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ORIGINAL ARTICLE

Randomized clinical trial

Alpha-lipoic acid improves vascular endothelial function in patients with type 2 diabetes: a placebo-controlled randomized trial

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ABSTRACT

Objective The aim of this study was to investigate the effect of alpha-lipoic acid (ALA) treatment on endothelium-dependent and -independent vasodilatation, assessed by forearm blood flow (FBF), in patients with type 2 diabetes mellitus.

Research design and methods A total of 30 subjects with type 2 diabetes were included in this randomized, controlled, double-blinded, parallel group study. FBF responses to intra-arterial acetylcholine (ACh) and glycerol trinitrate (GTN) were measured before and after 21 days of intravenous treatment with 600 mg alpha-lipoic acid or placebo.

Results FBF responses were comparable at baseline. After treatment, FBF reactivity to ACh and GTN was unchanged in subjects receiving placebo. By contrast, ALA treatment increased endothelium-dependent vasodilatation to ACh ($P < 0{\cdot}05$) but not to GTN compared with baseline.

Conclusions Intravenous ALA treatment improves endothelium-dependent vasodilatation in patients with type 2 diabetes, in the absence of effects on forearm vasomotor function. If this salutary action translates into vascular risk reduction remains to be established.

Keywords Acetylcholine, alpha-lipoic acid, forearm blood flow, glycerol trinitrate, type 2 diabetes.

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Introduction

Diabetes type 2 is associated with increased risk for cardiovascular disease [1]. The incidence of myocardial infarction in patients with type 2 diabetes without overt coronary heart disease is equivalent to that of nondiabetic patients with preceding coronary events [2]. Thus pharmacological and lifestyle interventions are mandatory in primary prevention of cardiovascular events in this population.

An early and reversible functional impairment of the conduit and resistance vasculature of different vascular beds can be detected in patients with diabetes before structural alterations occur [3,4]. The vascular endothelium plays a central role in the physiological maintenance of vascular function by regulating vascular tone, leucocyte adhesion, platelet activation and vascular remodelling, as a result of formation of vasoactive substances such as nitric oxide (NO), prostacyclin and endothelin [5,6].

The disulphide compound alpha (α)-lipoic acid (ALA) was shown to exert antioxidant properties *in vitro* and in animal experiments [7,8]. It is endogenously produced in small quantities in cells, and functions as a co-enzyme in the pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase mitochondrial enzyme complexes [8]. Treatment with ALA reduces elevated markers of oxidative stress in patients with diabetes [9]. In addition, ALA might also improve endothelial function via other mechanisms than reduction of oxidative stress. In patients with type 2 diabetes systemic infusion of ALA acutely improves endothelium-dependent vasodilatation [10], which has been attributed to restoration of NO bioactivity. However, data on effects of ALA on vascular function after prolonged treatment in type 2 diabetes is scarce.

This study was designed to test if 3-week treatment with intravenous ALA can influence forearm blood flow reactivity to the endothelium-dependent vasodilator acetylcholine (ACh) and to the endothelium-independent vasodilator glycerol trinitrate (GTN) in patients with type 2 diabetes.

Materials and methods

The study protocol was approved by the Ethics Committee of the Medical University of Vienna, adheres to the Declaration of Helsinki and is registered at Clinicaltrials.gov (NCT00490867). Subjects were informed about the aims, procedures and possible risks of the study and gave written informed consent. Inclusion criteria were type 2 diabetes diagnosed on a clinical basis, age of manifestation > 40 years and body mass index (BMI) > 25 kg m^{-2}. A total of 30 patients were recruited for this study, subject characteristics are summarized in Table 1.

The mean diabetes duration from diagnosis was 7 ± 6 years. Concomitant diseases are provided in Table 2. A total of 23 patients received oral antihyperglycemic therapy, five patients insulin and one patient insulin in combination with oral antihyperglycemic therapy. One patient did not receive antihyperglycemic therapy. Concomitant drug therapy shown in Table 2 was initiated before the trial and unchanged during the observation period. Exclusion criteria were history or signs of symptomatic and asymptomatic macrovascular disease and hypersensitivity to the trial drug.

