The Effects of Tetrahydro-iso-alpha Acids and Niacin on Monocyte-Endothelial Cell Interactions and Flow-mediated Vasodilation

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ABSTRACT
Niacin favorably modifies cardiovascular risk factors but is associated with flushing and shows limited benefit in improving endothelial function. We investigated whether combining anti-inflammatory tetrahydro-iso-alpha acids (THIAA) from hops with niacin would improve endothelial function. We hypothesized that the THIAA-niacin combination would demonstrate benefits not seen with niacin alone. In an in vitro model, a THIAA-niacin mixture inhibited several TNF-α-induced cytokines in human aortic endothelial cells and in human monocytes. It was significantly more efficacious than niacin alone. Subsequently, the effect of 125 mg THIAA and 500 mg niacin on endothelial-regulated flow-mediated vasodilation (FMD) was explored in a pilot study of 11 dyslipidemic volunteers. The 12-week treatment (2 tablets/day) resulted in a clinically relevant FMD increase compared to a trend toward an FMD decrease with placebo; the between-arm difference was statistically significant. THIAA-niacin treatment also improved total cholesterol, low-density lipoprotein cholesterol, and uric acid. No significant improvement in these parameters was observed with placebo. High-sensitivity C-reactive protein was significantly increased only in the placebo arm. Nutritional support with a THIAA-niacin combination may provide benefits for endothelial function in those with dyslipidemia.

Key Words
Endothelial function, flow-mediated vasodilation, niacin, hops, clinical trial

SINOPSIS
La niacina modifica favorablemente los factores de riesgo cardiovascular pero se asocia con la rubefacción y presenta un beneficio escaso en la mejora de la función endotelial. Investigamos si la combinación de ácidos tetrahydro-iso-alfa (tetrahydro-iso-alpha acids, THIAA) de lúpulo antiinflamatorios con niacin-

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Atherosclerosis, a chronic inflammatory disease of the arterial wall reflecting dysregulated lipid metabolism, pathological monocyte–endothelial cell interactions, and oxidative stress, is a major contributor to the morbidity and mortality of aging. In the presence of insults, such as oxidized lipoproteins, hyperglycemia, bacterial cell wall components, and pro-inflammatory cytokines, the vascular endothelium mediates early pathophysiological changes resulting in the initiation of atherosclerosis. Shear stress, the drag created by blood flow across the vascular endothelium, is the primary influence upon production of nitric oxide (NO) by a healthy vascular endothelium. In the presence of hyperglycemia and activation of phosphokinase C, production of NO is reduced, which results in impaired flow-mediated vasodilation (FMD). Contemporaneously, oxidation of low-density lipoprotein cholesterol (LDL-C) and localized immune/inflammatory signaling alter endothelial cell signal transduction. Activated endothelial cells express adhesion molecules, resulting in circulating monocyte adhesion to the endothelial cells. Monocyte chemottractant protein-1 (MCP-1) secreted by endothelial cells directs subendothelial migration of monocytes and their subsequent differentiation into macrophages. Rapidly accumulating lipoprotein particles, these lipid-laden macrophages form fatty streaks and secrete matrix metalloproteinases (MMPs), tissue factors, and pro-inflammatory cytokines that further amplify the feed-forward cycle of local inflammatory response.

Endothelial dysfunction is an early pathophysiological disturbance that has been causally and temporally related to the development of hypertension and atherosclerosis. FMD is a convenient and noninvasive measurement of endothelial function and is a valuable tool for the assessment of vascular health in intervention studies. FMD has been shown to be predictive of high risk for cardiovascular events in normal subjects and patients with systemic lupus erythematosus.

Nicotinic acid, or niacin, is a water-soluble vitamin (vitamin B3). It has been shown to reduce oxidative stress and vascular inflammation in vitro and in vivo and to favorably modify serum lipids in clinical studies. Niacin reduces the atherogenic LDL-C and very low–density lipoprotein cholesterol (VLDL-C), increases the atheroprotective high-density lipoprotein cholesterol (HDL-C), and improves atherosclerotic outcomes. A recent study showed that niacin had limited benefit (restricted to a subgroup of participants with low HDL-C) for treating endothelial dysfunction. Flushing, liver dysfunction, and gastrointestinal symptoms associated with higher doses of niacin limit its broad applicability for the treatment of dyslipidemia and cardiovascular disease. Additional clinical concerns include an unfavorable impact on glucose homeostasis and a propensity to elevate uric acid levels.

