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α-Lipoic acid can improve endothelial dysfunction in subjects with impaired fasting glucose

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Abstract

Several studies showed that impairment of endothelium-dependent arterial dilation (EDAD) exists in subjects with impaired fasting glucose (IFG). The crucial mechanism of this endothelial dysfunction remains unclear. We hypothesized that oxidative stress may be partially responsible for the impairment in EDAD in subjects with IFG. Thus, the present study was designed to assess whether the antioxidant α-lipoic acid can improve endothelial dysfunction in subjects with IFG. Sixty subjects with newly diagnosed IFG and 32 healthy individuals with normal glucose tolerance were enrolled. Subjects were randomized into 2 groups: untreated experimental group (n = 30) and α-lipoic acid treatment group (n = 30, α-lipoic acid 600 mg via intravenous infusion once a day for 3 weeks). We measured EDAD at baseline and after 3 weeks of intervention. At baseline, EDADs in α-lipoic acid and untreated experimental groups were 4.03% and 4.14%, respectively, which were significantly lower than that in controls (5.72%) ($P < .001$). After 3 weeks of intervention, there was a remarkable increase in EDAD (reaching 5.10%; ΔEDAD, 26.5%) ($P < .01$) and a significant decrease in plasma thiobarbituric acid reactive substances (TBARS) (29.1%) ($P < .05$) in IFG subjects treated with α-lipoic acid. Endothelium-dependent arterial dilation and TBARS remained unchanged before and after intervention in the untreated experimental group. The absolute changes in EDAD showed a significant negative correlation with the changes in TBARS ($r = -0.444$, $P = .014$). Our data showed that IFG subjects have impaired endothelial function and that antioxidant α-lipoic acid can improve endothelial function through a decrease of oxygen-derived free radicals.

In 1999, the American Diabetes Association introduced the concept of impaired fasting glucose (IFG), a prediabetic state initially defined by fasting plasma glucose of 110 to 125 mg/dL (6.1-6.9 mmol/L), in which those afflicted were significantly more likely to develop diabetes [1-3]. However, for nonfatal and fatal cardiovascular disease among participants with IFG, the evidence is less consistent [4,5].

Endothelial dysfunction represents a very early step in the development of atherosclerosis [6]. The reduced nitric oxide (NO)–mediated endothelium-dependent arterial vasodilation (EDAD) occurring in endothelial dysfunction is a predictor of cardiovascular risk in high-risk subjects [7], and its improvement seems to predict treatment-induced risk reduction. Several studies have shown that endothelial dysfunction exists in subjects with IFG [8,9] and that regular aerobic exercise training can improve endothelial dysfunction [9]. However, the crucial mechanism of endothelial dysfunction in subjects with IFG remains unclear.

Recently, it was well documented that the endothelium can generate oxidative stress in the presence of cardiovascular risk factors [10] and that oxidative stress can damage endothelial function [11]. Subjects with IFG are characterized by chronic inflammation [12], dyslipidemia [9], and endothelial dysfunction [9], as well as the increased prevalence of atherosclerotic lesions and cardiovascular events [4]. Recently, one study showed that the plasma concentration of coenzyme Q_{10}, a potent lipophilic antioxidant, is significantly decreased in subjects with IFG compared with healthy subjects [13]. Therefore, we hypothesized that oxidative stress may be partially responsible for the impairment in EDAD in subjects with IFG. Thus, the present study was designed to assess whether the antioxidant α-lipoic acid can improve endothelial dysfunction in subjects with IFG.

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1. Subjects and methods

1.1. Subjects

From January 2004 to January 2008, a total of 60 subjects with IFG referred to our hospital for healthy examination (age range, 42-65 years of age; mean, 58 ± 8 years) were studied. All subjects with IFG were newly diagnosed with 75-g oral glucose tolerance test performed twice within 2 weeks, and the diagnosis of IFG fulfilled the diagnostic criteria proposed by the American Diabetes Association [1]. During the same period, 32 healthy individuals with normal glucose tolerance (age range, 40-67 years; mean, 59 ± 9 years) were selected as controls. All individuals were not related. Obese (body mass index >30 kg/m^2) subjects, smokers, and those with hypertension, clinically detectable coronary artery disease, and other diseases were excluded from the study. In addition, no subject was taking any drugs, such as estrogen supplements, thyroxine, diuretics, or antihypertensive or hypolipidemic drugs. All subjects gave informed consent. The study protocol was in agreement with the guidelines of the ethics committee at our hospital.