All participants completed the study per protocol. During the study period, all subjects received dietary advice from specialists and instructions on other diabetes-related topics including training recommendations at a specialized diabetes centre in Lower Austria (Alland). Patients were randomized in a 1 : 1 ratio to receive ALA or matching placebo infusions (physiologic saline solution).

Study protocol

On trial days 1 and 23, forearm blood flow experiments were conducted. On day 2–22 intravenous doses of 600 mg ALA or placebo were administered in the morning.

Forearm blood flow

Forearm blood flow was measured by venous occlusion plethysmography, using a mercury-filled Silastic strain-gauge plethysmograph (EC – 6, D.E. Hokanson, Inc) as previously described [11]. Bilateral plethysmography was used, expressing responses in the intervention arm as a ratio of blood flow recorded in the control arm, because this is more reproducible than unilateral plethysmography [12,13]. A 27G needle was inserted into the brachial artery of the non-dominant arm. After a 20-min resting period baseline forearm blood flow measurement experiments were performed for ACh and GTN, with a 15 min washout period between the drugs to re-establish baseline conditions. Blood pressure was measured at 15-min intervals and pulse rate was monitored throughout the infusion period.

This invasive and technically burdensome technique was shown to deliver reliable, reproducible results for assessment of endothelial function. Compared with other techniques such as assessment of flow mediated dilation of the brachial artery, it was shown to have a lower intra-subject variability, thus, significant changes could be detected with a lower sample size [14].

Table 1 Subject characteristics

	α-lipoic acid (*n* = 15)		Placebo (*n* = 15)	
	Baseline	**Treatment**	**Baseline**	**Treatment**
Age (years)	55 ± 8		56 ± 6	
BMI (kg m^{-2})	29·7 ± 2·5		31·0 ± 1·8	
Systolic blood pressure (mmHg)	140 ± 14	129 ± 13	151 ± 14	133 ± 17*
Diastolic blood pressure (mmHg)	82 ± 8	70 ± 8*	85 ± 9	65 ± 9*
Heart rate (beats per minute)	79 ± 10	64 ± 9*	77 ± 11·6	60 ± 10*
HbA1c (%)	7·3 ± 1·5	6·9 ± 1·3*	7·5 ± 1·1	6·9 ± 0·9*
Total cholesterol (mg dL^{-1})	210 ± 54	160 ± 36*	208 ± 44	176 ± 45*
HDL-cholesterol (mg dL^{-1})	52 ± 16	49 ± 11	52 ± 13·2	47 ± 13
LDL-cholesterol (mg dL^{-1})	115 ± 39	82 ± 33*	121 ± 42	103 ± 42
Triglyceride (mg dL^{-1})	205 ± 132	160 ± 145*	177 ± 87	128 ± 47*
Creatinine (mg dL^{-1})	0·91 ± 0·19	—	0·86 ± 0·16	—

Characteristics of patients randomized to receive alpha (α)-lipoic acid or placebo at baseline and 2 weeks after treatment. Data are presented as mean ± SD.
*$P < 0·05$ vs. baseline, Wilcoxon matched pairs test.

Table 2 Concomitant diseases and medications

Disease	α-lipoic acid (*n* = 15)	Placebo (*n* = 15)	Medication	α-lipoic acid (*n* = 15)	Placebo (*n* = 15)
Arterial hypertension	13	12	Metformin	12	10
Hyperlipidaemia	8	6	Sulfonylurea	7	1
Chronic osteoarthritis	3	2	Glitazone	3	1
Peripheral neuropathy	2	2	Insulin	2	4
Hyperuricaemia	2	1	Antihypertensive medication	12	10
Struma	1	1	Lipid lowering medication		
			Statins	9	4
			Fibrates	1	—
Chronic obstructive pulmonary disease	1		Proton pump inhibitor	—	2
Psoriasis		1	ASS	2	3
Glaucoma	1		5-ASS	1	—
Ocular maculopathy	1		Allopurinol	—	3
Myclonic muscle twitches	1		Pulmonary antiobstructive therapy	—	1
Splenectomy	1		Thyroid hormone	1	1
Benign prostate hyperplasia	1		Antidepressant	—	1
			Gabapentin	—	1
			Nicergolin	1	—
			Folic acid	1	—

Concomitant medication in patients (*n*) receiving alpha (α)-lipoic acid or placebo.

