDL-cholesterol and hsCRP) were unchanged in each group. However, FMD was significantly improved at 8 weeks after ALA therapy in both groups. Group I-baseline : 4 weeks : 8 weeks=4.1±3.3 : 6.5±2.2 : 8.0±2.7, Group II-baseline : 4 weeks : 8 weeks=5.5±3.7 : 7.4±3.3 : 9.3±2.7, $p<0.05$. The level of fibrinogen was observed to have an inverse correlation with FMD at 8 weeks after ALA therapy in Group I ($p<0.05$). **Conclusion :** ALA improves endothelial function in both diabetic and hypertensive patients. **(Korean Circulation J 2006; 36:559-564)**

KEY WORDS : Alpha lipoic acid ; Hypertension.

Introduction

There is growing evidence that oxidative stress plays an important role in the development and progression of cardiovascular disease.[1)2)] Moreover oxidative stress has been thought to contribute to the development of complications in both diabetes and hypertension.[3)] Common conditions predisposing to atherosclerosis such as hyperlipidemia, hypertension, diabetes and smoking are closely related to the development of endothelial dysfunction.[4-8)] Endothelial function has been evaluated by endothelium-dependent vasomotion, partially based on the assumption that endothelium-derived nitric oxide (NO) has a pivotal role in anti-inflammatory and antithrombotic activity. A common mechanism underlying endothelial dysfunction has been associated with increased vascular production of reactive oxygen species (ROS), and indirectly associated with inflammation.

Alpha-lipoic acid (ALA) is a thiol antioxidant compound that has direct free- radical scavenging properties, and has been shown to benefit vascular and endothelial function.[9-12)] In many studies, ALA treatment has been shown to improve diabetic-induced endothelial dysfunction, probably due to the antioxidant effect of ALA.[13)14)] However, the effect of ALA treatment in patients with hypertension associated endothelial dysfunction is unknown.

The purpose of this study was to investigate whether ALA can improve endothelial vasomotor function and

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inflammation in hypertensive patients, as it does in diabetic patients.

Subjects and Methods

Subjects

The study population included men and postmenopausal women who had been diagnosed with type 2 diabetes (group I, n=20) and newly diagnosed with hypertension (group II, n=20). Patients who had a prior history of coronary artery disease, significant valvular heart disease, congestive heart failure, severe hepatic or renal disease, malignancy, nutritional deficiency, mood disorder and psychosis, stage III hypertension, and overt proteinuria were excluded. All patients gave their written informed consent to participate, and the protocol was approved by the Chonnam National University Hospital Institutional Review Board.

Experiment protocol

Although discussion continues about the therapeutic dosage, doses of ALA range from 200 to 1,800 mg/day[15]; all subjects were prospectively studied at baseline, and after the first 4-weeks of ALA oral administration (qd thioctacid HR® 600 mg/day, Bukwang, Korea), and after the second 4-weeks oral ALA administration (qd thioctacid HR® 1,200 mg/day, Bukwang, Korea). Patients were educated to fast overnight, to abstain from smoking, alcohol and caffeine and to hold vasoactive medication (angiotensin converting enzyme inhibitor, angiotensin receptor blocker, and other antioxidant) at least 1 week. During the study period, the oral hypoglycemic agent (glibenclamide) was maintained in patients in group I and thiazide was maintained in group II patients. Simvastatin was continued in some patients during the study period as well [group I: 8 (40%), group II: 2 (10%)]. The presence or absence of the following cardiovascular risk factors were assessed in each subject: hypertension (systolic blood pressure >140 mmHg/diastolic blood pressure >90 mmHg), hypercholesterolemia (total serum cholesterol >240 mg/dL), diabetes mellitus (treated with an oral hypoglycemic agent, or having a fasting glucose level >126 mg/dL), family history of coronary artery disease (first- or second-degree relatives with premature cardiovascular disease), and a history of smoking (having smoked >5 cigarettes per day within the last month). The baseline clinical parameters (such as body mass index and waist circumference) and laboratory parameters (such as lipid profiles, highly sensitive C-reactive protein, and microalbuminuria), which represents inflammation were also examined.

