Glycemic and oxidative status of patients with type 2 diabetes mellitus following oral administration of alpha-lipoic acid: a randomized double-blinded placebo-controlled study

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INTRODUCTION

Diabetes mellitus (DM) is among a leading cause of illnesses for people worldwide. Both type 1 and type 2 DM are commonly found in Thailand and most patients who suffer from DM also suffer from diabetic complications including retinopathy, neuropathy and nephropathy. Emerging evidences demonstrate oxidative stress by reactive oxygen species (ROS) increase and depletion of cellular antioxidant systems in diabetic patients as a consequence of hyperglycemia. The incidence of oxidative stress has been closely linked to the occurrence of diabetic complications.¹,² Sources of oxidative stress in diabetes could originate from several pathways including glycation reactions, decompartmentalization of transition metals, and a shift of the reduced-oxygen status of the diabetic cells.³ Various reactive species are produced under hyperglycemic conditions, then, play a role in the pathological alterations. This concept of oxidative stress is now widely accepted as an important basis in the onset and progression of diabetes and its complications including retinopathy, neuropathy and nephropathy in diabetic patients.¹ Oxidative stress status in diabetes could be clearly demonstrated by the increase of some specific biomarkers such as lipid hydroperoxides, DNA adducts and protein carbonyls.

Experiments supporting the utilization of antioxidants strongly show their effectiveness in diminishing or preventing damages caused by oxidative stress in diabetes. Among those, alpha-lipoic acid (thioctic acid, 1,2-dithiolane-3-pentanoic acid, 1,2-dithiolane-3-valeric; ALA), a natural occurring potent antioxidant, has been known to exert beneficial actions against oxidative stress caused by hyperglycemia. An increase glucose uptake through recruitment of the glucose transporter-4 (GLUT 4) to plasma membranes, mimicking the action of insulin in stimulating glucose uptake as well as improvement of glucose disposal in patients with type 2 diabetes are well evidently described as principal mechanisms of ALA in...
diabetes. Moreover ALA is capable of inducing the synthesis of endogenous glutathione by reducing the glutathione precursor molecule cysteine. Together with its reduced form, dihydrolipoic acid, which also exerts powerful antioxidant activity, ALA acts to scavenge free radicals, regenerate thioredoxin, vitamin C and glutathione which in turn can recycle vitamin E. Due to its powerful antioxidant properties, ALA is particularly suited to the prevention and/or treatment of diabetic complications that arise from an excess oxidative stress.

ALA has been shown to exhibit renoprotective effects in diabetic rats not only by improving glycemic control but also its antioxidant activity. Clinical studies in humans also showed improvement in insulin sensitivity in patients with type 2 DM after oral administration of ALA, as well as the attenuation of proteinuria in patients with type 1 and type 2 DM. Administration of ALA has shown improvement in DM patients due to its antioxidative properties such as improvement in lipid profile, oxidative pattern, inflammation. Whereas a study in adolescents with type 1 DM reported no change in clinical measurement including total antioxidant status and oxidative damage. Therefore, the dose-response effects ALA on oxidative biomarkers as well as glycemic control in DM patients has still been inconclusive. To develop better understanding of the preventative and therapeutic potentials of ALA in diabetic complications, this randomized double-blind placebo-controlled study aimed to determine whether ALA is effective in controlling glycemic status and exerting antioxidant action in patients with type 2 DM by measuring its effect on glycemic control and oxidative biomarkers following a treatment period of six months.