Study medications

Cumulative doses of acetylcholine (25, 50, 100 nmol min^{-1}; Clinalfa, Läufelfingen, Switzerland) and glycerol trinitrate (4, 8, 16 nmol min^{-1}; G. Pohl Boskamp GmbH, Hohenlockstedt, Germany) were infused intra-arterially over an infusion period of 3 min per dose level [13].

Alpha-lipoic acid (Thioctacid®; VIATRIS Pharma GmbH, Vienna, Austria) was infused intravenously at a dose of 600 mg over 30 min. A 250 mL physiologic saline solution (0·9%) served as vehicle [15]. An equivalent volume of saline solution was prepared as placebo treatment.

Hemodynamic and laboratory analysis

Haematology, blood coagulation, clinical chemistry and urine analysis were carried out according to standard procedures by the Clinical Institute for Medical and Chemical Laboratory Diagnostics, Allgemeines Krankenhaus Wien. Noninvasive measurements of blood pressure were taken on the upper arm by an automated oscillometric device. Pulse rate was recorded from a finger pulse-oxymetric device.

Biometric methods

Descriptive data are presented as mean ± SD. Resting blood flow was expressed as percent of control arm (FBF ratio, %) and changes over baseline calculated for each dose-response curve. As a result of the normal distribution of forearm blood flow data, the effect of ALA was assessed by repeated measure ANOVA. The other outcome measures were tested for normal distribution using the Kolgormorov–Smirnov test. The Student's paired *t*-test or the Wilcoxon matched pairs test was used to compare changes. A $P < 0{\cdot}05$ was considered as the level of significance.

A sample size calculation [16] was based on *a priori* assumptions of a $\alpha = 0{\cdot}05$ and $\beta = 0{\cdot}20$. Most studies including own trials report a standard deviation for repeated measurements of forearm blood flow of max. $\sigma = 0{\cdot}1$ [13]. In a previous study, intra-arterial administration of ALA completely reversed

endothelial dysfunction in patients with type 2 diabetes [10]. We assumed that long-term treatment would have to exert half of this effect to be of clinical relevance. Thus, it was estimated that a study in 15 participants per group has the statistical power of 80% to detect a minimum of 8% difference in forearm blood flow ratio, changes smaller than that were considered to be irrelevant.

Results

Groups of patients were comparable at baseline (Table 1). Systemic haemodynamics, the lipid profile and HbA1c improved after 2 weeks compared with baseline in both treatment groups (Table 1). Concomitant medication was unchanged during the study.

Endothelium-dependent vasodilatation

ACh caused a dose-dependent vasodilatation, which was similar between groups at baseline and unchanged in subjects receiving placebo treatment (P = 0·18 vs. baseline) (Fig. 1). By contrast, FBF reactivity to ACh was significantly enhanced in patients on ALA (P = 0·00003 vs. baseline). The difference between the ALA- and placebo-treated patients was significant on day 23 (P = 0·037).

Endothelium-independent vasodilatation

Vasodilatation to GTN was dose-dependent and comparable between groups at baseline. Forearm blood flow was unchanged after treatment with placebo or ALA (Fig. 2).

Adverse events

No adverse events or side effects were detected in our study. Intravenous lipoic acid was well tolerated by all patients.

Discussion

This study demonstrates that intravenous treatment with ALA for 21 days improves endothelium-dependent vasodilatation in the forearm resistance vasculature of patients with type 2 diabetes. While the mechanism of this functional improvement cannot be derived from the present experiments, the lack of effect on endothelium-independent vasodilatation suggests that this action is caused by augmented NO bioactivity stimulated by ACh.