Tetrahydro-iso-alpha acids (THIAA), a family of reduced iso-alpha acid compounds derived from Humulus lupulus (hops), have exhibited potent effects on key cell signaling pathways mediating inflammation. In a mouse model of rheumatoid arthritis (RA), THIAA decreased bone, joint, and cartilage degradation, reduced carrageenan-induced footpad swelling, and reduced plasma levels of interleukin (IL)-6 in a dose-dependent manner. Since systemic chronic inflammation associated with RA in humans has been associated with atherosclerosis and increased cardiovascular events, THIAA’s antiinflammatory properties may be efficacious in ameliorating the inflammation-mediated monocyte-endothelial interaction. Supporting this notion is a recent publication that demonstrated that THIAA indeed attenuated monocyte adhesion to endothelial cells and suppressed multiple inflammatory biomarkers in both monocyctic and endothelial cell lines.

We hypothesized that the THIAA+niacin combination would demonstrate benefits not seen with niacin alone. We compared the effect of niacin to THIAA+niacin mixture on inflammatory marker inhibition in tumor necrosis factor (TNF)-α-activated monocytes and endothelial cells. Subsequently, the THIAA+niacin combination was given to participants with dyslipidemia to determine its effect on FMD and lipid profiles.

METHODS AND MATERIALS

Chemicals and Reagents

The human monocytic cell line THP-1 was purchased from ATCC (Manassas, Virginia) and maintained in RPMI1640 in the presence of 10% serum according to the manufacturer’s instructions. Human aortic endothelial cells (HAECs) were purchased from Lonza (Walkersville, Maryland) and maintained in endothelial basal medium (EBM)-2 in the presence of 10% serum according to the manufacturer’s instructions. TNF-α was purchased from Sigma (St Louis, Missouri). THIAA was supplied by Hopsteiner (New York, New York), and the chemical composition has been described. Niacin was supplied by Glanbia Nutritional (Carlsbad, California). The tablet for the clinical trial contained 2 active ingredients: 125 mg THIAA and 500 mg niacin (1:4 w:w in an extended-release formulation) and inactive ingredients hydroxypropylmethylcellulose, microcrystalline cellulose, cellulose, stearic acid, silicon dioxide, and magnesium stearate. The placebo tablet with identical appearance contained microcrystalline cellulose, cornmeal, stearic acid, cellulose, silicon dioxide, and magnesium stearate.

TNF-α-induced Inflammatory Markers in HAECs

HAECs were pre-incubated with various concentrations of THIAA, niacin, and THIAA+niacin (1-20 μg/mL) for 1 hour and then stimulated with TNF-α (10 ng/mL) for 8 hours. Concentrations of IL-6, IL-8, MCP-1, and regulated upon activation, normal T-cell expressed, and secreted (RANTES) in the medium were measured by Milliplex MAP Human Cytokine/Chemokine Panel (Millipore, Billerica, Massachusetts) according to the manufacturer’s instructions. Analytes were quantified...
using a Luminex 100 IS System (Luminex Corp, Austin, Texas), and the data were analyzed using a 5-parameter logistic method.

**TNF-α-induced Inflammatory Markers in THP-1 Monocytes**

Cells were pre-incubated with varying concentrations of THIAA, niacin, and THIAA+niacin (1-20 μg/mL) for 1 hour and then stimulated with TNF-α (10 ng/mL) for 18 hours. Concentrations of cytokines in the medium were measured by Milliplex MAP Human Cytokine/Chemokine Panel (Millipore, Billerica, Massachusetts) according to the manufacturer’s instructions. Analytes were quantified using a Luminex 100 IS System and the data were analyzed using a 5-parameter logistic method.

**TNF-α-induced MMP-9 Levels in THP-1 Cells**

THP-1 cells were pre-incubated with varying concentrations of THIAA, niacin, and THIAA+niacin (1-20 μg/mL) for 1 hour and then stimulated with TNF-α (10 ng/mL) for 18 hours. MMP-9 concentration in the medium was determined by a Human MMP-9 Immunoassay Kit (GE Healthcare Life Sciences, Piscataway, New Jersey) according to the manufacturer’s instructions.