1.2. Study design

All eligible individuals, including 60 subjects with IFG and 32 healthy individuals with normal glucose tolerance underwent brachial arterial study described below, after which subjects were divided into either the α-lipoic acid group (α-lipon 300 Stada manufactured by STADApharm, Bad vilbd, Germany) or the untreated experimental group, with 30 cases in each group. The α-lipoic acid group (250 mL 0.9% sodium chloride + 600 mg α lipon 300) was treated via intravenous infusion at a rate of 4 mL/min once a day for 3 weeks. The untreated experimental group only received 250 mL 0.9% sodium chloride via intravenous infusion at a rate of 4 mL/min once a day for 3 weeks.

1.3. Laboratory methods

Venous blood was collected after a 12-hour fast at baseline for all subjects and at 3 weeks for IFG subjects. Serum lipids, lipoproteins and other parameters, serum total cholesterol (TC) (reference range, 3.10-5.69 mmol/L), low-density lipoprotein cholesterol (LDL-C) (reference range, 2.10-3.10 mmol/L), triglycerides (reference range, 0.41-1.88 mmol/L), and high density lipoprotein cholesterol (HDL-C) (reference range, 1.16-1.82 mmol/L) were measured enzymatically. Apolipoprotein (Apo) A-1 (reference range, 1.01-1.50 g/L) and Apo B (reference range, 0.74-1.20 g/L) were measured by immunoturbidimetry. Serum lipoprotein (a) (Lp[a]) concentration (reference range, 0-300 mg/L) was measured by an enzyme-linked immunosorbent assay method. Blood glucose levels (including fasting blood glucose [FBG] and postprandial 2-hour blood glucose [2-h BG]) were measured by a glucose oxidase procedure. C-reactive protein (CRP) concentration was measured by using the CRP (latex) ultrasensitive assay (reference range, 0-3.0 mg/L). Nitrite/nitrate, stable metabolites of NO, was measured using the method reported by Kawano et al [14]. The plasma lipid peroxide content was determined using thiobarbituric acid reactive substances (TBARS) as markers [15,16]. Briefly, 2.0 mL of trichloroacetic acid–thiobarbituric acid–HCl reagent was added to 1.0 mL of sample and vortexed. To minimize peroxidation during the assay procedure, butylated hydroxytoluene was added to the thiobarbituric acid reagent mixture. Results were expressed as malondialdehyde equivalent content (nanomoles MDA per milliliter plasma). The intraassay coefficients of variation for these assays were 1% to 2% (TC, HDL-C, blood glucose, CRP), 2% to 3% (LDL-C, nitrite/nitrate), 2% to 4% (Apo A-1, Apo B, and TBARS), and 4% to 7% (Lp[a]).

1.4. Brachial arterial study

The vascular studies of the brachial artery were performed noninvasively, as described by us previously [9,17,18]. High-resolution ultrasound was used to measure changes in arterial diameter in response to reactive hyperemia (with increased flow producing an endothelium-dependent stimulus to vasodilation) and to glyceryltrinitrate (GTN, an endothelium-independent vasodilator) (128XP/10 with a 7.0-MHz linear array transducer; Acuson, Mountain View, CA). The intra- and interobserver variability in our laboratory for repeated measurements of artery diameter was 0.09 ± 0.10 and 0.08 ± 0.13 mm, respectively.

The subjects rested in the supine position for 10 minutes before the first scan and remained supine throughout the study. The target artery (the brachial 2-15 cm above the elbow) was scanned in longitudinal section, and the center of the vessel was identified when the clearest images of anterior and posterior walls of the artery were obtained. The transmit zone was set to the level of the anterior vessel wall. Depth and gain settings were optimized to identify the lumen to vessel wall interface. Images were magnified with the resolution box function leading to a television line width of approximately 0.05 mm. Machine settings were kept constant during each study.

