Pharmacokinetics, Tolerability, and Fructosamine-Lowering Effect of a Novel, Controlled Release Formulation of \( \alpha \)-Lipoic Acid

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Running Title: Controlled release lipoic acid reduces fructosamine
Abstract

Objective– (1) To determine the pharmacokinetics, safety, and tolerability of a novel, controlled release oral formulation of α-lipoic acid (LA), (2) To investigate whether sustaining the concentration of LA in plasma would have a beneficial effect on glycemic control in patients with type 2 diabetes.

Methods–(a) Pharmacokinetic Study: A single, 600 mg dose of either controlled release LA (CRLA) or quick release LA (QRLA) was administered orally to twelve normal human subjects. The plasma profile of LA was followed for twenty-four hours post-dose, and pharmacokinetic analyses performed. (b) Safety and Tolerability Study: Twenty-one patients with type 2 diabetes were given 900 mg CRLA daily for six weeks, followed by 1200 mg CRLA daily for an additional six weeks. Active treatment was followed by a three-week washout period. Throughout the study, patients continued on their pre-study anti-diabetic medications which included metformin (Glucophage®), sulfonylureas (Amaryl®, Glyburide®, Glucotrol®), acarbose (Precose®), troglitazone (Rezulin™), and insulin (either as monotherapy or in combination). CRLA was evaluated for safety and tolerability, and for effects on glycemic control.

Results–The T_{max} (time to maximum plasma concentration) of LA administered as CRLA was 1.25 h, and was approximately 2.5-fold longer compared to the T_{max} for QRLA (T_{max} = 0.5 h; P < 0.02). No significant side effects or changes in either liver or kidney function, or hematological profiles following the
administration of CRLA were observed. In fifteen patients, plasma fructosamine was reduced from $313 \pm 48.6 \, \mu M$ (mean $\pm$ SD) to $283 \pm 48.7 \, \mu M$ ($30.1 \pm 9.7 \, \mu M$; $P < 0.05$) after twelve weeks of treatment with CRLA.

Conclusions—CRLA increased the plasma concentration of LA over time in healthy subjects, and was safe, well-tolerated and significantly reduced plasma fructosamine in patients with type 2 diabetes.

Keywords: antioxidant, controlled release, diabetes, fructosamine, glucose, lipoic, lipoic acid, pharmacokinetics


Introduction

\(\alpha\)-Lipoic acid (LA) is an eight-carbon fatty acid that is synthesized in trace quantities in organisms ranging from bacteria to man (1-3). LA functions naturally as a cofactor in several mitochondrial enzyme complexes responsible for oxidative glucose metabolism and cellular energy production (4;5). When administered exogenously, LA and its reduced form, dihydrolipoic acid (DHLA), act as multifunctional antioxidants (1;2). LA has been prescribed in Germany for over thirty years for the treatment of diabetes-induced neuropathy (6-8), and results from several recent controlled clinical studies indicate that this compound is safe, well-tolerated, and efficacious (8).

In addition to the beneficial effects of LA on diabetes-induced neuropathy, several clinical studies point to an improvement in insulin sensitivity and whole-body glucose metabolism in patients with Type 2 diabetes following continuous intravenous (i.v.) infusion of LA (9-11). It has been reported that i.v. infusion of LA markedly increases insulin-mediated glucose disposal (~30-50%) (9;10), whereas oral administration of LA has only marginal effects (<20%) (12;13). Furthermore, the currently available oral forms of LA have not been reported to reduce glucose, fructosamine, or HbA1c levels in patients with diabetes (12-20). It is possible that this limitation of orally administered LA might be a function of its abbreviated duration in plasma (compared to i.v. LA), resulting from extensive first-pass metabolism (> 50%) and/or short plasma half-life (<0.5 h) (21).
regard, the superior ability of i.v. LA to improve insulin sensitivity might be due to the ability of i.v. administration to achieve a higher plasma concentration of LA, and/or to maintain it for a longer duration. A continuous infusion (over 20 minutes) of 200 mg LA resulted in a peak plasma level of approximately 8 µg/ml, and detectable levels were still observed six hours after the start of infusion (21). In contrast, oral administration of a 200 mg tablet resulted in a peak plasma level of approximately 0.66 µg/ml, which returned baseline < 3 hours after dosing (22).

