Journal of Complementary and Integrative Medicine

Volume 6, *Issue* 1 2009 *Article* 32

Effects of R-Alpha Lipoic Acid on HbA1c, Lipids and Blood Pressure in Type-2 Diabetics: A Preliminary Study

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Abstract

R-alpha lipoic acid (R-ALA) supplementation improves blood glucose in diabetic animals, but there have been no long-term clinical trials in humans testing its use for glucose control (HbA1c). This double-blind study pre-/post-test control group (PL) design sought to determine the effect of R-ALA on HbA1c. Twenty type-2 diabetics were randomly assigned to 200 mg capsules of R-ALA (n=13; 8M 5F) or PL (n=7; 2M 5F) 3 times daily, 30 minutes before meals (600 mg total) for 91 days. Samples were obtained for HbA1c at baseline and day 91. No significant differences between R-ALA and PL groups were found at baseline or day 91. However, three distinct reactions to the supplement were noted. The first group (n=3) responded to R-ALA with a >25% drop in HbA1c range from 6.1-12.5 to 6.2- 9.0 mg/dL and/or halved their anti-diabetic medication. The second group (n=5) had no change in HbA1c. The third group (n=5) had changes in medication or concurrent chronic adverse events that should have raised HbA1c, but did not beyond that of the placebo. Conclusions: Three months of R-ALA supplementation may lower HbA1c in a small number of individuals. However, to further confirm these findings, larger studies of longer duration are needed.

KEYWORDS: blood sugar, R-alpha lipoic acid, HbA1c

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*The authors would like to thank Michelle Herzau for her support with manuscript preparation and Glucorell, Inc., (Orlando, Florida) for provision of the R-ALA and PL.

INTRODUCTION

Type-2 diabetes may account for 90–95% of all diagnosed cases of diabetes, and is a progressive disease that often is present long before it is diagnosed (Franz, 2003). It is characterized by insulin resistance, which results in a delayed insulin response, ineffective suppression of glucose production in the liver, and decreased uptake of glucose by the cells. Subsequently, hyperglycemia and hyperinsulinemia ensue contributing to obesity, dyslipidemia, hypertension and atherosclerosis (Franz, 2003). Blood glucose levels are more difficult to control when insulin resistance is present (Cline, et al. 1999). The Diabetes Control and Complication Trial (DCCT, 1993) and a study by Franz (1995) both noted that a decreased control of blood glucose increased the severity and incidence of diabetic complications.

Alpha-lipoic acid (ALA) exists in two enatiomers, the natural form R-alpha lipoic acid (R-ALA) and the synthetic form S-alpha lipoic acid (S-ALA), which differ in pharmacological activity in the human body (Breithaupt- Grögler, et al. 1999). R-ALA is synthesized in the mitochondria (Packer, et al. 2001; Evans and Goldfine, 2000; Jordan and Cronan, 1997). Chemical synthesis of ALA results in a racemic (RAC-ALA) mixture of about 50% R-ALA and 50% S-ALA. There is evidence that supplemental RAC-ALA decreases insulin resistance in type 2 diabetics. RAC- ALA increases glucose uptake into the cell (Jacob, et al. 1996; Estrada, et al. 1996; Jacob, et al. 1995; Konrad, et al. 1999; Jacob, et al. 1999; Kishi, et al. 1999) through the use of the GLUT-4 transporters to the plasma membranes, the same glucose transporter system that insulin uses (Estrada, et al. Yaworsky, et al. 2000). Both RAC-ALA and S-ALA are rapidly metabolized and eliminated; however, evidence shows that R-ALA is better absorbed than S-ALA (Breithaupt- Grögler, et al.).

It has been suggested that type-2 diabetes may be due to a defect in the pyruvate dehydrogenase complex responsible for oxidizing and transporting pyruvate in the cytoplasm to Acetyl-CoA in the mitochondria (Thorburn, et al., 1990). Glucose disposal improves with ALA use through increased acetyl CoA production, decreased gluconeogenesis, and free fatty acid oxidation (Konrad, et al.; Walgren, et al., 2004). Animal and in vitro studies suggest that since R-ALA is used in the mitochondria it may be more effective in improving insulin sensitivity resulting in greater glucose uptake than RAC- ALA (Estrada, et al; Constantinescu, et al. 1995; Streeper, et al. 1997; Hofmann, et al. 1995). This is important since chronically elevated blood glucose levels as detected by high HgbA1c values are strongly linked to incidence and severity of diabetic complications such as dyslipidemia, hypertension and atherosclerosis (Franz, 2003; DCCT). To date there have been no human clinical trials on the R-ALA and its effect on HbA1c, blood pressure and lipid levels.

