

Safety test of a supplement, 5-aminolevulinic acid phosphate with sodium ferrous citrate, in diabetic patients treated with oral hypoglycemic agents

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ABSTRACT

Objective: This study aimed to examine the safety of 5-aminolevulinic acid phosphate (5-ALA) with sodium ferrous citrate (SFC) in diabetic patients treated with one or more oral hypoglycemic agents (OHAs).

Background: Recent intervention studies performed in the USA and Japan have shown that a nutritional supplement of 5-ALA with SFC efficiently reduced blood glucose levels in pre-diabetic population without any adverse events. Thus, it was anticipated that 5-ALA with SFC may potentially be taken as a beneficial supplement by diabetic patients who were being treated with OHA therapy. Nevertheless, it is important to examine its safety and efficacy in diabetic population.

Methods: This study was a prospective single-blinded, randomized, placebo-controlled and parallel-group comparison study. Medically treated diabetic patients between the ages of 30 and 75 were recruited from the Tokyo metropolitan area of Japan and 45 subjects were selected after screening. These subjects were randomly assigned to three groups: daily intake of 15mg 5-ALA, 50mg 5-ALA, and a placebo (n=15, respectively). The supplement or placebo was administered for 12 weeks followed by a four week washout period. The primary endpoint was safety and

occurrence of hypoglycemic attack, while the secondary endpoint was changes of fasting blood glucose (FBG) and hemoglobin A1c (HbA1c).

Results: Adverse events related to 5-ALA with SFC were not observed in all the groups. Abnormalities in blood and urine tests were not observed either. Significant decrease in FBG was not detected in all the groups. However, there was a small but significant decrease in HbA1c at 4 and 8 week in the 15 mg 5-ALA group. Significant decrease in HbA1c was not observed in the 50 mg 5-ALA group, although a tendency to decrease after 4 weeks was apparent.

Conclusion: 5-ALA with SFC is a safe and potentially beneficial supplement if taken by diabetic patients treated with OHAs.

Trial registration: UMIN 000008038

Key words: type 2 diabetes, 5-aminolevulinic acid (5-ALA), sodium ferrous citrate (SFC), oral hypoglycemic agent (OHA), hemoglobin A1c (HbA1c), fasting blood glucose (FBG)

INTRODUCTION:

The number of diabetic patients, especially those with type II diabetes, has been expanding in Japan [1] as in other countries recently [2, 3]. The main causes of increase in type II diabetes are considered to be excessive calorie intake and shortage of exercise. Inadequate management of diabetes leads to the development of complications, such as retinopathy, nephropathy, and neuropathy, which deteriorate the quality of life and shorten life expectancy. Incidence of diabetic complications can be reduced if appropriate treatments are performed by maintaining HbA1c levels below 7.0% and blood glucose levels close to normal [4]. However, a large number of diabetic patients, treated with OHAs or insulin injections with controls that do not satisfy these criteria, exist.

Dietary supplements are widely used in Japan but since they are intended to be taken by healthy people for the maintenance and promotion of health, it is important that tests for safety are performed on healthy and borderline subjects. Next, if dietary supplements are to be administered to medically treated patients, safety tests are imperative as otherwise there is possibility that that it would worsen the disease. However it appears that the issue of safety with dietary supplement has not been attended properly as adverse events with the use of dietary supplements have been frequently reported both in healthy people and disease patients [5-11].

Disease exacerbation caused by dietary supplements has become a growing concern in Japan, so it is critical to examine the safety of dietary supplements in patients in addition to healthy subjects.

It has recently been shown that a dietary supplement, 5-aminolevulinic acid phosphate (5-ALA) with sodium ferrous citrate (SFC), reduces blood glucose level in pre-diabetic populations without adverse events in the USA and Japan [12, 13]. 5-ALA is a natural amino acid and it is a precursor of heme, a major component of hemoglobin and myoglobin. 5-ALA is also an essential constituent of cytochromes and thus, it is important for cellular energy production in mitochondria [14]. It has been shown that exogenously applied 5-ALA with SFC increases the activity of complex IV in the mitochondrial electron transport chain in experimental animals [14] and increases the basal metabolic rate and suppresses fat accumulation in rats [15]. These findings appear to be compatible with the blood glucose lowering effect of pre-diabetes in humans [12, 13]. Therefore if diabetic patients take 5-ALA supplement in addition to OHAs or insulin, there might be a risk of reducing blood glucose to a level that triggers hypoglycemia (hypoglycemic attack). Since 5-ALA is readily accessible to diabetic patients without a physician's prescription, it is desirable to obtain the safety test data of 5-ALA in these patients. Based on this consideration the present study was performed.