**Pilot Study**

To investigate the effect of THIAA+niacin on FMD in 11 volunteers with dyslipidemia, a randomized, placebo-controlled trial was conducted at Metagenics’ Functional Medicine Research Center (Gig Harbor, Washington). Inclusion criteria were (1) age between 30 and 60 years, (2) LDL-C ≥ 130 mg/dL (3.37 mmol/L), (3) HDL-C ≤ 50 mg/dL (1.30 mmol/L) for men or ≤ 60 mg/dL (1.55 mmol/L) for women, and (4) willingness to maintain current dietary and exercise practice during the study. Key exclusion criteria were (1) use of dietary supplements that contained the active ingredient(s) in this study with the exception of multivitamins that contain no more than 25 mg niacin; (2) use of nonsteroidal antiinflammatory drugs or COX-2 inhibitors in the preceding 2 weeks or oral corticosteroids in the preceding 4 weeks; (3) a weight of ≥ 300 lbs (136 kg); (4) a history of coronary artery disease, arrhythmia, cerebrovascular accident, HIV infection, cancer, or significant liver or kidney disease; and (5) pregnancy or breastfeeding. Fifty-six individuals were screened, and 11 were enrolled. Primary reasons for exclusion included preexistent cardiovascular disease and failure to meet entrance lipid criteria. Eleven participants completed the trial. The study was approved by the Copernicus Group Independent Review Board and conducted in accordance with the Declaration of Helsinki as revised in 1983, and informed written consent was obtained from each participant prior to enrollment in the trial.

At the beginning of the trial, eligible participants provided fasting blood samples and had their brachial FMD measured by the study doctor. Participants were then randomized to receive either the placebo tablet (n = 4) or the THIAA+niacin combined tablet (n = 7; 1 tablet twice daily with food) for 12 weeks, during which they were instructed to maintain their normal dietary and exercise practice. Participants returned to the clinic every 2 weeks for evaluation of compliance and any adverse events. At the end of 12 weeks, participants provided fasting blood samples and had their FMD measured by the same study doctor.

Blood samples collected at baseline and at end of trial were sent to Quest Diagnostics (Seattle, Washington) for analyses of lipids, glucose, high-sensitivity C-reactive protein (hs-CRP), and uric acid. FMD measurements were performed on a MicroMaxx Ultrasound System (SonoSite, Bothell, Washington) using the protocol following the guidelines reported by Corretti et al.22 Participants were instructed to fast for 12 hours, minimize physical activities, and rest for 15 minutes in a supine position prior to the procedure. The participant’s blood pressure was monitored every 3 to 5 minutes using an automated sphygmomanometer with the blood pressure cuff placed around the participant’s left arm. An automatic inflation, narrow-width occlusion cuff was placed as high as possible on the participant’s right arm. The brachial artery of the right arm, approximately 5 to 10 cm above the antecubital fossa, was scanned with a 10.5 MHz operating frequency. The cuff was then inflated to 50 mmHg above the participant’s systolic pressure or at least 200 mmHg for initial occlusion of the brachial artery. After 5 minutes of occlusion, the pressure in the cuff was rapidly released and post-stimulus image acquisition was recorded until 3 minutes after the cuff release. The relative increase in diameter compared to the baseline diameter was calculated (as percentage) using Vascular Research Tools version 5.7.6 (Medical Imaging Associates, LLC, Coralville, Iowa).

**Statistical Analysis**

For in vitro data, repeated measures analysis of variance (ANOVA) was applied to analyze the effects of THIAA, niacin, and THIAA+niacin combination. Data were analyzed using GraphPad Prism software (San Diego, California) and reported as mean ± standard error (SE). For the pilot clinical study data, 2-sample t-tests were performed to compare biomarkers between the THIAA+niacin arm and the placebo arm at baseline and at end of trial. t-tests were also used to compare changes from baseline between the 2 arms. For within-arm changes from baseline, paired t-tests were conducted to determine significance. The probability of a type I error was set at the nominal 5% level. Clinical data were analyzed using SAS (software version 8.1, SAS Institute, Cary, North Carolina) and reported as mean ± standard error (SE).