PURPOSE

The purpose of this study was two fold: to investigate the effect of oral administration of R-ALA in type 2 diabetics on blood pressure, $HbA1_C$, and lipids (LDL, HDL, total cholesterol and triglycerides) and 2) to monitor liver and kidney function to assess the safety of R-ALA supplementation. It was hypothesized that three months of oral supplementation, three times daily, of 200 mg R-ALA (600 mg total) to type-2 diabetics would lower HbA1c, LDL, total cholesterol, triglycerides, and blood pressure through a decrease in insulin resistance, improved glucose utilization, and reduced protein glycation.

METHODS

Experimental Approach to the Problem

This double-blind study used a pre-test/post-test, control-group design. Twenty-three subjects were assigned randomly to receive R-ALA (n=13) 600 mg or an equivalent dose of microcellulose (PL)(n=10) for 91 days. Due to the small sample size and short duration of the study, subjects for this pilot study were randomized to uneven sized groups, with a greater number of subjects assigned to the test group.

Subjects

Twenty-three type-2 diabetics, 21-65 years, who were non-smokers and otherwise healthy participated in this 91-day study. Subjects were recruited by advertising in the local newspaper and by sending informational flyers to physicians and diabetic clinics throughout a small Midwestern area. Individuals who, in the three months prior to the study, had been hospitalized, had lost or gained 10% of their body weight, were pregnant or lactating, had previously taken R-alpha lipoic acid, or had changed either prescribed or over-the-counter (OTC) supplements that could affect measured parameters were excluded from participation.

Twenty-three participants were randomly assigned to receive R-ALA (n=13; 8 males, 5 females) or microcellulose (the placebo)(n=10). During the trial period, three subjects from the placebo group were dropped from the study. One was excluded for non-compliance, one for extremely high liver enzymes, and one on the recommendation of the subject's endocrinologist, reducing the placebo group to n=7 (2 males, 5 females). The Institutional Review Boards at both Northern Illinois University and University of Illinois at Chicago granted approval for the study. Participants provided written clearance from their

DOI: 10.2202/1553-3840.1297

physicians and signed written informed consent forms prior to participation in this study.

Preliminary Screening

During the preliminary session, subjects completed a survey questionnaire, a 24-hour diet recall, and an exercise log.

Supplementation (Days 1-91)

Subjects received 200 mg capsules provided by Glucorell, Inc., (Orlando, Florida) of R-ALA (n=13) or a placebo (PL) of microcellulose (n=7), which were identical in appearance and placed in identical sealed containers. Subjects were instructed to take one capsule 30 minutes before each meal three times per day (600 mg total per day) for 3 months (91 days). To verify compliance with instructions, subjects returned the empty containers to the primary investigator on follow-up visits. Subjects also gave an oral report of their compliance.

Blood Sampling

Subjects fasted for 8 hours prior to having their blood drawn. Blood samples were obtained on Days 1 and 91 of the study.

Experimental Design

On day one, each subject's height was measured (in) using a secured tape measure. A Tanita BF 556 digital scale Tanita Corporation (Arlington Heights, IL), measured weight (lbs) to determine body mass index **(**BMI)(Quetelet Index: (weight (lbs)/(height (in) ^{2}) x 708) (Gottschlich, 2001). Resting blood pressure (BP) was determined using a standard sphygmomanometer. An experienced phlebotomist drew 8 ml blood for determination of HbA1c, lipid, kidney, and liver function profiles. Subjects were requested to maintain the same diet, exercise, and body weight throughout the 91 days; compliance was verified by comparing pre- and post-treatment weight, 24-hour diet-recalls, and exercise logs.