In this preliminary, open-label study, we evaluated the pharmacokinetics, safety, and tolerability of a novel, controlled release oral formulation of α-lipoic acid (LA). This formulation was designed to maintain the plasma concentration of LA over time using controlled release drug delivery technology (polymeric cellulose resins). In addition, we also investigated whether this agent would result in a beneficial impact on glucose control in patients with Type 2 diabetes. We report here that this agent was safe, well-tolerated, and significantly reduced plasma fructosamine in patients with type 2 diabetes.

Materials and Methods

Subjects and Study Design: Pharmacokinetic Study. The pharmacokinetic profile of controlled release α-lipoic acid (CRLA) was evaluated in an open-label, single-dose, randomized, two-way crossover design. The study was sponsored by Medical Research Institute (San Bruno, CA; www.lipoic.com), and conducted by
Covance Clinical Research Unit at their Madison, WI study site. Twelve healthy male volunteers received a single dose of two 300 mg tablets of either CRLA (Medical Research Institute) or three 200 mg capsules of quick release LA (QRLA; Solgar, Leonia, NJ) after an eight-hour overnight fast (23). Subjects did not eat during the first four hours after dosing. Subjects were randomly assigned to sequence 1 (QRLA then CRLA) or to sequence 2 (CRLA then QRLA), with a washout of at least 3 days between treatments. Blood samples for the determination of plasma LA levels were collected via an indwelling catheter as follows: 0 hour (pre-dose); 5, 10, 15, 20, 30, 45 minutes; and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, and 24 hours post-dose. The concentration of LA in plasma was determined by a validated, high-performance liquid chromatography assay employing fluorescence detection (24). The lower limit of quantitation of LA was 15 ng/ml, and the upper limit was 500 ng/ml. Pharmacokinetic analyses of LA were computed using WinNonlin Professional software (version 3.0, Pharsight, Inc.). Plasma assays and statistical analyses were performed by Covance Laboratories, Inc. (Madison, WI).

Subjects and Study Design: Safety and Tolerability Study. The safety and tolerability of CRLA was assessed along with effects on glycemic control in an open-label, longitudinal design on 21 patients with Type 2 diabetes, who acted as their own control. The study was sponsored by Medical Research Institute, and conducted by Dr. Laurence A. Gavin within his private practice setting at Seton Medical Center (Daly City, CA). To be included in the study, patients were
required be diagnosed with type 2 diabetes (C-peptide > 1.2 ng/ml), under adequate control (HbA$_{1c}$ > 7.5\% and < 10.5\%), and with a disease duration < 35 years. Patients with a history of cerebrovascular disease, congestive heart failure, advanced nephropathy, diastolic blood pressure > 100 mmHg, or BMI > 35 were ineligible for enrollment.

As this study was intended primarily to assess the safety and tolerability of a new formulation, patients were permitted to continue their pre-study anti-diabetic medications concurrently to facilitate patient recruitment. These medications included metformin (Glucophage®, Bristol-Myers Squibb, Princeton, NJ), sulfonylureas (Amaryl® and Glyburide®, Hoechst Marion Roussel, Kansas City, MO; Glucotrol®, Pfizer, New York, NY), acarbose (Precose®, Bayer, West Haven, CT), troglitazone (Rezulin™, Warner-Lambert, Morris Plains, NJ; withdrawn from market), and/or insulin. No dose change in these medications was made during the run-in period or during the course of the study.

The baseline clinical characteristics of the patients are shown in Table 1. The mean HbA$_{1c}$ level (%) was 8.2 ± 1.5. Following a run-in period of two weeks, patients received 12 weeks of active treatment of CRLA. The agent was administered as 900 mg daily (2 x 300 mg tablets 30 minutes before breakfast and 1 x 300 tablet 30 minutes before dinner) for 6 weeks, followed by 1200 mg daily (2 x 300 mg tablets before breakfast and 1 x 300 tablet before both lunch and dinner) for 6 weeks. A three-week washout period followed active treatment.
Patients were monitored on a regular basis for glucose and lipid control, liver enzymes, along with other clinical markers including physical examination, vital signs, and adverse experience queries.