METHODS:

Study design. This study was a prospective single-blinded, randomized, placebo-controlled and parallel-group comparison study. The study protocol was approved by the Institutional Review Board (IRB) of the Institute of Medical Science, University of Tokyo, Japan and registered to University Hospital Medical Information Network (UMIN) as UMIN000008038.

Diabetic patients treated with one or more OHAs were recruited from the patient panel of TES Holdings Co. Ltd. by internet advertisement. Total number of the registered patients was about 1000 and 81 candidates applied to this study from Tokyo metropolitan area of Japan. OHAs included sulfonylurea, DPP-4 inhibitor, α -glucosidase inhibitor, metformin, pioglitazone, glinide and GLP-1 analogue. The inclusion criteria for the diabetic patients were: (1) between the ages of 30 and 75 from whom written consent was obtained, (2) treated with OHAs, (3) without hypoglycemic attack for 3 months before inclusion, and (4) whose diabetic medication not to be altered during the study period. The exclusion criteria for the diabetic patients were: (1) treated with insulin, (2) with porphyria, hemochromatosis or viral hepatitis, (3) pregnant or possibly pregnant, (4) photo-hypersensitive, (5) enrolled in another clinical trial, or had a history of enrollment in another

trial in the past 3 months, (6) taking anti-convulsant, anti-arrhythmic agents or coronary vasodilators, (7) allergic to drugs or food, (8) severely anemic (hemoglobin (Hb) < 8 mg/dl), (9) uncontrolled dependent on alcohol, and (10) severely psychotic patients. Patients deemed inappropriate to this study were judged by the principal investigator.

Primary endpoint of this study was safety and occurrence of hypoglycemic attack (defined by symptoms including abnormal sensation of hunger, anxiety, palpitation, sweating, and tremor, which could be improved by glucose ingestion). Secondary endpoint was the changes of FBG and HbA1c. The study period was from July 2012 to June 2013, and data were finally summarized in December 2013. The Data and Safety Monitoring Committee approved the results and the conclusion of this study in April 2014.

Patient selection and study schedule. Eighty-one candidates applied to this study. Because the recommended dose of 5-ALA with SFC as a supplement is 15 mg/day in Japan, we have chosen this dose as a low dose and 50 mg/day as a high dose. After the screening examination, 45 patients were selected and randomized equally to one of the three study groups according to age, sex, sulfonylurea, and HbA1c: (1) low dose 5-ALA with SFC (15 mg 5-ALA and 17.2 mg SFC daily); (2) high dose 5-ALA with SFC (50 mg 5-ALA and 57.4 mg SFC daily); and (3) control (placebo capsule with identical color and size). All participants provided signed, informed consent according to the Declaration of Helsinki before enrolling in the study. Study subjects were administered with test or placebo capsules, and follow-up examinations were carried out 4, 8, and 12 weeks after the baseline examination. At week 16, a follow-up examination was carried out. Every examination included a medical interview, physical examination, measurement of blood pressure, pulse rate and body weight, blood test, urinalysis, and a dietary survey. A daily diary was used to monitor adverse events.

Blood and urine samples were obtained during a fasting state in the morning. Blood test consisted of blood count (WBC, RBC, Hb, Ht, MCV, MCH, MCHC, platelet) and blood chemistry (total protein, albumin, BUN, creatinine, uric acid, AST, ALT, γ -GTP, ALP, LDH, CPK, TG, LDL-cholesterol, HDL-cholesterol, total bilirubin, Na, K, Cl, Fe, FBG, HbA1c, glycosylated albumin, lactic acid, insulin and transferrin). Urinalysis included pH, urobilinogen, occult blood, bilirubin, ketone, glucose, protein, creatinine and 8-hydroxy-2'-deoxyguanosine (8-OHdG).

Statistical Analysis. With regard to the occurrence of hypoglycemic attack, differences among

three groups were examined by Fisher’s exact test. Differences in blood glucose and HbA1c were examined by two way factorial analysis of variance. Differences in quantitative data of blood count and chemistry were examined by two way factorial analysis of variance, and difference in qualitative data was examined by Fisher’s exact test.

RESULTS:

Characteristics of patients in the present study are shown in Table 1. Age and sex, and the baseline body weight, BMI, systolic & diastolic blood pressure, and heart rate were not significantly different among three groups. The numbers of oral hypoglycemic agents were 2.13 ± 1.03 (mean ± SD) in the 15 mg 5-ALA group, 2.00 ± 1.00 in the 50 mg 5-ALA group, and 1.93 ± 0.91 in the control group. Content of oral hypoglycemic agents and the number of patients are shown in Table 1.