Blood Analysis

A total of 8 mL of venous blood was collected into two separate tubes by an experienced phlebotomist. A 3-mL sample of blood was ejected into a tube containing ethylenediaminetretraacetic acid to analyze HgbA1C using whole blood. A 5-mL sample of blood was extracted into a serum-separating tube containing a biologically inert polymer barrier to separate cells from serum

following centrifugation. This latter sample determined total cholesterol, triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), blood urea nitrogen (BUN), and creatinine (CRE), all in mg/dL. Aspartate amino transferase (AST) and alanine amino transferase (ALT) were determined in U/L.

The latter samples were centrifuged at 2000g at 21° C for 10 minutes. Plasma then was aspirated and stored at 4° C until analysis was completed. Within a week of being drawn, samples were run in duplicate to establish reliability using a Dade Behring Dimension® RXL clinical chemistry system (Deerfield, Illinois) and Dade Behring systems kit # REF DF27, REF DF48, REF DF69A, REF DF41A, REF DF43A.

Statistical Analysis

SPSS for Windows (Version 13.0, 2004, Chicago, IL) was used to analyze the data. Histograms of the data showed that the non-categorical dependent variables had statistically non-normal distributions in either one or both study groups, for all dependent variables. Because the degree of non-normality, and sometimes the direction of skewness, was different for the two study groups, data transformation could not be done to obtain statistical normality. For this reason, nonparametric statistical methods were used to analyze the data. The Mann-Whitney test was conducted to compare the study groups pre and post on the non-categorical variables. A significance level of $\alpha = 0.05$ was used for all statistical tests.

Results

For the twenty subjects who completed the trials, there was no significant mean differences for age (53.14 ± 5.9 versus 56 ± 6.7) between those receiving PL or R-ALA respectively. Frequencies for physical characteristics of subjects at baseline are shown in Table 1. At baseline (Day 1), and Day 91 there were no statistically significant differences in weight, blood pressure, BMI, BUN, CRE, AST, ALT, CHOL, TG, HDL, LDL, or HbA1c between the groups (Table 2). All parameters were within normal reference ranges for both groups except baseline TG: 169 PL/226 R-ALA mg/dL (1.899 PL/2.539 R-ALA mmol/L) and HbA1c: 6.9 PL/8.1 R-ALA mg/dL (0.383 PL/0.450 mmol/L).

DOI: 10.2202/1553-3840.1297

Table 1. Frequencies for Physical Characteristics of the Subjects at Baseline

	R-ALA (n=13)	Placebo (n=7)
Male	8	2
Female	5	5
Duration of Diabetes		
<10 yrs	8	4
10 to 20 yrs	4	2
>20 yrs	1	1
Ethnicity: Caucasian	11	7
Hispanic	2	0
Other	0	0

Diabetes control, at baseline, was achieved in subjects by diet alone (2PL/4R-ALA), by oral antidiabetic medication (4PL /8R-ALA), and/or by insulin (1PL/1R-ALA). Many subjects used multiple antidiabetic methods to achieve control. Other medications that subjects took at least three months prior to and during the study in the PL and R-ALA groups respectively included various antihypertensives (6/13), antihyperlipidemics (3/6), anti-inflammatories (2/6), antidepressants (1/4), gastrointestinal remedies (2/5), allergy medication (2/5), thyroid medications (0/1), multivitamins (4/6), vitamins C (1/2), and E (1/0), calcium (1/2), magnesium (1/0), cinnamon (0/1), and bilberry (0/1). Other conditions not implied above included heart arrhythmia (0/1), and sleep apnea (0/1).

Table 2. Group Means and Mean Differences for Physical Characteristics and Biochemical Parameters