Flow increase was induced by inflation of a blood pressure tourniquet placed around the forearm distal to the target artery to 300 mm Hg. The cuff was released after 5 minutes; and after cuff deflation, the artery was scanned continuously for 90 seconds. Fifteen minutes was allowed for vessel recovery; sublingual GTN (400-μg spray) was then administered; and 5 minutes later, the last scan was done. The electrocardiogram was monitored continuously.

Vessel diameter was measured by 2 observers unaware of clinical details and the stage of the experiment. The arterial diameter was measured at a fixed distance from an anatomical maker, such as a bifurcation, with ultrasonic calipers. Measurements were taken from the anterior to the posterior “m” line at end diastole, incident with the R wave on the electrocardiogram. The mean diameter was calculated

Table 1
Clinical and biochemical characteristics in IFG subjects before and after intervention as well as in control groups

	Control group	α-Lipoic acid group		Untreated experimental group	
		Before therapy	After therapy	At baseline	After intervention
No. of subjects	32	30	30	30	30
Age (y)	59 ± 9	58 ± 10	58 ± 10	58 ± 9	58 ± 9
Sex (M/F)	18/14	16/14	16/14	15/15	15/15
SBP (mm Hg)	111.8 ± 7.9	113.5 ± 9.6	116.1 ± 10.2	116.6 ± 8.0	112.3 ± 9.9
DBP (mm Hg)	72.5 ± 6.4	74.1 ± 7.1	75.3 ± 8.2	74.9 ± 7.9	72.7 ± 6.6
BMI (kg/m^2)	23.8 ± 2.1	23.3 ± 1.8	23.3 ± 1.6	23.6 ± 1.5	23.9 ± 1.8
FBG (mmol/L)	4.65 ± 0.67	6.62 ± 0.52†	6.50 ± 0.48†	6.58 ± 0.53†	6.52 ± 0.54†
2-h BG (mmol/L)	6.83 ± 0.85	6.97 ± 0.81	6.88 ± 0.90	6.86 ± 0.83	6.84 ± 0.79
TC (mmol/L)	4.27 ± 0.49	5.15 ± 0.56†	5.21 ± 0.52†	5.22 ± 0.50†	5.25 ± 0.61†
LDL-C (mmol/L)	2.06 ± 0.44	3.47 ± 0.57†	3.41 ± 0.53†	3.52 ± 0.51†	3.48 ± 0.53†
HDL-C (mmol/L)	1.22 ± 0.30	1.19 ± 0.35	1.20 ± 0.38	1.21 ± 0.41	1.18 ± 0.33
Triglyceride (mmol/L)	1.28 ± 0.68	2.04 ± 0.93†	1.95 ± 0.85†	2.12 ± 0.83†	2.09 ± 0.92†
Apo A-1 (g/L)	1.23 ± 0.27	1.20 ± 0.24	1.22 ± 0.26	1.19 ± 0.28	1.22 ± 0.27
Apo B (g/L)	1.07 ± 0.22	1.12 ± 0.30	1.12 ± 0.26	1.15 ± 0.24	1.13 ± 0.25
Lp(a) (mg/L)	172 (30, 292)	159 (41, 291)	163 (38, 290)	155 (48, 310)	162 (45, 306)
CRP (mg/L)	1.28 ± 0.32	1.99 ± 0.30*	1.58 ± 0.25*	1.86 ± 0.41*	1.79 ± 0.35*
TBARS (nmol/mL)	1.58 ± 0.52	2.47 ± 0.54*	1.75 ± 0.57‡	2.41 ± 0.59*	2.25 ± 0.66*
Nitrite/nitrate (μmol/L)	60.94 ± 8.45	61.24 ± 7.83	60.11 ± 8.23	61.73 ± 8.03	60.48 ± 8.51

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
* $P < .05$.
† $P < .001$, compared with control.
‡ $P < .05$, compared with subjects before treatment.

from 4 cardiac cycles. For the hyperemia scan, vessel diameter was measured 45 to 60 seconds after cuff release. Diameter changes were derived as percentage change relative to the first baseline scan (100%). Baseline blood flow (measured during the first baseline scan) was estimated by multiplying angle-corrected, pulsed Doppler recordings of the flow-velocity integral by JI and the square of the radius of the artery.