MATERIALS AND METHODS

Volunteer subjects

Thirty eight out-patients with type 2 diabetes mellitus from the Diabetes Clinic, Warinchamrap Hospital, Thailand were enrolled in this randomized, placebo-controlled trial. Study protocol was approved by the Ethical Review Committee for Research in Human Subjects, Ministry of Public Health, Thailand and the Ethics Committee for Human Research, Khon Kaen University in accordance with the Declaration of Helsinki and the ICH-GCP. Subjects were informed about the purpose and risks of the study and informed consents were obtained prior to the initiation of the study. Inclusion criteria included glycemic status and microalbuminuria (20-200 mg/dL). Exclusion criteria were treatment with antihypertensive agents and any kind of antioxidants. Subjects were randomly divided into five groups (n = 7-8 each) to receive either placebo or different doses of ALA (300, 600, 900 or 1200 mg/day) on a double-blind basis for six months along with their regular diabetic medications (metformin, glibenclamide, combined meformin and glibenclamide or chlorpropamide) and hypoglycemic drugs were periodically adjusted by physicians. Any drop out was replaced following the same inclusion and exclusion criteria. All subjects were asked to maintain their regular life style and concomitant medication including hypoglycemic medications.

ALA capsules and placebo

Racemic alpha-lipoic acid (ALA) was purchased from Degussa (Alipure®, Italy). Capsules of 300 mg ALA and placebo were formulated and manufactured by General Drugs House Co., Ltd. (Bangkok, Thailand). Specifications of ALA capsules were tested for assay for active ingredient, weight variation, and dissolution following USP26-NF21. All products were kept in light protecting and moisture resistant containers throughout the study before given to the subjects. Subjects were instructed to take ALA or placebo capsules 30 minutes before meals followed by a glassful of water. Subjects' compliance was assessed by pill count and medication diary. Doses of ALA were divided accordingly for the dosages of 600, 900 and 1,200 mg/day. All subjects were inquired to take ALA or placebo three times per day in order to ensure the blinding process.

Clinical parameters

Laboratory parameters (fasting blood glucose, microalbumin, liver enzymes, lipid profiles and hematological parameters) were analyzed by Vitalab Selecta XL Chemistry Analyzer (Vital Scientific NV, Netherlands). Hemoglobin Alc (HbA1c) was analyzed with automated D-10 Hemoglobin Testing System (Bio-Rad Laboratories, USA).

Measurement of oxidative markers

Urinary Pgf2α-Isoprostanestes (F2α-IsoP)

Standard 8-iso prostaglandin F2α was obtained from Cayman and dissolved in DMSO. Determination of F2α-IsoP in this study was carried out using LC-MS/MS as modified from Liang et al. Briefly, all of the urine samples were aliquoted and stored at -80°C until analysis. The freshly thawed urines were mixed and centrifuged at 3,500 rpm for 10 min. Three milliliters of urine supernatant was applied on a C18 solid phase extraction (SPE) cartridge (Bond Elut C18; 3 CC/500 mg;Variant®, Harbor City, CA, USA). Previously conditioned with 5 mL of ethanol and equilibrated with 5 mL of deionized water. After washing with 5 mL of water, 5 mL of ethanol:water (5:95, v/v) and 2 mL of hexane, the cartridge was then eluted with 4 mL of ethyl acetate. The sample eluent was evaporated to dryness under a stream of nitrogen gas and reconstituted in 50 μL of acetonitrile:water (20:80, v/v) before the injection onto a column. The LC-MS/MS analysis was carried out with an Agilent 1100 LC system consisting of a degasser, a binary pump, an autosampler and a column heater. The column outlet was coupled to an Agilent MSD ion Trap XCT mass spectrometer equipped with electrospray ionization (ESI) source. Data acquisition and mass spectrometric evaluation was carried out with Data Analysis software (Bruker). For the chromatographic separation, a Zorbax XDB-C18 column (2.1x50, 3.5μm) with an identical guard column (4x10, 5μm). Mobile phase consisted of 5 mM ammonium acetate (pH 6.0) (A) and methanolic:acetonitrile (5:95, v/v) (B). The HPLC separation was carried out with a solvent gradient program of 15% to 100% B within 11 min, a linear decrease from 100-15% B within 1 min. The sample was delivered at flow rate 200 μL/min. A switch valve was used to inject
only the components eluted between 7.0-9.0 min into the mass spectrometer chamber.