Endothelial function test

Brachial artery ultrasound testing, for evaluation of peripheral endothelium function, was performed following a protocol similar to that described by Celermajer at al.[16] Longitudinal brachial artery images were obtained with a high-resolution (10 MHz) linear-array vascular transducer (Phillips, ATL Ultramark HDI 5000®, Netherlands). Subjects were studied during the morning hours, after more than 8 hours fasting, under quiet conditions while they were in the supine position. After a 10 minute resting period, baseline two-dimensional images of the right brachial artery were analyzed approximately 2 cm above the antecubital fossa. A blood pressure cuff placed proximal to the imaging transducer on the upper arm was inflated to at least 50 mmHg above systolic pressure for 5 minutes. The vessel was monitored continuously for 1 minute after deflation of the cuff, and reactive hyperemia was confirmed by a pulse-wave Doppler study. After an additional 10 minutes of resting, subjects were given sublingual nitroglycerin (600-μg tablet).

Endothelium-dependent vasomotion (EDV) was expressed as percent flow mediated dilation (FMD) which was defined as the maximal brachial artery diameter after 60 sec of reactive hyperemia compared with the baseline vessel diameter. Endothelium-independent vasodilation was expressed as percent nitroglycerin-mediated dilation (NMD) which was defined as the maximal brachial artery diameter 5 minutes after administration of nitroglycerin compared with the baseline vessel diameter. Brachial artery measurements were performed with ultrasonic calipers by independent observers.

According to our hospital data, the interobserver and intraobserver variability were 1.5±0.3% and 1.3±0.5%, respectively.

Statistical analysis

Statistical analysis was performed using SPSS for windows, version 12.0 (Chicago, Illinois, USA). Data are expressed as mean±SEM. Independent t test and Pearson correlation were performed to demonstrate association with FMD. Clinical characteristics, laboratory finding and endothelial function were studied (baseline, 4 weeks and 8 weeks). We compared baseline variables with 4 and 8 week data , respectively. For all analyses, a $p<0.05$ was considered statistically significant.

Results

Baseline characteristics

Twenty patients in Group I: 16 men, 4 women, 54.9±10.2 years and twenty patients in Group II: 15 men, 5 women, 56.5±9.0 years were enrolled, and completed the 8-week study. Characteristics of the study population are listed in Table 1. There were no significant differences in the baseline characteristics of group I and group II, except for the blood glucose level.

Changes in clinical and laboratory variables after ALA administration

There were no significant interval changes after ALA administration in either group I or group II (Table 2, 3) except for the fibrinogen level. The fibrinogen level decreased in group 1 after the second 4-week 1200 mg ALA therapy (p=0.005).

Endothelial function test

In group I, there were no significant differences in baseline, FMD and NMD diameters. However, when comparing the baseline percent FMD, there were statistical differences in both the 4-week (p=0.01) and the 8-week percent FMD (p=0.001). In group II, there were no differences in the baseline, FMD and NMD diameters. However, when comparing the baseline percent FMD, there were statistical differences in the 8-week percent FMD (p=0.001) without differences in the 4-week percent FMD (p= 0.09)(Table 4).

Relationship between fibrinogen and FMD

There was no correlation between fibrinogen and FMD in group II. However, there was negative correlation between fibrinogen and FMD in group I. Decreased fibrinogen levels were associated with an increased percent of FMD (Fig. 1).