Table 1. Baseline characteristics of three groups

	5-ALA 15 mg		5-ALA 50mg		placebo	
	mean	SD	mean	SD	mean	SD
Age (years)	60.5	7.8	60.3	8.8	60.9	8.0
Sex						
Male	12		12		12	
Female	3		3		3	
Body weight (kg)	66.63	9.63	65.89	11.01	68.51	12.13
BMI (kg/m ²)	23.83	3.04	24.16	2.52	25.08	2.67
Systolic blood pressure (mmHg)	123.1	13.9	119.6	14.9	117.9	13.4
Diastolic blood pressure (mmHg)	77.3	9.2	75.1	5.9	73.2	9.1
Heart rate (/min)	75.3	11.3	75.7	11.1	74.3	14.8
Number of anti-diabetic drugs	2.13	1.09	2.00	1.00	1.93	0.91
Content of drugs	no. of patients		no. of patients		no. of patients	
sulfonylurea	9		11		10	
DPP-4 inhibitor	10		7		9	
metformin	5		2		2	
α-glycosidase inhibitor	4		6		6	
pioglitazone	3		4		1	
glinide	1		0		0	
GLP-1 agonist	0		0		1	

Combination drugs composed of two OHAs were prescribed to two patients. Each component was counted as a single drug in Table 1. It appeared that the prescribed drugs were not biased among the three groups. Blood count, blood chemistry and urinalysis were neither

significantly different among the groups. Representative data are shown in Table 2. Evaluation of the primary endpoint (safety and hypoglycemic attack) was performed on candidates who took 5-ALA with SFC more than once, and that of the secondary endpoint was performed for those who completed the entire study. The primary endpoint could be assessed in all 45 subjects while the secondary endpoint could be assessed in 37 subjects. The numbers of dropout subjects were two in the 15 mg 5-ALA group, five in the 50 mg 5-ALA group, and one in the control group. The reasons for dropout were changes of oral hypoglycemic agents determined by the physician in charge, difficulty to continue visit for this study or occurrence of transient ischemic attack (TIA).

Table 2. Baseline laboratory data of three groups

	5-ALA 15 mg (n=15)		5-ALA 50mg (n=15)		placebo (n=15)	
	mean	SD	mean	SD	mean	SD
WBC	5973.3	1255.5	6266.7	1784.3	6326.7	1612.7
Hb	13.83	1.38	14.52	0.96	14.23	1.29
Plt	21.25	4.82	23.15	5.35	21.66	6.39
TP	7.29	0.40	7.30	0.30	7.30	0.37
Alb	4.41	0.20	4.43	0.26	4.52	0.28
BUN	15.2	3.7	14.2	4.0	15.1	5.0
creatinine	0.825	0.170	0.806	0.174	0.841	0.164
UA	5.70	1.18	5.35	1.12	5.50	1.50
AST	19.9	10.3	20.4	5.7	21.2	6.5
ALT	20.3	11.7	23.2	10.7	24.3	10.4
r-GTP	30.4	20.9	33.3	24.4	36.9	25.3
ALP	196.7	39.8	212.5	62.5	211.4	56.1
LDH	175.1	18.8	177.3	29.7	179.2	25.7
TG	133.2	73.3	125.1	91.8	127.6	76.1
LDL	115.3	28.8	115.0	37.1	118.1	30.9
HDL	49.5	8.3	53.5	16.7	53.7	11.7
Fe	95.6	31.0	113.5	31.9	109.3	32.0
fasting blood glucose	136.3	31.1	131.0	16.2	134.2	27.1
HbA1c	7.01	1.08	6.92	0.53	7.05	0.91
glycoalbumin	19.63	3.67	18.93	3.50	18.19	3.55
insulin	7.08	6.37	5.55	2.41	6.37	3.04
8-OHdG	12.92	5.64	15.18	7.53	11.79	8.90

TIA occurred in one subject when he was on the train during the visit to our hospital. TIA persisted for only a few minutes and his consciousness was fully recovered. It was the 29th day after taking 15 mg 5-ALA with SFC. It was concluded that TIA was ascribed to atherosclerosis of the brain artery and not to the test supplement. However, this subject was excluded from the study as decided by the principle investigator. Seventeen days after the termination of the study, stomach bleeding occurred in another subject. He checked in the hospital and blood transfusion

was carried out. After 6 days he was recovered and discharged. This event was categorized as a serious adverse event and it was reported to IRB. However, since this subject belonged to the control group this adverse event was not related to 5-ALA with SFC. No adverse events related to 5-ALA with SFC was observed in the test groups. Abnormalities in blood and urine tests were not observed.