1.5. Statistical methods

Data were reported as the mean ± SD. Data among different groups were compared with analysis of variance. The difference in each parameter between before and after treatment was compared using the Student *t* test (2-tailed) for paired data, and that between patients and controls was compared by the Student unpaired *t* test. Correlations were determined by Spearman analysis. The Lp(a) concentrations were log-transformed before analysis. All analyses were carried out by using the statistical package SPSS 11.5 (SPSS, Chicago, IL).

2. Results

The clinical characteristics and biochemical results of the control subjects and α-lipoic acid as well as untreated experimental groups are given in Table 1. At baseline, FBG, TC, triglyceride, LDL-C, CRP, and TBARS concentrations were significantly higher in subjects with IFG (including α-lipoic acid and untreated experimental groups) than those in control ($P < .001$). Other parameters, that is, systolic blood pressure, diastolic blood pressure, and 2-h BG, did not differ among control and α-lipoic acid as well as untreated experimental groups ($P > .05$). The vascular characteristics of the groups are listed in Table 2. Endothelium-dependent arterial dilations in α-lipoic acid and untreated experimental

Table 2
The results of brachial artery studies in IFG subjects before and after intervention as well as in control groups

	Control group	α-Lipoic acid group		Untreated experimental group	
		Before therapy	After therapy	At baseline	After intervention
No. of subjects	32	30	30	30	30
Baseline vessel (mm)	3.85 ± 0.73	3.83 ± 0.76	3.91 ± 0.66	3.88 ± 0.62	3.87 ± 0.72
Baseline flow (mL/min)	79.75 ± 33.44	80.12 ± 30.65	79.44 ± 35.54	80.38 ± 32.52	81.14 ± 35.26
EDAD (%)	5.72 ± 0.61	4.03 ± 0.52†	5.10 ± 0.54* ‡	4.14 ± 0.56†	4.23 ± 0.63†
GTN-induced dilation (%)	20.05 ± 2.23	20.48 ± 2.42	21.36 ± 2.51	20.333 ± 2.28	21.2 ± 2.38

* $P < .05$.
† $P < .01$, compared with control.
‡ $P < .05$, compared with subjects before treatment.

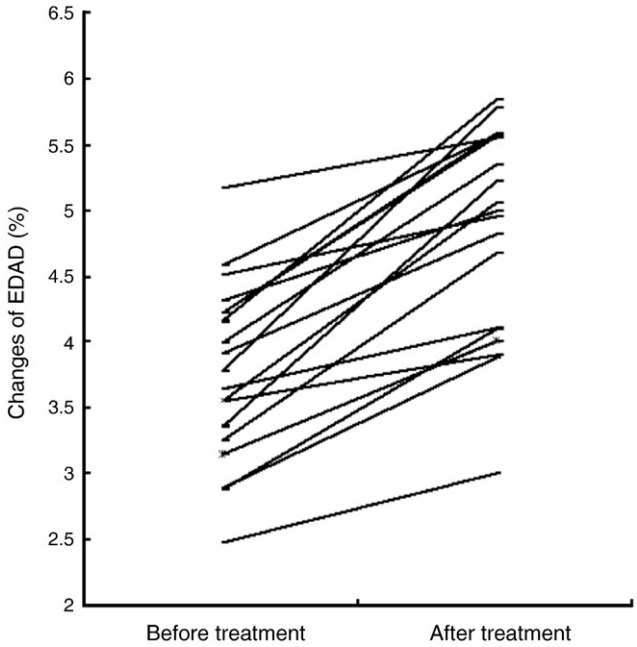

Fig. 1. Changes of EDAD before and after treatment in α-lipoic acid group.