	Day 1		Day 91		Differences (Final – initial)	
	R-ALA	PL	R-ALA	PL	R-ALA	PL
Weight (lbs)	221.6 ± 65.0	225.6 ± 55.0	222.2 ± 64.1	226.5 ± 55.4	0.6 ± 4.2	0.97 ± 3.8
BMI	33.8 ± 8.3	33.3 ± 5.1	33.9 ± 8.2	33.4 ± 5.1	0.09 ± 0.6	0.14 ± 0.5
Systolic BP (mmHg)	127.6 ± 11.3	123.9 ± 7.8	133.9 ± 16.9	130.3 ± 12.6	6.2 ± 16.3	6.4 ± 13.3
Diastolic BP (mmHg)	78.3 ± 5.8	76.3 ± 6.5	78.1 ± 6.6	78.6 ± 8.1	-0.23 ± 8.8	2.3 ± 7.8
BUN (mg/dL)	20.5 ± 7.6	17.4 ± 3.4	20.2 ± 6.0	18.1 ± 7.6	-0.3 ± 4.1	0.7 ± 5.1
CRE (mg/dL)	0.93 ± 0.22	0.94 ± 0.13	0.95 ± .018	0.96 ± 0.17	0.02 ± 0.10	0.02 ± 0.17
ALT (Units/L)	48.0 ± 10.9	47.4 ± 19.1	45.4 ± 10.5	47.8 ± 16.7	-2.6 ± 9.9	0.4 ± 6.5
AST (Units/L)	23.7 ± 6.3	28.5 ± 21.5	21.6 ± 6.7	29.1 ± 21.6	-2.1 ± 4.2	0.6 ± 4.8
CHOL(mg/dL)	191.5 ± 54.4	173.1 ± 33.9	185.9 ± 34.5	170.7 ± 28.5	-5.6 ± 36.8	-2.4 ± 10.0
*TG(mg/dL)	226.0 ± 268.1	169.6 ± 41.7	186.4 ± 126.8	162.6 ± 42.3	-39.6 ± 193.2	-7.1 ± 53.8
HDL (mg/dL)	45.7 ± 11.8	41.9 ± 6.1	43.1 ± 11.8	39.8 ± 7.5	-2.6 ± 3.5	-2.2 ± 2.0
LDL (mg/dL)	103.5 ± 36.4	97.2 ± 26.9	105.8 ± 37.1	98.4 ± 26.4	2.3 ± 18.7	1.1 ± 14.4
HbA1c (mg/dL)	8.1 ± 2.1	6.9 ± .7	7.7 ± 1.7	6.9 ± .8	-0.37 ± 1.2	-0.05 ± 0.3

Values are means ± SD. R-ALA (n=13) PL (n=7) *except in TG R-ALA (n=12) PL (n=7)
There were no significant differences from Day 1 to Day 91.

Subjects appeared to be compliant in maintaining weight, diet, and exercise routines per pre-/post supplement 24 hour diet recalls, exercise logs and measured weights. Compliance with taking the supplement three times per day as assessed per pill count were >90% (5/8), 75–90% (2/2) and 66–74% (0/3) in PL/R-ALA groups, respectively. In the PL group, there was one complaint of perceived short-term rise in daily blood glucose (BG) levels and one complaint of

DOI: 10.2202/1553-3840.1297

influenza; two subjects had minor medication additions not related to or affecting the parameters of the study. In the R-ALA group, there were initial minor, and short-term (lasting < two weeks) complaints of: headache (2), heartburn (1), or a rise in daily fasting BG (1). There were 5 subjects with a complaint of daily fasting BG rise that lasted over one month. There was one event of neuralgia not believed to be related to the R-ALA. One subject reported escalating gastric distress due to the R-ALA (abdominal pain, flatulence, and constipation) and completed the study two weeks early. Two subjects reported incidents consistent with hypoglycemic events (dizzy, shaky, headache, and nausea); for both subjects glimepiride was subsequently reduced by half. Four additional subjects had changes in medications during the 3-month study. Two of the medication changes are known to raise BG levels, and two would not affect the parameters of the study.

Using all subjects who completed the study for an intent-to-treat analysis, there were no significant differences in any of the tested parameters. There were minor, not significant, downward trends in the R-ALA group (as opposed to upward trends in the PL) in diastolic blood pressure, AST, and ALT. In the R-ALA group, CHOL, TG, and HbA1c showed a greater downward tendency although not statistically significant from the PL group.

In using HbA1c as the primary indicator, however, it was noted that those who were taking the R-ALA reacted in 3 distinctly different ways.

1. Two subjects had dramatic decreases in HbA1c, 2.3 and 3.5 mg/dL (0.128 and 0.194 mmol/L) and one subject's physician decreased antidiabetic medication by half during the three months of the study. All subjects in this group had decreased or normalized blood pressure, CRE, ALT, AST, CHOL, TG, and LDL. All were on glimepiride.
2. Five had no change in HbA1c, no adverse effects, and reported no problems. When this group was separately compared with the PL group, statistically there were no differences. This group reported fewer hypoglycemic episodes (1), fewer hyperglycemic episodes (2), and more energy (3).
3. Five reported increases in their BG levels lasting more than a month. These five included those with medication changes and the concurrent adverse conditions that would increase BG levels. Even with reported higher fasting BG levels, none had HbA1c increases greater than those on the PL, and 2 had no change in HbA1c.