The secondary endpoint of this study was the change of FBG and HbA1c. It was evaluated in 13 subjects in the 15 mg 5-ALA group, 10 subjects in the 50 mg 5-ALA group, and 14 subjects in the control group (the number of subjects is different between Table 1 and Table 3). Significant decrease in FBG was not detected in all groups but a small increase at week 12 in the 50 mg 5-ALA group was observed (Table 3). A small but significant decrease in HbA1c was found at week 4 and 8 in the 15 mg 5-ALA group. Serum insulin levels appeared to decrease at week 4, 8, and 12 in the 15 mg 5-ALA group, but the change was not statistically significant. A significant decrease in HbA1c was not observed in the 50 mg 5-ALA group, although it showed a tendency to decrease after 4 weeks.

Table 3. Changes of fasting blood glucose, HbA1c, and insulin

	Before	4 week	8 week	12 week	washout
Fasting blood glucose (mg/dl)					
5-ALA 15mg (n=13)	136.7±9.2	128.4±6.7	131.0±7.3	134.5±6.8	138.4±7.3
5-ALA 50 mg (n=10)	128.2±4.4	123.4±5.2	128.7±4.1	142.1±6.8*	135.5±8.0
placebo (n=14)	133.4±7.5	130.6±6.7	129.1±3.9	138.0±4.8	137.8±5.7

* significant $p < 0.05$ as compared to before intake of 5-ALA

	Before	4 week	8 week	12 week	washout
HbA1c (%)					
5-ALA 15mg (n=13)	7.14±0.31	6.94±0.28*	6.89±0.23*	6.98±0.24	7.06±0.26
5-ALA 50 mg (n=10)	6.88±0.17	6.70±0.12	6.80±0.13	6.85±0.18	7.07±0.20
placebo (n=14)	7.09±0.25	7.03±0.20	6.98±0.20	7.05±0.17	7.15±0.20

* significant $p < 0.05$ as compared to before intake of 5-ALA

	Before	4 week	8 week	12 week	washout
Insulin					
5-ALA 15mg (n=13)	5.41±3.32	4.43±1.89	4.78±2.45	4.38±2.17	5.45±2.60
5-ALA 50 mg (n=10)	5.89±2.28	5.59±1.83	4.76±2.18	5.57±2.40	4.99±1.75
placebo (n=14)	6.46±3.13	5.89±2.41	7.84±5.58	6.71±3.53	7.41±3.41

Data are expressed as mean ± SD.