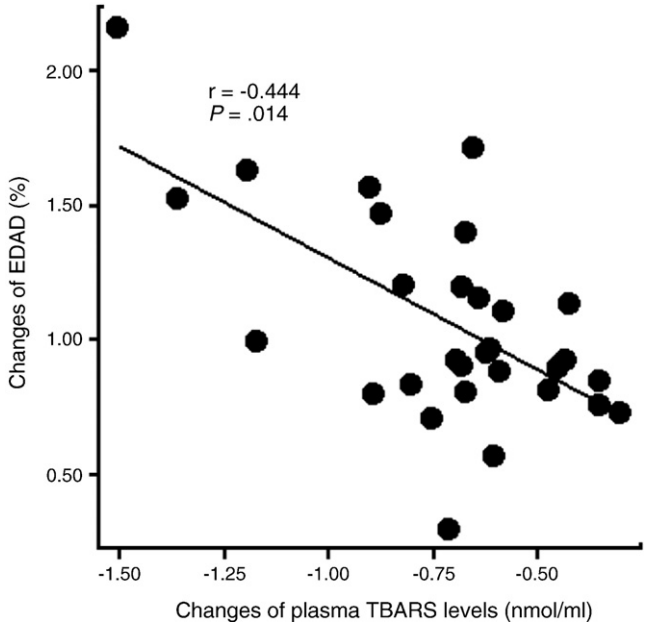

Fig. 2. Spearman correlation analyses to evaluate correlation of change in EDAD with change in TBARS before and after treatment in α-lipoic acid group.

groups were 4.03% and 4.14%, respectively, which were significantly lower than that in control (5.72%) ($P < .001$). The baseline vessel size (diameter), GTN-induced arterial dilation, and baseline flow were not significantly different among the 3 groups ($P > .05$).

After 3 weeks of intervention, there was a remarkable increase in EDAD (reaching 5.10%; ΔEDAD, 26.5%) in IFG subjects treated with α-lipoic acid ($P < .01$). As shown in Fig. 1, all subjects showed a marked increase in EDAD during the course of treatment intervention. Other vascular parameters such as baseline vessel and baseline flow did not change markedly in both α-lipoic acid and untreated experimental groups (Table 2). Furthermore, a significant decrease in TBARS (29.1%) was observed over the α-lipoic acid treatment period ($P < .05$). Other clinical parameters such as serum lipids and glucose (including FBG and 2-h BG) did not significantly change during the intervention period in both α-lipoic acid and untreated experimental groups (Table 1).

To reveal the possible causes of EDAD changes before and after α-lipoic acid therapy in IFG subjects, Spearman correlation coefficient was calculated between changes in EDAD and those in TBARS. The absolute changes in EDAD showed significant negative correlation with the changes in TBARS ($r = -0.444$, $P = .014$) (Fig. 2).

3. Discussion

The current study demonstrates that impaired EDAD exists in subjects with IFG and improves significantly after 3 weeks of α-lipoic acid treatment. However, it was still lower than that in control. The results suggest that endothelial dysfunction in subjects with IFG may be related in part to oxidative stress. As far as we know, this is the first report on the relation between endothelial dysfunction and oxidative stress in subjects with IFG.

Previous studies have suggested an association between IFG and atherosclerosis [19-21]. In a population-based cohort of middle-aged men and women, IFG emerged as an independent risk factor for atherosclerosis [20]. Recently, several studies showed that impairment of EDAD exists in subjects with IFG [8,9]. In the present study, the results are in good agreement with those reported in the previous studies [8,9]. The possible explanations for the impairment of endothelial function in IFG subjects are as follows: (1) Multiple studies have found that elevated plasma TC, LDL-C, and TG levels were related to the attenuation of EDAD [9,17,18]. Therefore, endothelial dysfunction in IFG is partially dependent on the altered lipid profiles observed in this study. (2) C-reactive protein has been recently considered as a potential contributor to inflammatory diseases including atherosclerosis as well as a marker of cardiovascular risk [22]. More recently, several studies suggested that elevated plasma CRP level is associated with endothelial dysfunction in IFG and diabetes [9,17,18]. In the present study, our results showed that plasma CRP levels in IFG subjects were significantly higher than those in controls. Therefore, inflammation may partially contribute to the impaired endothelial function in IFG subjects. (3) It has been reported previously that FBG is associated with endothelial function in subjects with IFG [9]. In the present study, we also find similar results. This may be partially responsible for the impaired endothelial function at baseline.