Table 1. Baseline clinical characteristics of both diabetic patients (group I) and hypertensive patients (group II)

	Group I (n=20)	Group II (n=20)
Age (years)	54.9±10.2	56.5±9.0
Male (%)	16 (80)	15 (75)
Hyperlipidemia (%)	3 (15)	5 (25)
Premature CAD (%)	3 (15)	5 (25)
Smoking (%)	5 (25)	6 (30)
Blood sugar (mg/dL)	150.5±30.5	100.4±13.4*
Body weight (kg)	69.1±8.7	67.0±9.0
BMI (kg/m^2)	24.9±2.5	25.5±3.7
WC (cm)	91.0±6.0	89.7±8.5
TC (mg/dL)	184.6±47.3	188.0±37.8
HDL (mg/dL)	38.8±12.7	41.1±10.8
LDL (mg/dL)	121.4±34.5	135.1±27.5
TG (mg/dL)	204.0±147.4	186.9±125.8
TC/HDL	5.1±1.5	4.9±1.5
Fibrinogen (mg/dL)	349.6±74.7	313.1±63.6
hsCRP (mg/dL)	1.3±1.9	1.8±1.6
Microalbuminuria (μg/mL)	42.8±44.8	25.8±20.4

*: p<0.05. There were no statistical differences between group I and group II. BMI: body mass index, WC: waist circumference, TC: total cholesterol, HDL: high density lipoprotein, LDL: low density lipoprotein, TG: triglyceride, hsCRP: high sensitivity C-reactive protein, CAD: coronary artery disease

Table 2. Changes in clinical and laboratory variables of diabetic patients after α-lipoic acid administration

	Baseline	4 weeks	8 weeks
Blood sugar (mg/dL)	150.5±30.5	140.0±40.0	138.5±47.9
Body weight (kg)	69.1±8.7	68.4±9.4	67.9±9.8
BMI (kg/m^2)	24.9±2.5	24.7±2.7	24.5±2.8
WC (cm)	91.0±6.0	90.1±5.8	89.1±6.2
TC (mg/dL)	184.6±47.3	199.3±55.4	196.6±52.6
HDL (mg/dL)	38.8±12.7	38.6±11.3	35.8±9.2
LDL (mg/dL)	121.4±34.5	130.2±52.0	131.5±48.7
TG (mg/dL)	204.0±147.4	228.3±124.8	174.0±103.9
TC/HDL	5.1±1.5	5.5±1.7	5.7±1.7
Fibrinogen (mg/dL)	349.6±74.7	330.9±118.5	285.3±60.7*
hsCRP (mg/dL)	1.3±1.9	1.6±3.0	1.3±2.2
Microalbuminuria (μg/ml)	42.8±44.8	48.1±41.8	41.6±37.2

*: p<0.05. BMI: body mass index, WC: waist circumference, TC: total cholesterol, HDL: high density lipoprotein, LDL: low density lipoprotein, TG: triglyceride, hsCRP: high sensitivity C-reactive protein

Table 3. Changes in clinical and laboratory variables of hypertensive patients after α-lipoic acid administration

	Baseline	4 weeks	8 weeks
Blood sugar (mg/dL)	100.4±13.4	98.4±12.1	108.2±15.1
Body weight (kg)	67.0±9.0	67.3±9.5	66.7±9.5
BMI (kg/m^2)	25.5±3.7	25.6±3.8	25.5±3.8
WC (cm)	89.7±8.5	89.0±9.0	88.5±8.9
TC (mg/dL)	188.0±37.8	204.7±23.0	195.3±31.5
HDL (mg/dL)	41.1±10.8	40.5±8.2	38.4±9.5
LDL (mg/dL)	135.1±27.5	135.4±27.3	135.8±35.4
TG (mg/dL)	186.9±125.8	195.3±207.9	147.1±104.3
TC/HDL	4.9±1.5	5.2±1.0	5.3±1.2
Fibrinogen (mg/dl)	313.1±63.6	301.8±58.5	288.5±73.2
hsCRP (mg/dL)	1.8±1.6	1.1±1.0	1.3±1.5
Microalbuminuria (μg/ml)	25.8±20.4	23.7±22.8	28.2±26.2

There were no statistical differences in both the 4 and 8 week groups. BMI: body mass index, WC: waist circumference, TC: total cholesterol, HDL: high density lipoprotein, LDL: low density lipoprotein, TG: triglyceride, hsCRP: high sensitivity C-reactive protein