**RESULTS**

**THIAA+niacin Inhibited TNF-α-mediated Inflammatory Markers in HAECS and THP-1 Cells**

TNF-α incubation increased the expression of MCP-1, RANTES, IL-6, and IL-8 in HAECS. Niacin pre-incubation (1-20 μg/mL) reduced the TNF-α-mediated
expression of these markers in a dose-dependent manner. The expression of MCP-1, RANTES, IL-6, and IL-8 was reduced by up to 85%, 40%, 52%, and 54%, respectively, at 20 μg/mL of niacin (Figure 1). THIAA+niacin pre-incubation (1-20 μg/mL) reduced the TNF-α-mediated expression of MCP-1, RANTES, IL-6, and IL-8 by up to 90%, 53%, 59%, and 61%, respectively, at 20 μg/mL of THIAA+niacin (Figure 1). THIAA+niacin was more efficacious ($P < .001$) for inhibiting these markers than niacin alone.

Similarly, TNF-α incubation increased the expression of MCP-1, RANTES IL-1β, and MMP-9 in THP-1 cells (IL-6 and IL-8 levels were below detectable limits in THP-1 cells). Niacin pre-incubation prior to TNF-α stimulation decreased the expression of MCP-1, RANTES, and MMP-9 but not of IL-1β (Figure 2). THIAA+niacin pre-incubation, on the other hand, reduced the TNF-α-induced expression of all 4 markers and was more efficacious for inhibiting these markers than pre-incubation with niacin alone (Figure 2).

THIAA+niacin Favorably Affected Lipid Profile and Flow-mediated Vasodilation in Patients With Dyslipidemia

The mean age of participants in the THIAA+niacin arm, including 3 men and 4 women, was 49.7 ± 8.2 years old (mean ± SD). Mean baseline body mass index (BMI) was 33.1 ± 5.4 kg/m². Mean age in the placebo arm (1 man and 3 women) was 56.1 ± 0.3 years old and their mean BMI was 33.0 ± 7.7 kg/m². Baseline serum lipids, glucose, hs-CRP, and uric acid did not differ between study arms. In the THIAA+niacin arm, there
was a significant decrease ($P < .05$) in total cholesterol, LDL-C, and uric acid at week 12 compared to baseline (Table). A trend toward a decrease in apolipoprotein B (apo B) ($P = .07$) and a trend toward an increase in glucose ($P = .08$) also were observed. In contrast, no differences in any measurements were observed within the placebo arm except for a significant increase in hs-CRP ($P = .03$) at week 12. A significant between-arm difference ($P < .05$) was seen in hs-CRP and glucose.

Baseline FMD measurements did not differ between arms. By the end of week 12, a trend toward an improvement was observed in the THIAA+niacin arm, whereas there was a trend toward a decrease in the placebo arm; the difference between arms was statistically significant ($P = .03$, Figure 3A). In the optional follow-up study in which 2 placebo arm participants (after completing the trial) volunteered to receive THIAA+niacin treatment for 10 to 12 weeks, the combined data (7 data points from the original THIAA+niacin arm plus the 2 new data points) showed a statistically significant improvement in FMD compared to baseline ($P = .049$, Figure 3B) and compared to the placebo arm ($P = .031$).

Fourteen adverse events, occurring in 7 subjects, were noted during the study. Events were mild to moderate in severity, and all events were either not related or unlikely to be related to the study treatment. During the study, 2 respiratory infections, mild headaches, one accidental fall, and back discomfort were noted. THIAA+niacin did not differ from placebo in regards to physical symptoms and reported adverse events.

**DISCUSSION**

In our in vitro study, we showed in endothelial cell and monocyte models that the THIAA+niacin mixture was more effective for inhibiting TNF-$\alpha$-
induced cytokine/chemokine expression than niacin alone. In the pilot clinical study, THIAA+niacin treatment for 12 weeks resulted in improved FMD, lipid profile, and uric acid in volunteers with dyslipidemia, whereas in the placebo arm an undesirable increase in hs-CRP was observed.

THIAA’s antiinflammatory properties have been demonstrated previously, including inhibition of PGE2 in lipopolysaccharide-stimulated RAW 264.7 macrophages18 and inhibition of RANTES, MCP-1, IL-6, IL-8, and MMP-3 in IL-1β-stimulated rheumatoid arthritis synovial fibroblasts19 as well as attenuation of monocyte-endothelial cell interaction.21 Results reported here demonstrate that niacin plus THIAA exhibited a more significant inhibition of these cytokines/chemokines than niacin alone. Moreover, niacin had little effect on expression of MCP-1 and IL-1β in THP-1 cells, whereas THIAA+niacin was effective at inhibiting MCP-1 and IL-1β. These results suggest that the THIAA+niacin combination may have an augmented and expanded range of biological effects not seen with niacin alone.