The following parameters were employed throughout all MS experiments for ESI with negative ion polarity, the capillary voltage was set to 4.0 kV, the drying temperature to 350°C, the nebulizer pressure to 45 psi, and drying gas flow to 10 L/min. The maximum accumulation time was 400 msec, the scan speed was ultraclean mode and the fragmentation time was 40 ms. To determine the product ions of F2-isoP, the deprotonated ion ([M-H]-) at m/z 353 was isolated, helium gas introduced into the trap to induce collision with analyte ions and the fragments detected over a scan range of m/z 150-400. The most intensive product ion was m/z 193. Throughout all measurement, F2-isoP was detected by multiple reaction monitoring (MRM). Full method validation was conducted under the Guideline of Industry Bioanalytical Method Validation.18

Urinary 8-Hydroxy-2'-deoxyguanosine (8-OHdG)

Urine samples were aliquoted and stored at -80°C until analysis. The freshly thawed urines were mixed and centrifuged at 3500×g for 10 min to precipitate solid matters. One milliliter of urine supernatant was mixed with 1 mL of 100 mM KH2PO4 (pH 6.0) and then applied on a Varian’s Bond Elut Certify cartridge previously conditioned with 10 mL methanol, 5 mL DI water and equilibrated with 10 mL of 100 mM KH2PO4 (pH 6.0). After washing with 1 mL of 100 mM hydrochloric acid, the cartridge was dried for 5 min under full vacuum and eluted with 1 mL of 100 mM KH2PO4 (pH 6.0):NH4OH (8:2). The sample eluent was evaporated to remove NH4OH under a stream of nitrogen gas. Samples were then subsequently injected into the HPLC-ECD system. The separation of 8-OHdG was carried out on a Phenomenex® C18 column (4.6×150 mm, 5 μm) with an identical guard column (4×10 mm, 5 μm). Mobile phase consisted of 50 mM KH2PO4 (pH 6.0), 2.5% acetonitrile, 1% methanol (solvent A) and the solvent mixture for wash step contained 50% acetonitrile and 50% methanol (solvent B).

The HPLC system consisted of a binary high pressure pump (Alltech model 105, USA) and automatic sample injector (Alltech 570, USA). The electrochemical cell was equipped with a glassy carbon working electrode operated at +0.65V versus a Ag/AgCl reference electrode (Precision instruments model 105, France). The system was operated at 10 nA full range detection. Data acquisition was performed by PeakSimple 3.29 Software.

Safety monitoring

Safety evaluations of all subject volunteers were regularly monitored by local health staffs and any adverse effects were immediately reported to the doctors. A grading or severity scale is provided following the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) which displays Grade 1 through 5 with unique clinical descriptions of severity.19

Statistical analysis

Values of FBG and HbA1C were expressed as mean ± SEM whereas those of urinary F2-isoP and 8-OHdG were expressed as median (95% confident interval (CI)). Measurements compared between pre- and post-treatment of two groups (ALA-treated group vs. placebo group) were performed by using Wilcoxon signed rank test. Kruskal-Wallis analysis of variance test was used to compare among placebo and ALA-treated group. Correlation analysis for dose-dependent effect of ALA was performed by using SPSS v.17 (Pearson correlation). A p-value of less than 0.05 was considered significant.

RESULTS

Subjects’ characteristics

Table 1 showed characteristics of subjects enrolled in the study (n=38) and divided into five groups (n=7-8 each). All groups of subjects were found to be comparable in terms of means of age, period of DM and body weight despite a heterogeneity of age (44.5±0.88 years) and period of DM (2.07±0.26 years) in each individual subject. Thirty three diabetic patients (86.8%) were prescribed hypoglycemic drugs including metformin, glibenclamide, both metformin and glibenclamide, and chlorpropamide whereas five patients (13.2%) were under non-medication diet control. Number of patients received medications did not differ significantly in each group. All patients were diagnosed with mild diabetic nephropathy based on levels of urinary albumin concentration of their morning spot urine as microalbuminuria (20-200 mg/L).