DISCUSSION

This was the first human study conducted to determine the effects of R-ALA supplementation on HgbA1c levels. All previous studies performed in humans have used the racemic form of ALA and did not show any significant changes in HbgA1C levels (Borcea, et al. 1999; Reljanovic, et al. 1999; Ziegler, et al. 1999; Ruhnau, et al., 1999). This study did not find a statistical difference in HbA1c, blood pressure, CHOL, HDL, LDL, TG, or liver and renal function values between those individuals receiving R-ALA and those receiving a PL, but 8 of the 13 subjects had a favorable response while receiving R-ALA supplementation. Three subjects responded extremely well to the R-ALA in that their antidiabetic medication was lowered by half and/or their HbA1c values dropped more than 25% (pre- R-ALA supplementation HbA1c 6.1-12.5 mg/dL (0.339-0.694 mmol/L) and post- R-ALA supplementation HbA1c's of 6.2-9.0 mg/dL (0.344-0.500 mmol/L), which concurs with the results of both in vitro (Yaworsky, et al. Streeper, et al. Hofmann, et al.) and rat studies (Walgren, et al. Saengsirisuwan, et al. 2004; Midaoui, et al. 2005; Song, et al. 2004). R-ALA supplementation increases pyruvate transportation into the mitochondria, increases pyruvate oxidation, and, in turn, allows glucose to enter the cytoplasm, thereby decreasing insulin resistance (Konrad, et al. Walgren, et al.). Post-prandial blood glucose levels drop, and in time, glycation indicators (HbA1c) also diminish (Vincent, et al. 2005).

All three of the subjects who responded well were on glimepiride, indicating a possible synergistic reaction, which future research can address, but were on comparatively few other medications (usually an antihyperlipidemic or miscellaneous OTC). Favorable improvements also were noted in CHOL with pre-R–ALA 206 mg/dL (5.282 mmol/L) vs. post-R–ALA 176 mg/dL (5.413 mmol/L); TG 127 mg/dL (1.427 mmol/L) vs. 102 mg/dL (1.146 mmol/L); and LDL 132 mg/dL (3.385 mmol/L) vs. 109 mg/dL (2.795 mmol/L). A statistically significant decrease in mean diastolic blood pressure was also noted pre-R-ALA 78 mm Hg (10.40 kPa) vs. post R-ALA 72 mm Hg (9.60 kPa).

Five of the thirteen subjects who were diet controlled or on metformin had no change in HgbA1c values pre- and post-R–ALA supplementation. Lipid and blood pressure changes were similar to the PL group (i.e., both lowered CHOL 2.4 mg/dL (0.062 mmol/L) and TG levels 7.0–7.1 mg/dL (0.079-0.080 mmol/L), while both systolic and diastolic blood pressure rose by 4 mm Hg (0.53 kPa) indicating that R-ALA did not affect this group. However, these same five subjects reported fewer hypoglycemic and fewer hyperglycemic incidents in their daily BG readings as well as more energy, which were all unexpected effects. It is possible that R-ALA normalizes extremes in diabetes, but this has not been

DOI: 10.2202/1553-3840.1297

tested, only alluded to in previous studies (Kishi, et al.1999; Jain and Lim, 2000; Arivazhagan, et al. 2003; Sharman, et al. 2004).

Five of the thirteen subjects receiving R-ALA had a more negative response which may have been due to supplementation or numerous other things. Two of the five were placed on medications that are well known for increasing blood sugar and, thus, would increase HbA1c values. The remaining three were more heavily medicated: multiple antidiabetic medications (including insulin), multiple anti-hyperlipidemics, pain medications, and other, frequently multiple, medications for various conditions. These three subjects also had BMIs of 39–51 (higher than others on the R-ALA supplement, but not statistically different); all had been diagnosed diabetic for more than 10 years, with an initial HbA1c range of 6.8-9.3 mg/dL (0.378-0.517 mmol/L) and final range of 6.8- 9.6 mg/dL (0.378-0.533 mmol/L).