THIAA+niacin was subsequently tested for effect on endothelial function in a pilot clinical trial. After dyslipidemic subjects consumed the THIAA+niacin tablets for 12 weeks (250 mg THIAA and 1000 mg niacin per day), the treatment produced favorable outcomes not observed in the placebo group. Participants in the THIAA+niacin arm experienced a mean 6.9% reduction in total cholesterol (P = .017), 11.8% reduction in LDL-C (P = .019), 7.7% reduction in uric acid (P = .017), and a trend toward a reduction in apoprotein B (P = .07) and Lp(a) (P = .07). We observed some favorable outcomes that are not generally seen with niacin treatment. For example, niacin treatment has been associated with increased uric acid and exacerbations of gout.23 Our data showed a statistically significant reduction in uric acid within the THIAA+niacin arm. Also, while it has been demonstrated previously that niacin has favorable outcomes on biomarkers of atherosclerosis, evidence for an impact of niacin on FMD is limited. Westphal24 failed to demonstrate an impact of niacin on FMD in 30 men with metabolic syndrome, only in a post-hoc analysis of subjects with coronary artery disease and HDL-C < 45 mg/dL but not in the intent-to-treat population with a baseline average

### Table Values and Percentage Changes After 12 Weeks of Lipid Markers, hs-CRP, Glucose, and Uric Acid in Each Study Arm

| Variable                  | Visit          | THIAA/niacin Arm (n=7) | Placebo Arm (n=4) | P     |
|---------------------------|----------------|------------------------|-------------------|-------|
|                          |                | Value                  | Change            | Value | Change |       |
| Cholesterol (mg/dL)       | Baseline       | 236.1 ± 8.0            | −17.0 ± 6.5       | 248.3 ± 18.8 | −2.3 ± 9.3 | .22  |
|                          | 12 weeks       | 219.1 ± 5.9            |                   | 246.0 ± 23.8 |                   |       |
| TG (mg/dL)                | Baseline       | 215.6 ± 59.1           | −28.7 ± 27.4      | 185.3 ± 31.5 | 27.0 ± 38.4 | .26  |
|                          | 12 weeks       | 186.9 ± 37.0           |                   | 212.3 ± 61.4 |                   |       |
| LDL (mg/dL)               | Baseline       | 152.9 ± 8.7            | −19.1 ± 6.1       | 160.5 ± 17.7 | −7.3 ± 4.3 | .21  |
|                          | 12 weeks       | 133.7 ± 6.6            |                   | 153.3 ± 14.3 |                   |       |
| HDL (mg/dL)               | Baseline       | 47.9 ± 2.7             | 0.3 ± 2.5         | 50.5 ± 1.6  | −0.3 ± 4.4 | .91  |
|                          | 12 weeks       | 48.1 ± 4.7             |                   | 50.3 ± 3.4  |                   |       |
| Cholesterol/HDL           | Baseline       | 5.00 ± 0.23            | −0.17 ± 0.34      | 4.98 ± 0.50 | 0.00 ± 0.35 | .75  |
|                          | 12 weeks       | 4.83 ± 0.54            |                   | 4.98 ± 0.64 |                   |       |
| TG/HDL                    | Baseline       | 4.95 ± 1.69            | −0.36 ± 0.37      | 3.73 ± 0.71 | 0.56 ± 0.97 | .31  |
|                          | 12 weeks       | 4.59 ± 1.45            |                   | 4.29 ± 1.35 |                   |       |
| Apo A1 (mg/dL)            | Baseline       | 142.3 ± 2.6            | −6.7 ± 8.0        | 146.3 ± 3.2 | −3.0 ± 2.6 | .67  |
|                          | 12 weeks       | 136.5 ± 9.9            |                   | 143.3 ± 4.5 |                   |       |
| Apo B (mg/dL)             | Baseline       | 112.6 ± 4.2            | −12.3 ± 5.6       | 131.3 ± 12.5 | −6.0 ± 4.7 | .47  |
|                          | 12 weeks       | 110.3 ± 5.6            |                   | 125.3 ± 9.5 |                   |       |
| ApoB/ApoA1                | Baseline       | 0.86 ± 0.02            | −0.03 ± 0.06      | 0.89 ± 0.07 | −0.02 ± 0.04 | .92  |
|                          | 12 weeks       | 0.83 ± 0.06            |                   | 0.87 ± 0.07 |                   |       |
| Lp(a) (nmol/L)            | Baseline       | 108.3 ± 30.5           | −9.3 ± 8.3        | 95.5 ± 72.3 | −1.0 ± 1.3 | .36  |
|                          | 12 weeks       | 99.0 ± 30.4            |                   | 94.5 ± 72.6 |                   |       |
| hs-CRP (mg/dL)            | Baseline       | 3.5 ± 1.0              | −0.3 ± 0.2        | 5.0 ± 2.0  | 0.7 ± 0.26 | .03  |
|                          | 12 weeks       | 3.3 ± 1.0              |                   | 5.7 ± 2.1  |                   |       |
| Glucose (mg/dL)           | Baseline       | 105.6 ± 12.5           | 3.3 ± 1.6         | 100.8 ± 4.7 | −4.3 ± 3.5 | .05  |
|                          | 12 weeks       | 108.9 ± 11.9           |                   | 96.5 ± 2.4 |                   |       |
| Uric acid (mg/dL)         | Baseline       | 6.6 ± 0.7              | −0.6 ± 0.2        | 7.6 ± 0.9  | 0.0 ± 0.1 | .11  |
|                          | 12 weeks       | 6.1 ± 0.5              |                   | 7.6 ± 0.9  |                   |       |