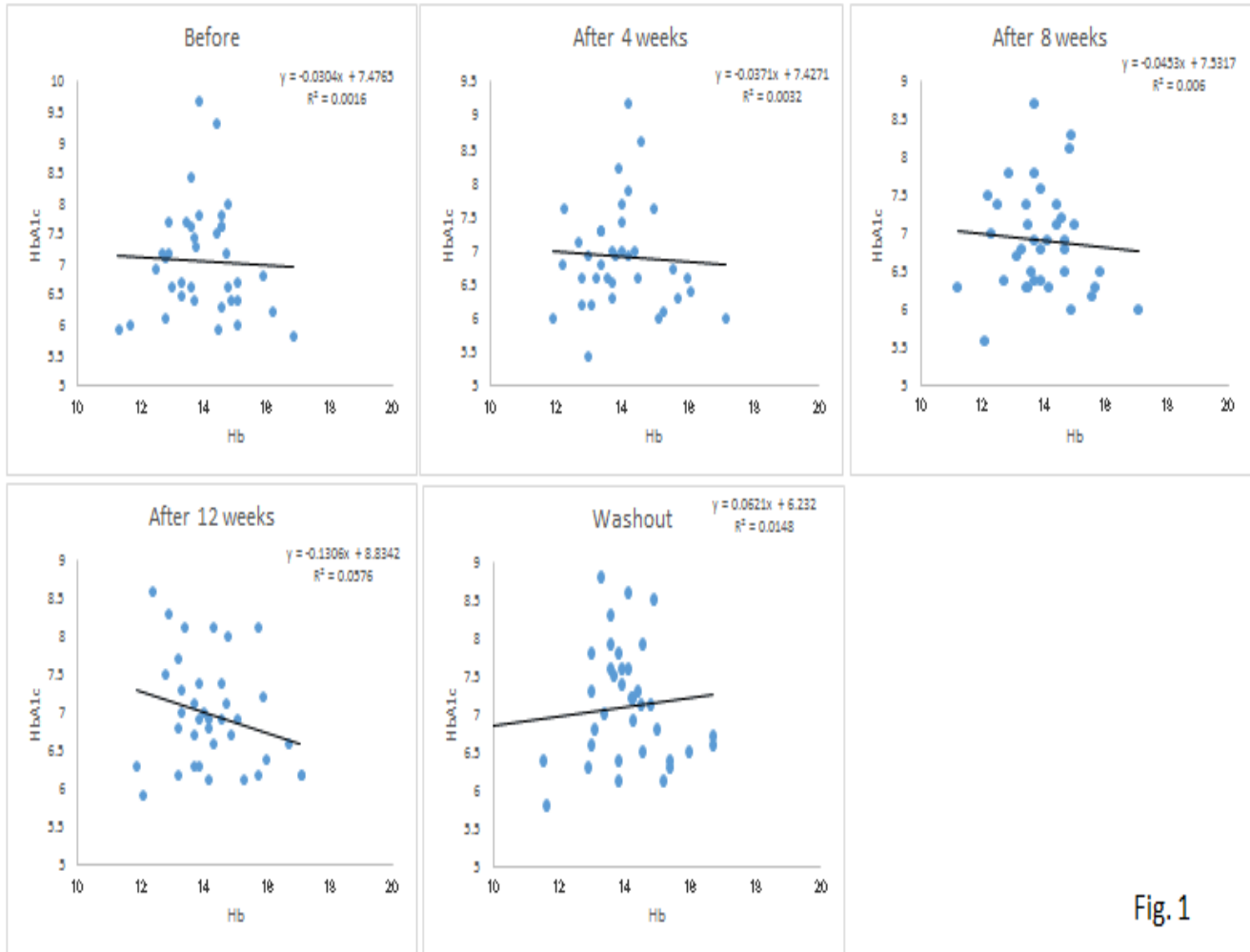


Fig. 1

Figure 1. Relationship between hemoglobin and HbA1c during study period. The ordinate (Hb) indicates the hemoglobin concentration and the abscissa (HbA1c), HbA1c level. Each point corresponds to the data from one subject who completed the study. Some symbols overlapped each other among subjects.

Since 5-ALA is a precursor of heme and SFC was included in the supplement, it was plausible to speculate that the intake of this supplement would have changed Hb, which, in turn, affected the HbA1c level. However, no significant changes of serum iron and Hb were observed during the study period among all the groups. We further analyzed the relationship between Hb and HbA1c, and that between glycosylated albumin and HbA1c. As shown in Figure 1, there was little correlation between Hb and HbA1c. On the contrary, HbA1c was strongly correlated to glycosylated albumin, which is not affected by serum iron or Hb [16] (Figure 2). These results indicate that HbA1c correctly represented the changes of blood glucose level.