Effects on fasting blood glucose and HbA1C levels

Fasting blood glucose (FBG) levels for all DM patients in this study were 131±4.16 mg/dL, reflecting the hyperglycemic status in this group of patients even with the control of hypoglycemic agents. After six months of treatment, FBG levels in the placebo group were found to be unchanged, whereas those levels in each ALA groups reduced during the course of treatment from month 0 to

Table 1. Subjects’ baseline characteristics

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>Sex (M/F)†</th>
<th>Age (yr) (mean ± SE)</th>
<th>Period of DM‡ (yr)</th>
<th>Weight (kg)</th>
<th>Fasting blood glucose (mg/dl)</th>
<th>Hypoglycemic agents (M/G/B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=8)</td>
<td>1/7</td>
<td>42.9 ± 2.52</td>
<td>1.56 ± 0.53</td>
<td>59.9 ± 2.78</td>
<td>122 ± 5.72</td>
<td>4/3/1</td>
</tr>
<tr>
<td>300 (n=8)</td>
<td>4/4</td>
<td>42.5 ± 1.12</td>
<td>1.49 ± 0.47</td>
<td>65.1 ± 1.88</td>
<td>141 ± 8.55</td>
<td>3/3/2</td>
</tr>
<tr>
<td>600 (n=8)</td>
<td>3/5</td>
<td>45.7 ± 1.68</td>
<td>1.77 ± 0.52</td>
<td>61.4 ± 2.96</td>
<td>136 ± 7.62</td>
<td>2/5/1</td>
</tr>
<tr>
<td>900 (n=7)</td>
<td>1/6</td>
<td>44.0 ± 2.00</td>
<td>3.40 ± 0.66</td>
<td>65.6 ± 5.50</td>
<td>130 ± 8.57</td>
<td>5/1/1</td>
</tr>
<tr>
<td>1,200 (n=7)</td>
<td>1/6</td>
<td>47.7 ± 2.18</td>
<td>2.33 ± 0.57</td>
<td>66.4 ± 2.35</td>
<td>125 ± 9.83</td>
<td>5/1/1</td>
</tr>
<tr>
<td>Total (n=38)</td>
<td>10/28</td>
<td>44.5 ± 0.88</td>
<td>2.07 ± 0.26</td>
<td>63.6 ± 1.43</td>
<td>131 ± 4.16</td>
<td></td>
</tr>
</tbody>
</table>

Results are shown as mean ± SE (Student t-test).
† Number of male and female subjects
‡ Years since first diagnostic of diabetic mellitus
month 6. Average means of differences between post-treatment and pre-treatment (average values at month 6 minus values at month 0) from each group were plotted and shown in Figure 1A. Only placebo group exhibited the increase of mean FBG at Month 6. Mean different values of FBG were found to be significantly correlated \((p = 0.004)\) with ALA doses, confirming dose-dependent effect of ALA in reducing FBG. When all patients in ALA groups were pooled and compared to the placebo treated group, there was a significant difference in the change of FBG \((p<0.05)\) (Figure 1B).

Similar circumstances were also observed with HbA1C. Baseline levels in ALA and placebo groups were considerably comparable with wide range of variations. After treatment with ALA for six months, only mean difference of HbA1C in the placebo group increased while the values of all ALA treatment groups were in minus ranges (less than zero), indicating the reduction of HbA1C following the administration of ALA. Due to the small sample size and high variations among the subjects, the changes between pre- and post-treatment in each group failed to reach a statistical significance. Only when all patients in the ALA groups were pooled and compared to the placebo group, was a significant difference in the change of HbA1C then observed \((p<0.05)\) (Figure 2B). Significant correlation \((p = 0.011)\) between ALA doses and HbA1C also confirmed dose-dependent effect of ALA on glycemic control in DM patients.