* Data are presented as mean ± SE.

### Abbreviations

Apo, apolipoprotein; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); TG, triglycerides; THIAA, tetrahydro-iso-alpha acids.

Conversion factors: Cholesterol, LDL, HDL, x 0.0259 (mmol/L); TG, x 0.0113 (mmol/L); Apo A1, Apo B, x 0.01 (g/L); Lp(a), x 0.0357 (μmol/L); Glucose, x 0.0555 (mg/dL).
HDL-C of 49 mg/dL. In our study (baseline average HDL of 48 mg/dL), the 12-week THIAA+niacin treatment resulted in improvement in FMD whereas the placebo treatment did not, and the between-arm difference was statistically significant. The minimal statistically significant improvement for absolute percentage change in FMD has been suggested to be 1.5% to 2%.22 Our pilot trial data showed a significant difference in FMD between the THIAA+niacin arm and the placebo arm, with an average 3% increase in the THIAA+niacin arm.

The mean 3.7% increase in glucose in the THIAA+niacin arm (\( P = .07 \)) was not unexpected. A large-scale review of randomized controlled trials and open-label studies of niacin reported that niacin (at ≤ 2.5 g/d) is associated with a 4% to 5% increase in fasting glucose levels, and the effects are modest, transient, or reversible.25

Although measures were taken to reduce technique-dependent error (all scans were performed and interpreted by the same blinded investigator), we recognize several limitations of this clinical study. As a pilot trial that was exploratory in nature, the sample size was not determined by power calculation. In retrospect, a 3-arm study (placebo vs niacin vs THIAA+niacin) would have provided additional insight on the contribution of THIAA alone. The treatment length was limited to 12 weeks, precluding an assessment of long-term benefits of THIAA+niacin. The study was conducted between July 2010 and March 2011. Despite instructions to maintain baseline dietary and exercise patterns, seasonal and holiday variations in participant behavior may have influenced study findings. A confirmatory clinical study addressing these limitations and with adequate statistical power is warranted. In addition, since THIAA+niacin appears to have beneficial effects on endothelial-regulated FMD in humans, future mechanistic studies using aortic endothelial cells and NO production as an endpoint would strengthen our understanding of its biological effects.

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**Figure 3** Percentage changes in flow-mediated vasodilation (FMD) after a 12-week treatment with THIAA/niacin or placebo. A, data from 11 subjects completed the study (\( N = 7 \) for THIAA/niacin arm and \( N = 4 \) for placebo). B, data from the optional follow-up study in which 2 placebo arm participants (after completing the trial) volunteered to receive THIAA/niacin treatment for 10-12 weeks and their data were combined with the original THIAA/niacin arm (\( N = 9 \)). Placebo arm data remained unchanged (\( N = 4 \)).
In summary, THIAA+niacin reduced endothelial/monocyte interactions in vitro and improved FMD and biomarkers of lipid metabolism, inflammation, and oxidative stress in a pilot study. Future studies will investigate the mechanisms underlying the THIAA+niacin effect on endothelial dysfunction and initiation of atherosclerosis. Overall, our results suggest that a THIAA+niacin combination may be a valuable component of a nutritional support program for subjects with dyslipidemia and atherosclerosis.

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