Six patients were not included in the final statistical analyses. These exclusions were made blinded to results. Four patients were excluded due to their recurring failure (≥3 instances) to adhere to their allocated diets. Diet was judged initially acceptable if it provided sufficient caloric intake to maintain body weight, and caloric distribution approximating the following: 50-60% carbohydrate, <30% fat, and 15-20% protein. Diets were evaluated at the beginning of the run-in phase, and monitored on a regular basis throughout the study. Failure to adhere was judged to have occurred if carbohydrate, fat, and/or total caloric intake grossly exceeded (>150%) a patient’s usual weekly intake based on patient interviews. One patient was excluded due to premature withdrawal due to a recurring illness not considered related to study medication, and one patient was excluded from analyses due to repeated missed laboratory values. Glucose, HbA$_{1C}$, clinical chemistry and hematology assays, and lipid panels were performed in the clinical laboratory at Seton Medical Center. Fructosamine and C-peptide assays were performed at Specialty Laboratories, Inc. (Santa Monica, CA). Intra- and inter-assay coefficients of variation were ≤5%.
Ethics. The protocols for the pharmacokinetic study and the safety and tolerability study protocol were approved by the Institutional Review Boards of Covance and the Seton Medical Center, respectively. For both trials, each subject was informed about the purpose and risks of the study, and had given their written consent to participate. The studies were conducted in accordance with US Title 21 Code of Federal Regulations commonly known as Good Clinical Practices (GCPs), which are consistent with the Declaration of Helsinki. CRLA is a commercially available, non-prescription product (see below) regulated by the US Dietary Supplement Health and Education Act (DSHEA), and did not require Investigational New Drug (IND) approval prior to the initiation of these clinical studies.

Controlled Release α-Lipoic Acid (CRLA). LA used in the formulation of CRLA was purchased from Antibioticos SA (Rodano, Italy). This material is of the highest purity commercially available (> 99.0%), and produced in accordance with current Good Manufacturing Practices (cGMPs). CRLA tablets were formulated and manufactured for Medical Research Institute in the US in accordance with cGMPs. CRLA is currently manufactured and distributed (since 1999) in the US by Medical Research Institute under the trade name of Glucotize™. The proprietary nature of CRLA is protected under US Patents #6,191,162 and 6,197,340, and additional patents are pending.
Results

Clinical Trial 1: Pharmacokinetic Study in Healthy Individuals

The mean plasma concentration profile of LA following oral dosing is shown in Figure 1. The median $T_{\text{max}}$ (time to maximum plasma concentration) for QRLA was 0.5 hours (range 0.25-1.5 h), which is indicative of rapid absorption with respect to LA. In comparison, the median $T_{\text{max}}$ for CRLA was 1.25 hours (range 0.5-4.5 h), representing a 2.5 fold increase ($P < 0.02$; ANOVA). For $C_{\text{max}}$ (maximum observed plasma concentration), mean values ($\pm$ SD) of 6675 ± 3703 ng/ml and 1793 ± 742 and were determined for the QRLA and CRLA treatments, respectively ($P < 0.002$; ANOVA). The mean ratio of $C_{\text{max}}$ for CRLA treatment to QRLA treatment was 27%, and is reflective of the decrease in $C_{\text{max}}$ typically observed in controlled release formulations. The maximum plasma concentration of 1793 ng/ml achieved by a single-dose administration of 600 mg of CRLA corresponds to approximately 10 $\mu$M. This plasma concentration persisted for approximately 2.5 hours after dosing (Figure 1). For $\text{AUC}_{0-24}$ (area under the plasma concentration-time curve from hours 0 to 24), mean values of 4466 ±1157 and 2621 ± 385 and ng $\cdot$ h/ml were determined for the QRLA and CRLA treatments, respectively ($P < 0.0001$; ANOVA). The mean ratio of $\text{AUC}_{0-24}$ for CRLA treatment to QRLA treatment was ~60%, and suggests a reduction in overall bioavailability of the CRLA formulation compared to QRLA. The mean terminal elimination half-life ($T_{1/2}$; time required for concentration in plasma to decline to one-half initial concentration, or rate of elimination) was 0.5 ± 0.61
hours for QRLA and 0.4 ± 0.22 hours for CRLA ($P < 0.39$). These values were not significantly different, presumably due to high inter-subject variability following treatment with QRLA.