**Effects on oxidative markers: Urinary \(F_2\text{-isoP}\) and \(8\text{-OHdG}\)**

By combining the C18 SPE sample preparation and LC-MS/MS determination of urinary \(F_2\text{-isoP}\), we were able to detect the amount of \(F_2\text{-isoP}\) in the urine samples with limit of detection as low as 0.2 ng/mL. Method validation was fully performed in compliance with the guideline as indicated in Materials and Methods. The measurement of urinary \(F_2\text{-isoP}\) in diabetic patients showed comparable levels in all groups prior to the supplementation of ALA or placebo. Those levels were also found to be insignificantly different among male and female subjects. After six months of the treatment, no significant difference in
changes of urinary F2-isoP was seen with the administration of either ALA or placebo when compared between pre- and post-treatment. The levels of urinary F2-isoP in all ALA-treated groups, however, increased in the placebo group (median; 728.32 vs. 1,624.27 pg/mg creatinine for pre- vs. post-treatment) (Figure 3).

The other oxidative biomarker conducted in this study was urinary 8-OHdG as determined by HPLC-ECD. Figure 4 illustrates the levels of 8-OHdG before and after ALA treatment compared to the placebo group. After six months, we observed a constant level in median values of urinary 8-OHdG in the placebo group compared between month 0 and month 6. Even though there was no significant difference in changes of urinary 8-OHdG levels in the ALA groups following the treatment period, the levels of 8-OHdG showed slight reductions in median values. No significant correlation was obtained between both oxidative biomarkers (urinary F2-isoP and 8-OHdG) and other parameters (FBG, HbA1C, serum creatinine, urinary creatinine, urinary microalbumin and lipid profiles).

**Data on the clinical outcomes of the DM subjects (serum creatinine, urinary creatinine, microalbumin, lipid profiles) were not different among the placebo and the ALA-treated groups when compared after the six-month trial period. However, liver function enzymes (alanine aminotransferase; ALT and aspartate aminotransferase; AST) slightly but not significantly reduced in the ALA-treated groups in a dose-dependent manner (data not shown).** Levels of urinary microalbumin were found to be reduced in all groups, including the placebo group.

**Safety**

Most participants in this study found the intervention to be well tolerated, despite the fact that some minor adverse effects were identified and recorded as possible adverse effects caused by ALA. One patient (2.63%) voluntarily dropped out from the study due to anorexia, two patients (5.26%) reported skin rash. Those two adverse events were categorized as Grade 2 and Grade 1 based on CTCAE, respectively. Some patients reported bitter taste in the throat after swallowing ALA capsules.
DISCUSSION

This randomized double-blind placebo controlled study demonstrated the effects of oral administration of ALA ranging from 300 mg/day to 1,200 mg/day for 6 months in patients with type 2 DM. We examined both glycemic parameters – fasting blood glucose (FBG), HbA1C – as well as two reliable oxidative biomarkers – urinary F2-isop and 8-OHdG – in type 2 DM patients who constantly took hypoglycemic drugs or were under diet control.

Hyperglycemia is the most pronounced mechanism in the pathogenesis of diabetic complications, which has been evidently linked to the elevation of free radicals and depletion of antioxidants in diabetic patients. Results from the administration of antioxidant appear to prove the pathogenic concept of occurrence of oxidative stress leading to diabetic complications. Our study showed a decreasing trend of blood glucose following the administration of ALA ranging from dose 300 mg/day to 1,200 mg/day, and only the placebo group exhibited a slight increase in both FBG and HbA1C after the six-month period. From the results of this study, we did not achieve statistical significant in changes of both FBG and HbA1C when compared between pre- and post-treatment. It is likely due to a small number of subjects in each group and high variation of the values. However, results clearly showed a dose-dependently decline in both glycemic parameters and only reached significant value when compare between the placebo group with pooled treatment groups. Similar result was reported by Morcos, et al., in which, after 18 months of ALA treatment (600 mg/day),16 an increase of HbA1C was seen in the control but not ALA treated groups. Our study confirmed previous finding with additional information of dose-response effect of ALA on HbA1c.