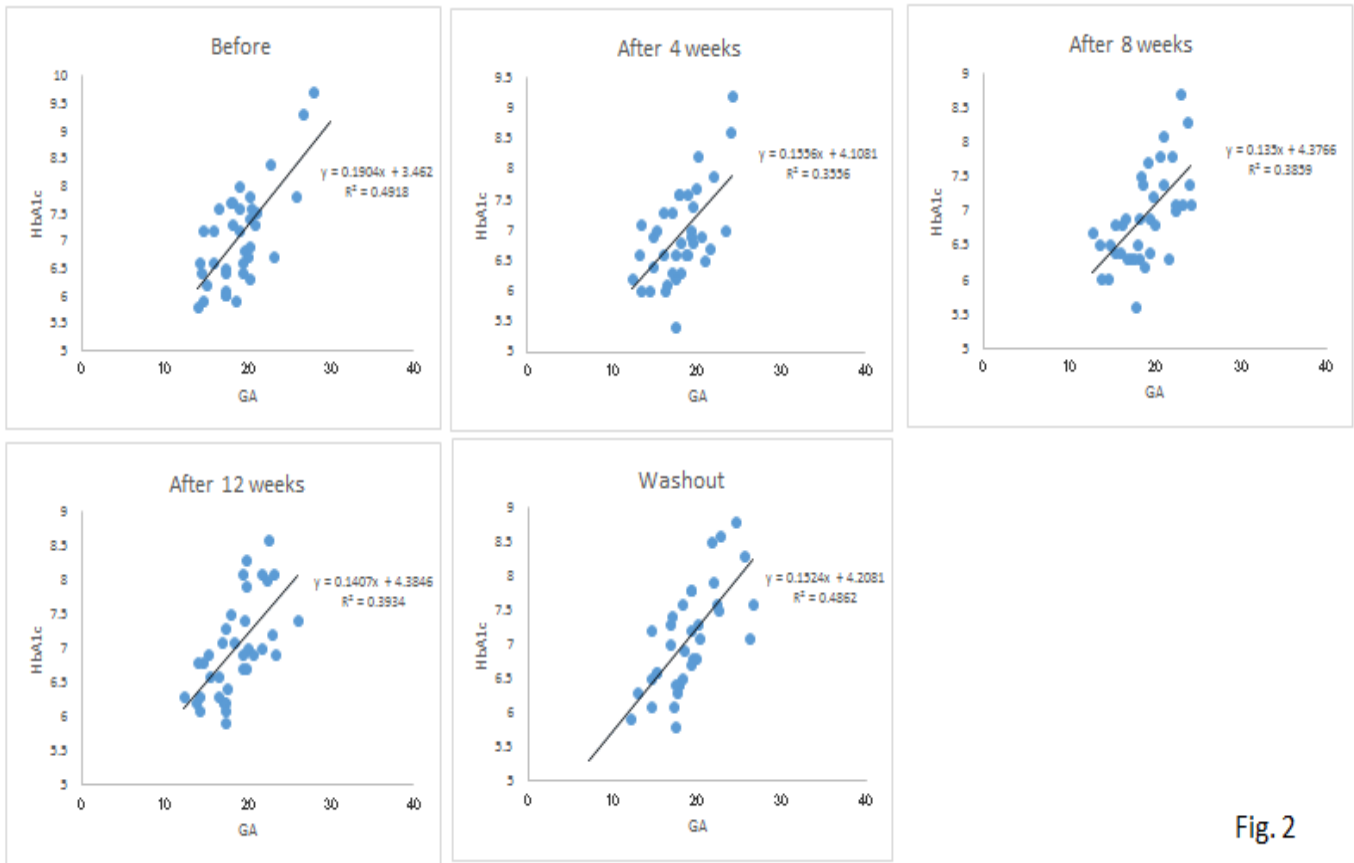


Fig. 2

Figure 2. Relationship between glycosylated albumin and HbA1C during study period. The ordinate (GA) indicates glycosylated albumin level and the abscissa (HbA1c), HbA1c level. Each point corresponds to the data from one subject who completed the study. Some symbols overlapped each other among subjects

DISCUSSION:

The results of the present study showed that the supplemental use of 5-ALA with SFC appears to be safe for diabetic patients who are treated with OHAs. However the number of the subjects in this study is small, a larger scale study is necessary to draw a clear conclusion. In the Hawaii study (n=154), 5-ALA with SFC significantly reduced blood glucose level after a two h oral glucose tolerant test (OGTT) in pre-diabetic participants [12]. The effect was especially prominent among the subjects with baseline of two h OGTT levels greater than 140 mg/dl both in the 15 mg and 50 mg 5-ALA groups. In the Hiroshima study (n=212), 15 mg 5-ALA with SFC significantly reduced all of the fasting glucose level, glycosylated albumin, and blood glucose level after two h of OGTT in mildly hyperglycemic participants [13]. Thus, it has been demonstrated that 5-ALA with SFC improves glucose metabolism in pre-diabetic subjects.

5-ALA with SFC is a supplement available at drug stores without a doctor's prescription and therefore it is probable that medically treated diabetic patients purchase this supplement, and take it in addition to prescribed drugs. In such occasion, the additional use of 5-ALA with SFC might lead to hypoglycemia or other adverse effects in diabetic patients who are under medical treatment. Therefore, the purpose of our study was designated to examine the safety and the occurrence of hypoglycemic attack. Our study revealed adverse events were not triggered by 5-ALA with SFC with absence of hypoglycemic attack in type II diabetes patients who were under medicinal treatment with OHAs.

The HbA1c level, which was set as the secondary end point in this study, was significantly reduced at 4 and 8 weeks in the 15 mg 5-ALA group. Serum insulin did not increase at 4 or 8 weeks but rather decreased during these periods, suggesting that 5-ALA improved the glucose metabolism via insulin-independent fashion. HbA1c showed a decrease in the 50 mg 5-ALA group but the change was not statistically significant. The average decrease in HbA1c by 5-ALA with SFC was less than 0.25% (range: 0.03-0.25%). It has been previously reported that the reduction of HbA1c was from 0.2 to 2% by metformin [17], 0.5 to 1.5% by sulfonylurea [17, 18], that by α -glucosidase inhibitor, up to 1% [17], that by DPP-4 inhibitors, 0.6 to 1% [19-22], and 0.5 to 1.1% by GLP-1 analogue [22]. Furthermore a meta-analysis of the treatment of type II diabetes with dietary fiber has revealed that intervention by dietary fiber had an effect of HbA1c with an average decrease of 0.26% [23], while another meta-analysis of dietary supplement cinnamon showed a 0.09 % decrease in mean HbA1c [24]. Taken together, the effect of 5-ALA with SFC on HbA1c in diabetic patients appears to be lower than those by OHAs and comparable to dietary supplements. It has been long established that exercise and diet are beneficial to diabetes mellitus. Exercise for more than 8 months significantly reduces HbA1c by 0.66% without significant decrease of body weight [25]. Nutrition therapy was shown to be able to reduce HbA1c by 1 to 2% in type II diabetic patients [26, 27]. Thus, exercise and diet are very effective to control blood glucose level in diabetes. This observation was applicable even in the case in healthy people and pre-diabetic subjects.