**Clinical Trial 2: Safety and Tolerability Study in Individuals with Type 2 Diabetes**

There were no significant side effects reported following the administration of CRLA to patients with type 2 diabetes. Two patients reported a slight metallic taste following the dose increase to 1200 mg/day, but this effect was transient and did not require either individual to withdraw from the study. There were no significant changes in liver enzymes, liver or kidney function, or hematological profiles (data not shown). Thus, CRLA was well tolerated and safe at daily doses of 900 mg for six weeks followed by 1200 mg for six weeks.

CRLA exhibited a significant effect with regard to the reduction of plasma fructosamine. At baseline, the mean plasma fructosamine was 313 ± 48.6 µM (SEM; $n = 15$), and after six weeks of treatment was 307 ± 43.0 µM ($P < 0.465$; Figure 2). At this point, the dose of CRLA was increased to 1200 mg/day. After three weeks on the higher dose, the mean plasma fructosamine was reduced to 275 ± 42.6 µM ($P < 0.033$; Figure 2). At the completion of active treatment (twelve weeks), the mean plasma fructosamine was 283 ± 48.7 µM ($P < 0.05$; Figure 2), corresponding to an overall mean decrease from baseline of 30.1 ± 9.7 µM. After a three-week washout, the mean plasma fructosamine rose to 304 ± 56.8 µM ($P < 0.454$; Figure 2). No significant changes were observed in either
fasting plasma glucose or HbA\textsubscript{1c}. At baseline, fasting plasma glucose and HbA\textsubscript{1c} were 157 ± 34 mg/dl and 8.2 ± 1.5 % (mean ± SD), respectively. At the completion of active treatment (twelve weeks), fasting plasma glucose and HbA\textsubscript{1c} were 168 ± 36.5 mg/dl ($P < 0.37$) and 8.2 ± 0.84 % ($P < 0.94$), respectively. A trend toward a reduction in C-peptide was observed. At baseline, the mean plasma C-peptide was 5.0 ± 3.8 ng/ml and after twelve weeks of treatment fell to 4.2 ± 2.8 ng/ml (Table 1). The overall mean decrease from baseline was 0.84 ± 0.72 ng/ml ($P < 0.26$). No significant changes were observed in triglycerides, total, high-density, or low-density lipoprotein cholesterol, body weight, or body mass index following treatment (Table 1).

**Discussion**

This is the first report of the development, use, and clinical assessment of a controlled release formulation of LA. This approach was initiated and pursued to test the hypothesis that limitations of the current oral QRLA with respect to effects on insulin sensitivity and metabolic control (compared to \textit{i.v.} infusion) might be a function of the abbreviated duration for which LA is maintained in plasma.

Using controlled release drug delivery technology, the $T_{\text{max}}$ of LA was increased approximately 2.5-fold (1.25 hours for CRLA vs. 0.5 hours for QRLA), reflecting the slower release of LA from the formulation matrix. Importantly, the
plasma concentration of LA remained level for several hours in the controlled release formulation, whereas it fell more rapidly when delivered in quick release capsules. The therapeutic implication of maintaining LA in plasma for a longer duration than can be achieved with typical oral QRLA is suggested by the clinical benefit of LA on whole-body insulin sensitivity when administered by i.v. infusion (9-11).

CRLA exhibited decreased a $C_{\text{max}}$ compared to QRLA. This is also a formulation effect, since controlled release formulations are designed to reduce $C_{\text{max}}$ (25). The reason for the observed decrease in overall bioavailability of the CRLA (judged by lower a AUC) compared to QRLA is unknown. It is possible that there was a difference in the rate or extent of absorption of the two formulations. It cannot be determined from this study if the controlled release matrix constituents affected the absorption of LA. Another possibility is that the slower release of the CRLA promoted more extensive first-pass hepatic metabolism. The $T_{1/2}$ value was not significantly different between the two formulations. This suggests that the increased duration of CRLA was due to controlled plasma delivery as opposed to a decrease in the actual rate of elimination. The $T_{1/2}$ of the QRLA capsules used here is in good agreement with that reported for enteric-coated tablets (21).