Since insulin-resistance in peripheral tissues or impaired insulin secretion are associated with pathogenesis of type 2 DM, the main possible target to normalize glycemia and glucose homeostasis is then to enhance insulin action through the increase of glucose uptake via glucose transporter. Metformin, an antidiabetic drug, is one of
those agents found to mainly act to control blood glucose by increasing glucose transporter 4 (GLUT4) mRNA expression, providing effective mechanism for diabetes treatment. For ALA, its hypoglycemic action has also been well documented. It is postulated to be due to its action to engage the insulin-signaling pathway by enhancing muscle GLUT4 protein content, as well as increasing GLUT4 translocation to cell membranes which accelerates glucose uptake into muscle and fat cells. Therefore, it is likely that administration of ALA in DM patients who take metformin can be favorable for blood glucose controlling via the action through GLUT4.

Besides ALA action through GLUT4, oral administration of ALA was also reported to increase peripheral insulin sensitivity in DM type 1 patients and improve the impairment of endothelial function caused by hyperglycemia. Changes of glycemic control by ALA treatment appear to be a delayed process and not responsive to low dose of ALA (eg, 300 mg/day). Hahm et al reported unchanged of blood glucose and HbA1c in DM patients who received 300 mg/day ALA for 8 weeks. In our study, a slight increase in FBG and HbA1C were obtained from the placebo group but not in ALA treatment groups, including 300 mg/day group, confirming the ability of ALA to maintain blood glucose levels even at low dose if taken for a certain period of time.

Urinary F₂-isoserin, a specific biomarker of lipid peroxidation in human, was determined in this study to indicate the oxidative stress condition in type 2 DM patients both before and after ALA treatment with an acceptance of its reliability for the assessment of in vivo effects of antioxidants as well as a risk marker of diabetes. We chose to measure the levels of urinary F₂α-IsoP, instead of plasma F₂α-IsoP, to reflect systemic oxidative stress in the correlation with progressive diabetic nephropathy. This was due to the reason that increased production of F₂α-IsoP in the body did not lead to an increase in plasma F₂α-IsoP levels because of an increased elimination of this metabolite, and therefore and increased excretion in urine. While the levels of urinary F₂α-IsoP were found to be un-

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**Figure 4:** Distribution of urinary 8-OHdG levels in type 2 DM patients before and after six months of ALA and placebo administration. The lower and upper edges of the boxes are the 25th and 75th percentile, respectively. The black eclipses and lines within the boxes indicate means and medians, respectively. The lower and upper bars represent the 10th and 90th percentile. Individual values above the 90th percentile are shown as (■). The median notches of the boxes are 95% confidence interval.
changed in the ALA groups, the levels in the placebo group appeared to increase by approximately twofold (median values), indicating the possible effect of ALA to suppress the occurrence of lipid peroxidation in type 2 DM. However, the absence of a significant difference from this data could be presumably due to high variations of urinary F$_{2\alpha}$-isoP levels in the participating subjects.

The increased amount of 8-OHdG as a marker of oxidative DNA damage due to hyperglycemic status was also reported to be elevated in both plasma and tissues of streptozotocin diabetic rats$^{28}$ and accepted as a predictive factor for the progression of diabetic nephropathy.$^{29}$ Our preliminary results showed an approximate two-folds increase in the urinary 8-OHdG in diabetic patients, when compared to healthy non-diabetic subjects (data not shown), confirming the enhancement of oxidative damage to DNA in diabetic patients. However, there were no significant differences in urinary 8-OHdG levels in DM patients who received either ALA or placebo. Similar results were previously shown in adolescents with type 1 diabetes mellitus in which no significant change in oxidative damage was observed following the supplementation of ALA for 3 months.$^{30}$ Despite the extended treatment period and numerous information on antioxidant action of ALA, the absence of a potential effect against DNA damage as a result of ALA in this study could be accounted for limited ability of ALA to cope with continuous production of ROS during chronic hyperglycemia in diabetic patients.