Endothelium-dependent arterial dilation has been shown to be mediated by the endothelium-derived relaxing factor, which is now identified as NO [23]. Previous studies have established that oxygen-derived free radicals interfere with or destroy endothelial function by inactivating NO in normal vessels [24,25]. Plasma TBARS, a marker of oxygen-derived free radicals, are associated with EDAD in subjects with impaired glucose tolerance [26]. Reversing oxidative stress and the subsequent inhibition of lipid peroxidation should improve endothelial function. Paolisso et al [27] used 600 mg vitamin E per day in a double-blind trial and showed that 8 weeks of treatment improved EDAD of the brachial artery in type 2 diabetes mellitus. Vitamin C also can prevent the endothelial dysfunction that has been observed during transient hyperglycemia after oral glucose loading in healthy subjects [28]. Coenzyme Q_{10} is a lipid-soluble molecule derived mainly from endogenous synthesis. It plays an essential role as an electron carrier in mitochondrial oxidative phosphorylation [29] and may have an important role as an antioxidant [30]. Watts et al [31] demonstrated that coenzyme Q_{10} supplementation improves endothelial function of conduit arteries of the peripheral circulation in patients with type 2 diabetes mellitus.

α-Lipoic acid functions as a cofactor in multienzyme complexes, including pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, and branched-chain α-keto acid dehydrogenase [32]. α-Lipoic acid and its reduced form, dihydrolipoate, are potent antioxidants. They are amphiphilic and widely distributed in both cell membrane and cytosol. α-Lipoic acid has been used in Germany for patients with neuropathy for more than 30 years and is considered to be safe and efficacious for treatment of diabetic symptomatic polyneuropathy [33]. In 2010, one study showed that oxidative stress contributes to endothelial dysfunction and that α-lipoic acid improves NO-mediated vasodilation in diabetic patients [34]. Recently, another study suggested that α-lipoic acid improves endothelial dysfunction induced by acute hyperglycemia during oral glucose tolerance test in impaired glucose tolerance [26]. However, the effects of α-lipoic acid on endothelial function in subjects with IFG have not been demonstrated. In the present study, plasma TBARS levels decreased markedly after 3 weeks of α-lipoic acid treatment. Moreover, the absolute changes of TBARS were negatively correlated with those of EDAD during α-lipoic acid treatment. Other clinical and biochemical characteristics including lipid profiles and CRP did not change significantly before and after treatment. It is suggested that reversing oxidative stress is partially responsible for the improvement of endothelial function by α-lipoic acid. In contrast, the serum levels of nitrite/nitrate, the metabolites and the marker for production of NO, did not differ in any of the groups before and after treatment. Because the nitrite/nitrate concentration includes the oxidative products of NO [35], endothelial dysfunction exists in IFG subjects, probably through an increase of oxygen-derived free radicals and not through a decrease in production/release of NO, and results in a quenching of NO. α-Lipoic acid improves endothelial dysfunction by a decrease of oxygen-derived free radicals.

After 3 weeks of α-lipoic acid treatment. plasma TBARS levels were close to the controls; however, EDAD was still markedly lower than that in controls. This may be due to the higher levels of TC, TG, LDL-C, and CRP.

Some limitations of the present study should be mentioned. Firstly, 2 studies from one group suggested that α-lipoic acid improves insulin sensitivity in patients with type 2 diabetes mellitus [36,37]. However, we did not measure plasma insulin levels. Therefore, the changes of insulin sensitivity and its association to endothelial function during the intervention period could not be evaluated. It is worth noting that we did not find significant changes of FBG and 2-h BG during the α-lipoic acid intervention; we speculate that the short period of intervention may be responsible for this. Secondly, the number of study subjects is relatively small. It is difficult to exclude bias in the results, which should be confirmed in large studies. Thirdly, we did not evaluate the effect of oral α-lipoic acid on endothelial function in this study. Therefore, whether oral dosing of α-lipoic acid would have the same effect remains to be determined.

In conclusion, our data showed that IFG subjects have impaired endothelial function and that antioxidant α-lipoic acid can improve endothelial function through a decrease of oxygen-derived free radicals.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.metabol.2010.04.011.

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