Of these three, two subjects had pain (also known to increase blood sugar levels), and both lowered AST values by 5 U/L each, but their lipid values increased CHOL from 185 mg/dL (4.744 mmol/L) to 209 mg/dL (5.359 mmol/L), TG from 195 mg/dL (2.191 mmol/L) to 259 mg/dL (2.910 mmol/L), LDL from 103 mg/dL (2.641 mmol/L) to 115mg/dL (2.949 mmol/L) as did their blood pressure, from a mean of 138/77 mm Hg (18.40/10.27 kPa) to 155/86 mm Hg (20.67/11.47 kPa). The third subject, with an unexplained rise in BG levels lasting the full three months, had initially high BUN, CHOL, TG (LDL not calculated), with an ALT and an AST on the upper end of normal. This subject, although showing a 0.4 mg/dL (0.022 mmol/L) increase in HbA1c (similar to increases in the PL), completed the study with decreases in diastolic blood pressure by 15 mm Hg (2 kPa), BUN by 4 mg/dL (1.4 mmol/L) within normal, AST by 29 U/L, ALT by 11 U/L, CHOL by 100 mg/dL (2.564 mmol/L) but still high, TG by > 600 mg/dL (> 6.742 mmol/L) but still high. This subject submitted a daily BG log showing that weekly averages of fasting levels decreased each week, an indication that a study of longer duration is warranted.

The results from this latter group indicate several directions for future research. BMI may make a difference, as suggested by Konrad et al. in a study on lean and obese diabetics. It is possible that insulin resistance from obesity is an independent factor, but no known literature differentiates the various possible causes of type-2 diabetes and its relation to ALA. There may be medication interactions that have not yet been tested with R-ALA. There may be possible pro-oxidant responses, according to (Cakatay, 2006; Dicter, et al. 2002) and such incidents may indicate that R-ALA, especially from exogenous sources, functions first as an antioxidant in cells not regulated by insulin—that is, RBCs and nerve cells—before acting in the mitochondria of the muscle cell. Prior research (Borcea, et al.; Reljanovic, et al., Ziegler, et al. 1999; Ruhnau, et al.; Marangon, et al. 1999; Ziegler, et al. 1997) supports this hypothesis, noting beneficial changes

in neuropathy scores or decreased oxidation when racemic ALA is used in humans.

Limitations

The limitations in this study were small sample size, short study duration, and large inter-individual response to R-ALA among subjects. The large inter-individuality among subjects precluded finding statistically significant differences. Some of the inter-individual differences may have been due to age, gender and length of time individuals had diabetes. Since three months is the minimum time to assess hemoglobin glycation (HbA1c) changes of the red blood cell**,** a statistically significant difference may be seen if a larger, longer (six months minimum) study is designed to compare those with HbA1c changes to those without.

Although seven subjects did submit their daily BG logs, this study did not track daily BG (fasting or post-prandial) levels, or pre- and post-supplement fasting glucose levels, which may have provided valuable insight into glucose level changes. Three separate subgroups in a sampling of 13 subjects on the R-ALA can only yield observations for further research to determine if the trends noted can be substantiated.

Conclusions

With three months of supplementation of 200 mg R-ALA provided 3 times per day, a small number of type-2 diabetics lowered their HbA1C levels (>25%) and/or lowered their antidiabetic medication, with numeric, yet not statistically significant, improvements in blood pressure, CHOL, LDL, and TG. This may indicate that in some individuals, diabetes originates within the mitochondria of the cell, possibly due to a deficiency of R-ALA production within the mitochondria. All subjects whose HbA1c or medications were lowered have chosen to continue R-ALA on their own. It is not known if longer-term supplementation would benefit all type-2 diabetics, as there has been no long-term study using R-ALA. Three months of supplementation with 600 mg per day of R-ALA did not appear to be of any detriment to blood glucose control, liver or renal function based on laboratory indices which were monitored during this time period. This was true even for those test subjects who had adverse effects or medicine changes that normally would raise the HbA1c. The results of this study indicate that three months of R-ALA supplementation may lower HbA1c in a small number of type-2 diabetics; however, to confirm these findings, larger studies of longer duration are needed.

DOI: 10.2202/1553-3840.1297

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