In the present study, the intake of 5-ALA with SFC did not alter serum iron concentration and Hb. Therefore, the decrease of HbA1c by 5-ALA with SFC was not ascribed to the change of Hb. It was apparent that there was a close relationship between HbA1c and glycosylated albumin as shown in this study, and therefore it was considered that HbA1c correctly reflected the change of blood glucose level. Although HbA1c significantly decreased after 4 and 8 weeks in the 15 mg 5-ALA group, no significant change was observed in glycosylated albumin. It was

speculated that probably HbA1c is sensitive to blood glucose alteration more than glycosylated albumin. In the Hiroshima study, 5-ALA significantly decreased the glycosylated albumin in pre-diabetic subjects, but no significant change was observed in HbA1c [13]. The authors discussed that glycosylated albumin reflects the rapid change of blood glucose levels as compared to HbA1c, and that glycosylated albumin reflects postprandial glucose change better than HbA1c, which is represented by the significant decrease of the glucose level at two h of OGTT [13]. In the Hawaii study, there was a tendency that 5-ALA with SFC decreased HbA1c in pre-diabetic subjects although it was not statistically significant ($p=0.07$) [12]. Glycosylated albumin also tended to decrease by 5-ALA with SFC, but similar to our study, it appeared that HbA1c was more sensitive than glycosylated albumin ($p=0.22$). However it is a premature state to at present to speculate the cause for the discrepancy of the relationship between HbA1c and glycosylated albumin among three studies.

5-ALA with SFC has been shown to increase the metabolic rate in rats [15] and humans [Horiuchi et al. unpublished results]. It was anticipated that the application of 5-ALA with SFC would decrease body weight, but a significant decrease was not detected in either of the 5-ALA groups. Because the duration of the test period was 12 weeks, a longer application of 5-ALA might possibly exert some effect on body weight. It is also possible that body weight change may not be clearly detected in Japanese diabetic patients, because more than half of the diabetic patients are non-obese [28] as in other East Asian countries [29].

In summary, 5-ALA with SFC can be safely taken by diabetic patients treated with OHAs. 5-ALA with SFC showed some activity on HbA1c in diabetic patients, but the symptoms ascribed to hypoglycemia were not observed. The number of applicants and test period were limited in this study, and a larger scale and longer follow-up study are deemed necessary to establish the safety of 5-ALA with SFC and its effect on glucose metabolism in diabetic patients.

Competing interests: Dr. Yamashita and Dr. Watanabe have no conflict of interest. Mr. Kondo, Mr. Kawata, Dr. Tanaka, and Dr. Nakajima are employees of SBI Pharmaceuticals.

Authors Contributions: All authors contributed to this study.

Abbreviations: 5-ALA, 5-aminolevulinic acid ; SFC, sodium ferrous citrate; OHA, oral hypoglycemic agent; HbA1c, hemoglobin A1c; FBG, fasting blood glucose; OGTT, oral glucose

tolerance test; BMI, body mass index; TIA, transient ischemic attack; UMIN, University Hospital Medical Information Network; IRB, Institutional Review Board.

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REFERENCES:

1. Ministry of Health, Labour and Welfare of Japan, National Health and Nutrition Survey 2007. <http://www.mhlw.go.jp/bunya/kenkou/eiyou09/01.html>.
2. Chan JC, Malik V, Jia W, Kadowaki T, Yajnik CS. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* 2009; 301: 2129-2140.
3. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract* 2009; 94: 311-321.
4. American Diabetes Association, *Living with Diabetes, Treatment and Care*, 2009. <http://www.diabetes.org/living-with-diabetes/treatment-and-care/>
5. Cerda C, Bruguera M, Pares A. Hepatotoxicity associated with glucosamine and chondroitin sulfate in patients with chronic liver disease. *World J Gastroenterol* 2013; 19:5381-4.
6. Licata A, Macaluso FS, Craxi A. Herbal hepatotoxicity: a hidden epidemic. *Inter Emergen Med* 2013; 8:13-22.
7. Martin DJ, Partridge BJ, Shields W. Hepatotoxicity associated with the dietary supplement N.O.-XPLODE. *Ann Intern Med* 2013; 159:503-4.
8. Kuehn BM. Dietary supplement linked to cases of acute hepatitis. *JAMA* 2013; 310:1784.
9. Bunchorntavakul C, Reddy KR. Herbal and dietary supplement hepatotoxicity. *Aliment Pharmacol Therapeut* 2013; 37:3-17.
10. Patel DN, Low WL, Tan LL, Tan MM, Zhang Q, Low MY, Chan CL, Koh HL. Adverse events associated with the use of complementary medicine and health supplements: an analysis of reports in the Singapore Pharmacovigilance database from 1998 to 2009. *Clin Toxicol* 2012; 50:481-9.
11. Fujioka K, Yu Y. Vomiting from multivitamins: a potential drug interaction. *Greenway F. Am J Therapeut* 2011; 18:453-7.
12. Rodriguez BL, Curb JD, Davis J, Shintani T, Perez MH, Apau-Ludlum N, Johnson C, Harrigan RC. Use of the dietary supplement 5-aminiolevulinic Acid (5-ALA) and its

relationship with glucose levels and hemoglobin A1c among individuals with prediabetes.