Table 4. Effect of α-lipoic acid on both flow-mediated vasodilation and nitroglycerin-mediated vasodilation

	Baseline	4 weeks	8 weeks
Group 1 (diabetes)			
Baseline diameter (mm)	5.5±0.5	5.4±0.5	5.2±0.4
FMD diameter (mm)	5.7±0.6	5.7±0.5	5.6±0.5
NMD diameter (mm)	6.2±0.6	6.2±0.5	6.0±0.5
% FMD	4.1±3.3	6.5±2.2*	8.0±2.7*
% NMD	13.0±3.4	14.9±2.9	14.8±3.0
Group 2 (hypertension)			
Baseline diameter (mm)	5.6±0.6	5.4±0.5	5.3±0.5
FMD diameter (mm)	5.9±0.6	5.9±0.6	5.8±0.4
NMD diameter (mm)	6.3±0.6	6.4±0.5	6.2±0.5
% FMD	5.5±3.7	7.4±3.3	9.3±2.7*
% NMD	15.6±5.6	17.1±3.3	16.2±4.2

*: p<0.05. FMD: flow-mediated vasodilation, NMD: nitroglycerin-mediated vasodilation

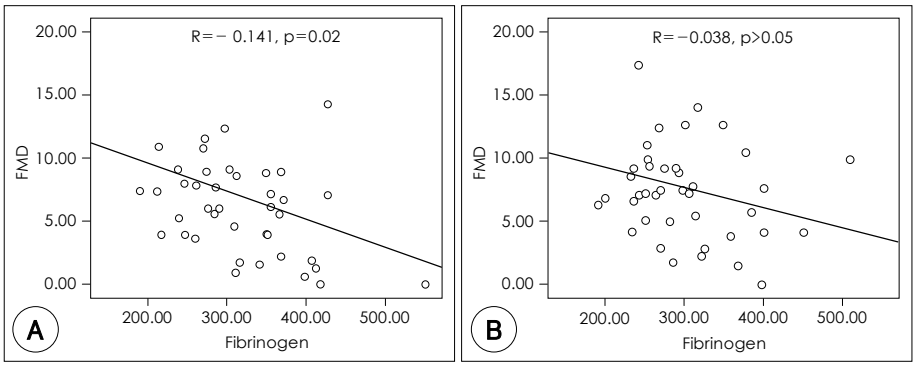

Fig. 1. Relationship between fibrinogen and flow-mediated vasodilation (FMD) in both diabetes (A) and hypertensives (B). There was a negative correlation between fibrinogen and FMD in diabetic patients (p=0.02). There was no correlation between fibrinogen and FMD in hypertensive patients (p=NS).

Discussion

Healthy endothelium plays a crucial role in regulating vascular tone and structure. An additional role of endothelium is not only mediation of endothelium dependent vasodilation, but also active suppression of thrombosis and vascular inflammation. Nitric oxide is a particularly important mediator of both endothelium-dependent vasodilation and anti-inflammatory and antithrombotic effects of endothelium. Endothelium dependent vasomotion is therefore thought to represent other important functions of endothelium.[17]

Common conditions predisposing to atherosclerosis have endothelial dysfunction; also considered a marker for atherosclerotic disease even in patients with cardiovascular disease.

The fact that many cardiovascular risk factors are present long before the development of diabetes has led to increasing support for the 'common ground' hypothesis in which type 2 diabetes and cardiovascular disease share common genetic and environmental antecedents.[18] The available data suggest that the decreased nitric oxide bioactivity in type 2 diabetic patients may be the result of nitric oxide breakdown associated with increased generation of ROS (reactive oxygen species) by a variety of causes.[19-21] In addition, hyperglycemia itself directly promotes endothelial dysfunction by overproduction of superoxide, depleting NAD+, decreasing glycolysis and ATP formation. These products produce acute endothelial dysfunction in diabetic blood vessels, and contribute to the development of diabetic complications.