Lipoic acid is a naturally occurring antioxidant with potent free-radical scavenging activity [8]. Incubation with lipoic acid has been shown to protect cultured endothelial cells against oxidative stress induced by high glucose [17] and to preserve cellular antioxidative defence mechanisms [18]. Furthermore, in diabetic animal models, lipoic acid has been demonstrated to have beneficial effects on vascular and endothelial function [19,20]. Lipoic acid and its reduced form, dihydrolipoic acid (DHLA), reacts with reactive oxygen species such as superoxide radicals, hydroxyl radicals, hypochlorous acid, peroxyl radicals and singlet oxygen [8]. Lipoic acid and DHLA have also been shown to be capable of regenerating other antioxidants such as ascorbic acid, glutathione, ubiquinol-10 and, indirectly, vitamin E [21]. Consistent with these experimental data, there is evidence that oral supplementation of ALA decreases oxidative stress in diabetic patients as assessed by measurement of plasma lipid hydroperoxides [9]. A recent study in patients with impaired glucose tolerance showed beneficial effects of short-term ALA (300 mg) on endothelial function [22].

As a result of its antioxidant potency, ALA, particularly in its reduced form of DHLA, may protect NO from inactivation by quenching oxygen-derived free radicals.

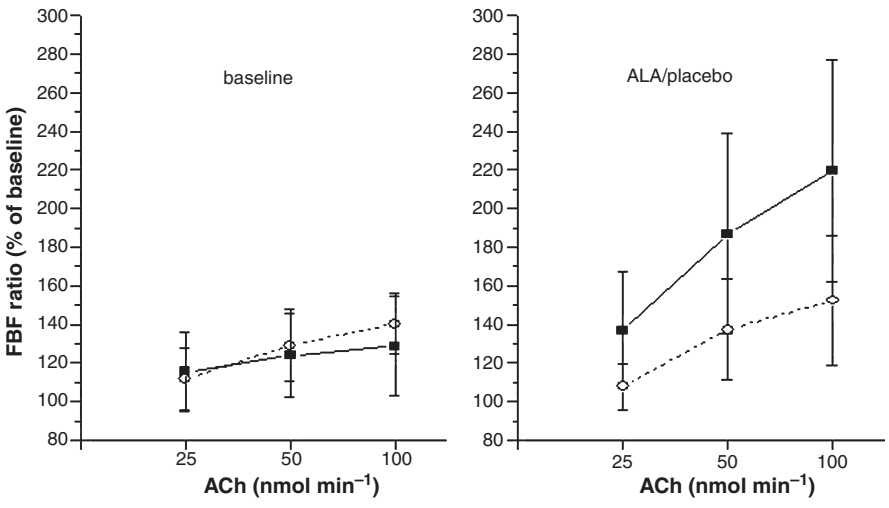

Figure 1 Forearm blood flow (FBF) ratio in response to intra-arterial acetylcholine (ACh) at baseline and after treatment with α-lipoic acid (ALA, solid squares) or placebo (open circles). Symbols are mean ± SD, n = 15/group.

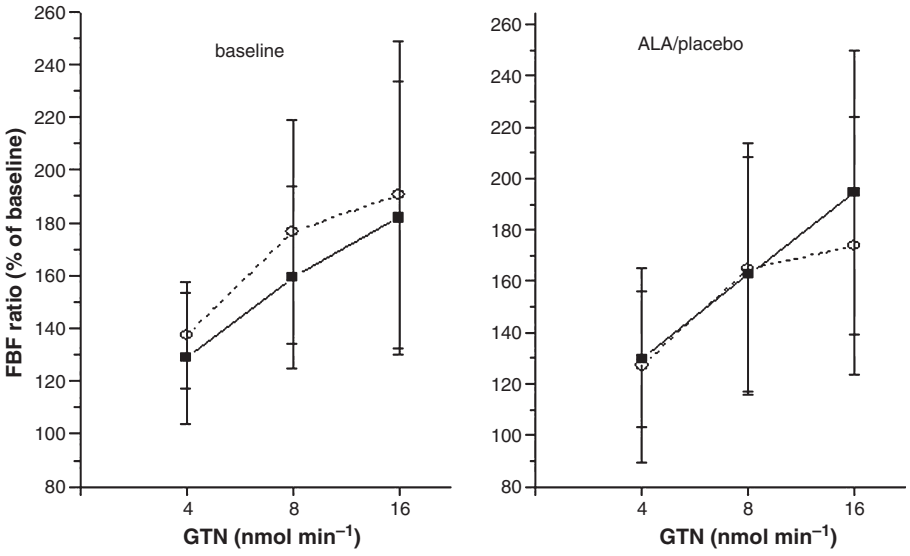

Figure 2 Forearm blood flow (FBF) ratio in response to intra-arterial glycerol trinitrate (GTN) at baseline and after treatment with α-lipoic acid (ALA, solid squares) or placebo (open circles). Symbols are mean ± SD, n = 15/group.