Even though allergic skin reactions and possible hypoglycemia in diabetic patients with ALA doses over 2,000 mg/day were previously reported,$^{31}$ we found minor skin rash (Grade 1, CTCAE) in two patients (5.26%) in which one patient voluntarily continued until the completion of the trial and the other patient dropped out. Upon taking oral antihistamine, the skin rash completely disappeared within one day. Other complaints included loss of appetite as well as a bitter taste in the throat when swallowing the capsules. During the course of study, anti-diabetic drug regimens were accordingly adjusted by physicians and any hypoglycemic signs were not observed. In this study, we were unable to demonstrate a positive correlation between levels of oxidative markers and glycemic status of the subjects despite the demonstration of the correlation in other studies.$^{32}$ Explanation can be achieved via the fact that the numbers of subjects in each group were quite small. Due to the short half-life of ALA (t½ ~ 30 min),$^{33}$ we expected a greater outcome of inhibitory actions of ALA supplementation against oxidative stress in daily multiple doses regimens. However, repeated doses of ALA (two or three times per day when dosages were divided) did not demonstrate this long-lasting achievement.

By conducting a placebo-controlled trial, we were able to demonstrate a comparison between DM subjects who received ALA and those who did not (placebo group). Overall ALA effects in DM patients suggested a clear dose-response relationship and the highest dosage examined in this study (1,200 mg/d) was the most preferable for glycemic control, despite the lack of statistical significance for oxidative biomarkers. DM subjects who received this dosage were evidently beneficial from ALA administration during the course of hypoglycemic agents.

In conclusion, this present study demonstrated that oral treatment of ALA could help improve glycemic status and its slightly effective against oxidative stress in Thai patients with type 2 DM when compared to placebo with tolerable minor adverse events. The in-trend reduction of FBG and HbA1C in a dose-dependent manner (ranging from 300-1,200 mg/day) appeared to reflect advantageous action of ALA during a regular course of anti-diabetic drug regimens. Results also provide more constructive information for the use of ALA as an adjuvant therapy in type 2 DM patients who constantly take oral hypoglycemic agents. However, more patients may need to be recruited in this study to overcome high variation among subjects.

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AUTHOR DISCLOSURES

None of the authors (SP, SS, AN, JK, BH and AS) report any conflict of interest with respect to the current study.

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Original Article

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補充硫辛酸對於第 2 型糖尿病患的血糖和氧化壓力的影響：隨機雙盲對照研究

對糖尿病患而言，即使血糖獲得良好控制，仍會由於體內自由基過多而誘發併發症。此次隨機雙盲臨床對照實驗想瞭解補充硫辛酸對於糖尿病患者的血糖和氧化壓力的影響。從門診招募 38 名第 2 型糖尿病患者，隨機分配到安慰劑組或試驗組(硫辛酸劑量分別為每日 300、600、900、1200 mg)。實驗進行 6 個月。實驗期前後，測量受試者的血糖值和氧化壓力指標。實驗結果顯示隨著硫辛酸服用劑量越高，空腹血糖和糖化血色素有逐漸下降的趨勢。安慰劑組的尿中 F₂α-IsoP 濃度在實驗期後升高，服用硫辛酸者則未增加，表示硫辛酸或許有助於抑制糖尿病患者的脂肪過氧化作用。然而各組尿液中 8-OHdG 及微白蛋白濃度和血清肌酸酐並無明顯差異。安全性評估方面，受試者除一些輕微副作用外，試驗劑量都在可忍受範圍。整體而言，硫辛酸有利於改善糖尿病患者的血糖值，也對防止氧化傷害稍有效益。

關鍵字：硫辛酸、糖尿病、PGF₂α-Isoprostanes(F₂α-IsoP)、8-羥脫氧鳥苷(8-OHdG)、氧化壓力