At doses of 900 mg/day for six weeks followed by 1200 mg/day for six weeks, CRLA was well tolerated, and did not produce any significant changes in
liver enzymes, liver or kidney function, or hematological profiles. No serious side effects were observed. These results are in good agreement with the long history of safety and tolerability of LA, whether administered by i.v. infusion or orally (8).

It cannot be determined from this study whether CRLA interacted with other medications, although no subject required an adjustment in dose of their concurrent medication. To assess the potential for drug-drug interaction between CRLA and other anti-diabetic medications, more systematic studies would be required. A recent study has found that co-administration of single oral doses of QRLA and glibenclamide, or QRLA and acarbose did not result in drug-drug interactions (26).

With respect to glycemic control, CRLA produced a reduction of plasma fructosamine, an effect that was statistically significant at weeks nine and twelve. This corresponds to weeks three and six following dose escalation to 1200 mg CRLA per day. At the completion of active treatment, the decrease in fructosamine from baseline was 30 µm, corresponding to an approximate 10% overall reduction. Following a three-week washout period, fructosamine increased towards the baseline value. This finding provides preliminary support for our hypothesis that maintaining the level of LA in plasma over time might result in an overall improvement in glycemic control.

The decrease in fructosamine was observed in the absence of a reduction in fasting plasma glucose. The reason for this is unknown, and will have to be
addressed in future studies in which post-prandial glucose levels are also taken. The decrease in fructosamine was also observed in the absence of a reduction in HbA1c. This might be attributable to the abbreviated duration of treatment at the effective 1200 mg dose (6 weeks total exposure), and/or statistical power too limited to detect a significant change, especially in light of the degree of variability of HbA1c at baseline. A larger double-blind, placebo-controlled study of longer duration would be required to address this question. In conclusion, in this preliminary open-label study, CRLA increased the plasma concentration of LA over time in healthy subjects, and was safe, well-tolerated and significantly reduced plasma fructosamine in patients with type 2 diabetes. Although encouraging, these preliminary results need to be confirmed in a larger, double-blind, placebo-controlled study in which HbA1c is the primary endpoint. If this goal is achieved, CRLA may emerge as a new, adjunctive, anti-diabetic treatment agent.
Acknowledgements

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Abbreviations: ANOVA, analysis of variance; AUC, area under the plasma concentration-time curve; $C_{\text{max}}$, maximum observed plasma concentration; CRLA, controlled release $\alpha$-lipoic acid; DHLA, dihydrolipoic acid; $\text{HbA}_1c$, glycated hemoglobin; LA, $\alpha$-lipoic acid; QRLA, quick release $\alpha$-lipoic acid; $T_{\text{max}}$, time to maximum plasma concentration; $T_{1/2}$, terminal phase elimination half-life
References


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Figure Legends

Figure 1. α-Lipoic acid concentration in plasma following single oral dose. Mean plasma concentration of quick release LA (QRLA) and controlled release LA (CRLA) in twelve healthy subjects after a single oral dose of 600 mg. For each formulation, plasma lipoic acid levels returned to baseline levels by 6 hours. Several data points that correspond to plasma values < 10 ng/ml are not shown in this plot. No error bars are shown for clarity, and since the statistical evaluation of these data is indicated in the text (See Results: Clinical Trail 1).

Figure 2. Effect of controlled release α-lipoic acid (CRLA) on plasma fructosamine in patients with Type 2 diabetes. Plasma fructosamine concentrations (mean ± SD; n = 15) during twelve-week active treatment and three-week washout phase. Initial dose of CRLA was 900 mg/day; dose was increased to 1200 mg/day after week six. P values are from paired t-test vs. baseline. Statistical significance was accepted at P < 0.05.
Table 1. Clinical Characteristics of Study Subjects at Baseline, During, and After Treatment