However, ALA might also improve endothelial function through other potential mechanisms. A recent study in healthy volunteers, for instance, showed augmented flow mediated dilation after ischaemia that was not influenced by antioxidants including ALA [23]. Additional interesting mechanisms for the beneficial effects of ALA include induction of endogenous antioxidants, inhibition of NF-kappa B and metalloproteinase-9 and upregulation of intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [24].

ALA was also shown to improve the age related decrease in phosphorylation of nitric oxide synthase in rats [25]. Another *in-vitro* study demonstrated inhibition of endothelial cell apoptosis by ALA [26].

In our study, LDL-cholesterol levels were reduced in the group receiving ALA. Although there were more patients receiving lipid-lowering drugs in the ALA group, an effect of this treatment is unlikely as it was stable for at least 3 months preceding the study and unchanged during the study. Thus, it might be speculated that ALA might have influenced LDL-cholesterol levels. Experimental and clinical studies have shown reduction of (oxidized) LDL by ALA [27,28].

Pharmacokinetic studies have demonstrated a plasma half life of about 30 min of ALA in healthy subjects [29] and of approximately 33 min in patients with type-2 diabetes [30]. It is therefore presumable that relevant circulating ALA concentrations were absent during forearm function studies. Thus, the sustained pharmacodynamic action with improvement of ACh reactivity indicates that systemic NO bioactivity has been augmented by the infusion regimen.

In patients with diabetes, acute intra-arterial administration of ALA improved NO-mediated forearm blood flow reactivity which was not observed in control subjects. This effect of 0·2 mM ALA was similar to that achieved by 10 mM ascorbic acid [10]. As a corollary, a single intravenous dose of 300 mg ALA mitigated the detrimental effect of an acute oral glucose load on flow-mediated brachial artery dilation (FMD) as measured by ultrasound in subjects with impaired glucose tolerance. Moreover, endothelial-independent reactivity was unchanged. The present results are also consistent with data on dexlipotam, a tromethamine salt of R(+)-alpha-lipoic acid on endothelial function in patients with type 2 diabetes [31]. FMD increased significantly after a 4-week treatment with dexlipotam and this effect was more pronounced in subjects with poor metabolic control.

Hemodynamic conditions and metabolic parameters were improved in the subjects under study, independent of their infusion regimen. Surprisingly, this effect of rehabilitation at a specialized centre was already evident after only 2 weeks of life-style interventions and was observed in the absence of changes in concomitant drug therapy. Thus structured programmes should be initiated early in the course of type 2 diabetes and adherence to these activities stimulated. Blood pressure and blood lipids were positively influenced in both groups by the inpatient treatment at a specialized centre. However, forearm vascular reactivity was only significantly improved in the group receiving ALA. Therefore, ALA exerts positive effects in addition to standardized life-style intervention.

Limitations of our study

ALA was administered intravenously in our study. This is obviously restricted to hospitalized patients for a limited period as

in our study. Another limitation of our study might be that no further mechanistic insights in the action of ALA are provided. Therefore, it can only be speculated if the beneficial effects of ALA are caused by its antioxidative properties or by other mechanisms. Finally, forearm blood flow experiments were only performed on day 23, directly after the treatment period. The exact time point of initiation and the sustainability of ALA effects beyond day 23 remains to be elucidated.

In summary, ALA treatment improved endothelium-dependent vasodilation of the resistance vasculature in patients with type 2 diabetes. Although long-term studies with hard clinical endpoints are needed to confirm its effect, ALA could be a promising option for a new treatment or prophylaxis of cardiovascular complications.

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Disclosure

Authors have no conflict of interest to declare.

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