Clin Translation Sci 2012; 5: 314–320.

13. Higashikawa F, Noda M, Awaya T, Tanaka T, Sugiyama M. 5-aminolevulinic acid, a precursor of heme, reduces both fasting and postprandial glucose levels in mildly hyperglycemic subjects. *Nutr* 2013; 29: 1030-1036.
14. Maruyama K, Hagiya Y, Sugiyama Y, Tsuchiya K, Takahashi K, Abe F, Tabata K, Okura I, Nakajima M, Tanaka T, Ogura S. The effect of 5-aminolevulinic acid on cytochrome c oxidase activity in mouse liver. *BMC Res Notes* 2011; 4: 66.
15. Shimamura Y, Horinouchi I, Matsuda S, Tsuchiya K, Miyanari S, Kobayashi Y, Kuwahata M, Kido Y. Possibility of 5-aminolevulinic acid for nutritional supplement; Suppression of visceral fat accumulation in rats. In *Aminolevulinic acid: Science, Technology and Application* (Eds. Ichiro Okura, Tohru Tanaka) SBI ALA promo and Tokyo Institute of Technology Press, 2011, pp.109-116.
16. Koga M, Kasayama S. Clinical impact of glycated albumin as another glycemic control marker. *Endocr J* 2010; 57: 751–62.
17. Sherifali D, Nerenberg K, Pullenayegum E, Cheng JE, Gerstein HC. The effect of oral antidiabetic agents on A1c levels: a systematic review and meta-analysis. *Diabetes Care* 2010; 33: 1859-64.
18. Hirst JA, Farmer AJ, Dyar A, Lung TW, Stevens RJ. Estimating the effect of sulfonylurea on HbA1c in diabetes: a systematic review and meta-analysis. *Diabetol* 2013; 56: 973-84.
19. Inagaki N, Watada H, Murai M, Kagimura T, Gong Y, Patel S, Woerle HJ. Linagliptin provides effective, well-tolerated add-on therapy to pre-existing oral antidiabetic therapy over 1 year in Japanese patients with type 2 diabetes. *Diabetes Obesity Metabol* 2013; 15: 833-43.
20. Kadowaki T, Kondo K. Efficacy, safety and dose-response relationship of teneligliptin, a dipeptidyl peptidase-4 inhibitor, in Japanese patients with type 2 diabetes mellitus. *Diabetes Obesity Metabol*. 2013; 15: 810-818.
21. Cai L, Cai Y, Lu ZJ, Zhang Y, Liu P. The efficacy and safety of vildagliptin in patients with type 2 diabetes: a meta-analysis of randomized clinical trials. *J Clin Pharm Therapeut* 2012; 37: 386-398.
22. Umpierrez GE, Meneghini L. Reshaping diabetes care: the fundamental role of dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists in clinical practice. *Endocr Pract* 2013; 19: 718-28

23. Post RE, Mainous III AG, King DE, Simpson KN. Dietary fiber for the treatment of type 2 diabetes mellitus: a meta-analysis. *J Am Board Fam Med* 2012; 25: 16-23;
24. Akilen R, Tsiami A, Devendra D, Robinson N. Cinnamon in glycaemic control: systematic review and meta analysis. *Clin Nutr* 2012; 31: 609-15.
25. Boulé NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA* 2001; 286: 1218-27.
26. Pastors JG, Warshaw H, Daly A, Franz M, Kulkarni K. The evidence for the effectiveness of medical nutrition therapy in diabetes management. *Diabetes Care* 2002; 25: 608-613.
27. Pastors JG, Franz MJ, Warshaw H, Daly A, Arnold MS. How effective is medical nutrition therapy in diabetes care? *J Am Diet Assoc* 2003; 103: 827-831.
28. Kushiyama A, Yoshida Y, Kikuchi T, Suzawa N, Yamamoto M, Tanaka K, Okayasu M, Tahara T, Takao T, Onishi Y, Kawazu S. Twenty-year trend of increasing obesity in young patients with poorly controlled type 2 diabetes at first diagnosis in urban Japan. *J Diabetes Invest* 2013; 4: 540–545.
29. Kodama K, Tojjar D, Yamada S, Toda K, Patel CJ, Butte AJ. Ethnic differences in the relationship between insulin sensitivity and insulin response: a systematic review and meta-analysis. *Diabetes Care* 2013; 36: 1789-1796.