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Baseline</th>
<th>Week 6</th>
<th>Week 12</th>
<th>Week 15 (Washout)</th>
<th>Δ Week 12 vs. Baseline (P-value)</th>
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<tbody>
<tr>
<td>n</td>
<td>21</td>
<td>--</td>
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<tr>
<td>Age (years)</td>
<td>61 ± 11.1</td>
<td>--</td>
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<tr>
<td>Male, n (%)</td>
<td>9 (42.9%)</td>
<td>--</td>
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<td>--</td>
</tr>
<tr>
<td>Diabetes Duration (years)</td>
<td>11 ± 8.1</td>
<td>--</td>
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</tr>
<tr>
<td>Height (in)</td>
<td>67 ± 4.7</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Weight (lb)</td>
<td>195 ± 37.2</td>
<td>199 ± 40.0</td>
<td>193 ± 32.2</td>
<td>197 ± 35.6</td>
<td>-2.4 ± 12.7 (0.60)</td>
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<tr>
<td>Body Mass Index (kg/m²)</td>
<td>31.1 ± 4.7</td>
<td>31.2 ± 4.9</td>
<td>30.2 ± 4.6</td>
<td>30.9 ± 4.8</td>
<td>-0.9 ± 2.8 (0.35)</td>
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<tr>
<td>HbA1c (%)</td>
<td>8.2 ± 1.5</td>
<td>8.4 ± 0.6</td>
<td>8.2 ± 0.8</td>
<td>8.0 ± 0.7</td>
<td>0.03 ± 0.4 (0.94)</td>
</tr>
<tr>
<td>Fructosamine (µM)</td>
<td>313 ± 48.6</td>
<td>307 ± 43.0</td>
<td>283 ± 48.7*</td>
<td>304 ± 56.8</td>
<td>-30.1 ± 9.7 (0.05)</td>
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<tr>
<td>Fasting glucose (mg/dl)</td>
<td>157 ± 34.0</td>
<td>174 ± 41.4</td>
<td>168 ± 36.5</td>
<td>150 ± 46.9</td>
<td>10.4 ± 11.3 (0.37)</td>
</tr>
<tr>
<td>Fasting C-peptide (ng/ml)</td>
<td>5.0 ± 3.8</td>
<td>4.6 ± 2.7</td>
<td>4.2 ± 2.8</td>
<td>5.0 ± 3.2</td>
<td>-0.84 ± 0.7 (0.26)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>222 ± 109</td>
<td>213 ± 123</td>
<td>218 ± 124</td>
<td>240 ± 164</td>
<td>-4.4 ± 20.5 (0.84)</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>180 ± 42.6</td>
<td>185 ± 29.5</td>
<td>187 ± 33.9</td>
<td>190 ± 35.7</td>
<td>6.4 ± 7.7 (0.42)</td>
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<tr>
<td>HDL Cholesterol (mg/dl)</td>
<td>43.4 ± 9.2</td>
<td>43.2 ± 10.8</td>
<td>41.9 ± 8.2</td>
<td>46.3 ± 11.6</td>
<td>-1.57 ± 1.7 (0.38)</td>
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<tr>
<td>LDL Cholesterol (mg/dl)</td>
<td>94.5 ± 38.5</td>
<td>103 ± 30.1</td>
<td>105 ± 34.3</td>
<td>101 ± 40</td>
<td>10.9 ± 5.7 (0.08)</td>
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<tr>
<td>VLDL Cholesterol (mg/dl)</td>
<td>41 ± 18.2</td>
<td>34.3 ± 14.0</td>
<td>38.8 ± 17.3</td>
<td>38.7 ± 21.4</td>
<td>-2.23 ± 4.2 (0.60)</td>
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<tr>
<td>Blood Pressure (mm Hg)</td>
<td></td>
<td></td>
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<tr>
<td>Systolic</td>
<td>123 ± 11.1</td>
<td>122 ± 16.0</td>
<td>128 ± 14.7</td>
<td>134 ± 19.7</td>
<td>4.27 ± 3.6 (0.26)</td>
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<td>Diastolic</td>
<td>74.1 ± 7.3</td>
<td>68.0 ± 9.5</td>
<td>72.3 ± 10.3</td>
<td>73.5 ± 10.0</td>
<td>-1.86 ± 3.0 (0.55)</td>
</tr>
</tbody>
</table>

* P < 0.05 (paired t-test vs. baseline). Values represent mean ± SD except for Δ Week 12 vs. Baseline, which is mean ± SEM.
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Controlled release lipoic acid reduces fructosamine

Figures

Figure 1

Figure 2