Recently, efforts to improve endothelial dysfunction associated with hypertension have been pursued including both pharmacological and non-pharmacological therapies.[3][22-25] In some experiments, ALA prevents development of hypertension and hyperglycemia.[26] Physical exercise, calcium channel blockers such as a dihydropyridine like agents, ACE inhibitors and angiotensin II receptor blockers have been found to be effective. However, to date clinical studies evaluating efficacy of ALA in hypertensive patients are limited.

Lipoic acid has been used as a therapy for many clinical disorders, especially diabetes.[13] There are many reports demonstrating the improvement of endothelial dysfunction in diabetic patients in a dose-dependent manner. Lipoic acid supplementation has been reported to increase the unbound lipoic acid level, which can act as a potent antioxidant and reduce oxidative stress;[27] it is commonly marketed as an adjunct for the treatment of diabetic neuropathy. Lipoic acid is readily converted to its reduced form in various tissues, which increases intracellular levels of coenzyme NADPH, and NADH via increased glutathione availability. Lipoic acid also acts as a scavenger of several free radicals, including hydroxyl radicals and singlet oxygen and increases nitric oxide bioactivity.[28]

Because endothelial dysfunction is not specific to either diabetes or hypertension, but is rather a common marker of all major cardiovascular risk factors, we thought that improvement of endothelial function after ALA therapy in hypertension patients would be likely. We found that there was an improvement of endothelial function after both a regular dosage (ALA 600 mg/day for first 4-week) and after high dosage (ALA 1,200 mg/day for second 4-week) in diabetic patients. However, improvement of endothelial dysfunction in hypertensive patients was different. Significant improvement of endothelial function occurred not after a regular dosage (ALA 600 mg for first 4 weeks) but only after high dosage (ALA 1,200 mg for second 4 weeks). There are two possible explanations for this difference in response to ALA therapy in diabetic and hypertensive patients. First, although both diabetes and hypertension are conditions with increased oxidative stress, the direct effect of hyperglycemia on the vascular endothelium was dominant in diabetics. This effect might produce a more severe endothelial dysfunction at baseline in diabetic patients; therefore, the endothelial dysfunction was improved via the hypoglycemic effect of regular dose ALA.

We can explain the cause of the improvement of endothelial function, at lower dosage of ALA in diabetics, as a result of the hypoglycemic effect of ALA therapy. Second, the level of fibrinogen was decreased significantly by high dose ALA in diabetic patients. In another report, ALA was associated with a significant decrease of fibrinogen, factor VII, vWF, and triglycerides in diabetes.[29] An inverse correlation between fibrinogen and endothelial function, after ALA therapy in our study, was related to the possible antithromotic effects of ALA in diabetic patients rather than anti-inflammatory effects. Our results showed no change of hsCRP after ALA administration in either diabetic or hypertensive patients, as previously reported;[30] therefore, this suggested a possible antithrombotic effect of ALA.

There are several limitations in our study. First, our study had a small study population (n=40), and the study period was short (8 weeks) to determine the potential mechanisms by which ALA may be effective. It is possible that further differences might have been noted if the study had been extended for a longer duration or, conversely, that some of the effects may have been attenuated over time. Second, it is important to note that we could not discontinue the administration of some medications such as simvastatin, glibenclamide, and thiazide. The concomitant use of these agents might alter the effects of ALA on our study outcomes. Third, our study had no placebo group for comparison to the diabetes and hypertension groups. Fourth, in terms of other confounding vasoactive medications (angiotensin converting enzyme inhibitor, angiotensin receptor blocker and other antioxidant), the washout period in our study was relatively short.

Conclusion

This study demonstrated that ALA improves endothelial function in diabetic and hypertensive patients. Even though the percent FMD, in the hypertensive patients, improved significantly at a high dose but not at a regular dose of ALA, this study showed the possibility of improvement of endothelial function in hypertension after treatment with ALA. The mechanism by which this is achieved remains to be further clarified. Additional studies with a prospective, random, placebo controlled study design are now needed to determine the therapeutic parameters for ALA treatment of hypertensive patients.

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