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Effects of twelve weeks of capsaicinoid supplementation on body composition, appetite and self-reported caloric intake in overweight individuals

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ABSTRACT

We examined if 12 weeks of capsaicinoid (CAP) supplementation affected appetite, body composition and metabolic health markers. Seventy seven healthy male and female volunteers (30 ± 1 y, 171.2 ± 9.8 cm, 81.0 ± 2.2 kg, 27.5 ± 0.6 kg/m^2) were randomly assigned to ingest either low-dose CAP (2 mg/d; L-CAP, n = 27), high-dose CAP (4 mg/d; H-CAP, n = 22) from Capsimax or placebo (corn starch; PLA, n = 28) for 12 weeks. At baseline (0 WK), 6 weeks (6 WK) and 12 weeks (12 WK) waist: hip ratio, body composition via dual energy x-ray absorptiometry (DEXA, 0 WK and 12 WK only), self-reported Calorie intakes, appetite levels via Council on Nutrition Appetite Questionnaire (CNAQ) and serum metabolic health markers (0 WK and 12 WK only) were analyzed. Moreover, an oral glucose tolerance test (OGTT) was administered at 0 WK and 12 WK, and serum glucose and insulin responses were examined 30–120 min post test-drink consumption. Waist: hip ratio significantly decreased in L-CAP from 0 WK to 6 WK ($p < 0.05$), although supplementation did not significantly affect body composition. H-CAP consumed less kcal/d compared to PLA at 12 WK (difference = 257 kcal/d, $p < 0.05$) and L-CAP participants at 12 WK (difference = 247, $p < 0.05$). Twenty-three percent (9/39) of the originally-enrolled H-CAP participants reported GI distress, although no participants in the L-CAP group reported such adverse events. Interestingly, H-CAP participants presented significant increases in serum insulin as well as significant decreases in serum HDL cholesterol levels from WK0 to WK12. However, supplementation did not affect the insulin response to the administered OGTT and/or other indices of insulin sensitivity. These data suggest that H-CAP supplementation reduces self-reported energy intake after 12 weeks of supplementation, and L-CAP supplementation also reduces waist: hip ratio. Longer-term effects of capsaicinoid supplementation on basal insulin and cholesterol levels warrant further investigation.

1. Introduction

Capsaicinoids are 9–11-carbon bioactive vanillylamides isolated from chili peppers (Aza-Gonzalez, Nunez-Palenius, & Ochoa-Alejo, 2011). While numerous capsaicinoid compounds exist, it has been estimated that capsaicin and dihydrocapsaicin make up over 80% of the capsaicinoid species in *Capsicum* plants (Aza-Gonzalez et al., 2011). Dietary supplementation with capsaicinoids has been reported to exhibit a myriad of physiological effects. In particular, studies have reported that acute capsaicinoid ingestion can acutely reduce appetite (Janssens, Hursel, & Westerterp-Plantenga, 2014;

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Reinbach, Smeets, Martinussen, Moller, & Westerterp-Plantenga, 2009) and increase thermogenesis and metabolism (Saito, 2015), while long-term supplementation facilitates body weight maintenance in obese participants (Lejeune, Kovacs, & Westerterp-Plantenga, 2003; Whiting, Derbyshire, & Tiwari, 2012). Although the anti-obesegenic mechanisms of capsaicinoids are poorly understood, recent *in vitro* evidence reported that capsaicinoids activate transient receptor potential cation channel subfamily V member 1 (TRVP1) receptors in preadipocytes; an effect which increased intracellular calcium flux and promoted lipolysis (Chen et al., 2015). Other *in vitro* research has reported that low dose capsaicinoid treatments inhibit adipogenesis in preadipocytes as well as induce the expression of brown fat cell and anti-adipogenic genes (Baboota et al., 2014a). Regarding anorectic mechanisms, capsaicinoid supplementation in rodents has been reported to induce a hypothalamic gene expression signature that is associated with satiety (Baboota et al., 2014b). Thus, these reports collectively suggest that capsaicinoid supplementation is a viable strategy for weight management.

Herein, we sought to examine the effects of 12 weeks of low- and high-dose capsaicinoid supplementation on appetite and body composition in apparently healthy men and women. A secondary aim of this study was to assess if supplementation affected serum health markers. Given the aforementioned clinical trials and mechanistic research, we hypothesized that both supplementation regimens would promote decreases in appetite and improvements in body composition. Moreover, we posited that the high-dose regimen would elicit the most beneficial effects.

2. Methods

2.1. Participants

All experimental protocols were approved by the University of Mary Hardin-Baylor Institutional Review Board prior to the initiation of research activities (ISRCTN registry #10458693). Participants were recruited on the basis of the following inclusion criteria: a) male or female, b) between the ages of 18–56 years; c) apparently healthy and free from disease; d) have not taken any ergogenic supplements in the last 6 months; e) able to do everything required in the study; f) agree to not do strenuous activity 24–48 h before appointment g) agree to not smoke or use caffeine and tobacco for 12-h before appointment; h) not eat or drink anything for 12-h before appointment; i) agree to not drink alcohol 24-h before appointment; j) a BMI between 24.5 and 29.5 or a body composition that was in moderate or better body classification based on gender and age; k) provided written and dated informed consent to participate in the study. 77 healthy males and females (30 ± 1 y, 171.2 ± 9.8 cm, 81.0 ± 2.2 kg, 27.5 ± 0.6 kg/m^2) volunteers completed the research protocol and a consort flow diagram in Fig. 1 illustrates study attrition below.

2.2. Testing sessions

There were three testing sessions and these included a week 0 baseline visit (0 WK), a 6-week mid-point testing session (6 WK), and a 12-week post-study testing session (12 WK) (Fig. 2).

The following describes each sequence of tests performed for each testing session. First, participants arrived to the laboratory in the morning in a 12-h fasted state and 24–48 h of no strenuous physical activity. Body mass (and height during 0 WK only) was assessed and participants then received a whole-body dual x-ray absorptiometry (DEXA) scan for body composition assessment (for 0 WK and 12 WK only) (Hologic Wi; Hologic Inc., Bedford, MA). Waist and hip measurements were then obtained via measuring tape and recorded in centimeters. Participants then had venous blood drawn from their arm via standard phlebotomy techniques at 0 WK and 12 WK only, and a panel of blood health markers (metabolic health markers and complete blood counts) were assessed by sending samples to a commercial laboratory (Quest Diagnostics, Irving, TX). A subset of participants from each group (PLA, n = 16; L-CAP, n = 16; H-CAP, n = 19) then performed an oral glucose tolerance test (OGTT) at 0 W K and 12 WK whereby they consumed a test drink (Trutol 75 g glucose tolerance beverage suspended in 10 fl. oz. water; NERL Diagnostics, New York, NY) and had serum drawn 30 min, 60 min, 90 min, and 120 min after the test drink consumption; of note, participants were not allowed to drink water or any other fluids during this monitoring period. Serum glucose and insulin was also assessed by sending samples to a commercial laboratory (Quest Diagnostics). Finally, participants completed an adjusted Council on Nutrition Appetite Questionnaire (CNAQ) to assess appetite levels which has been previously validated (Wilson et al., 2005). The CNAQ study questionnaire is provided in Table 1.

2.3. Supplementation and dietary protocols

Following 0 WK testing, participants were randomly assigned to

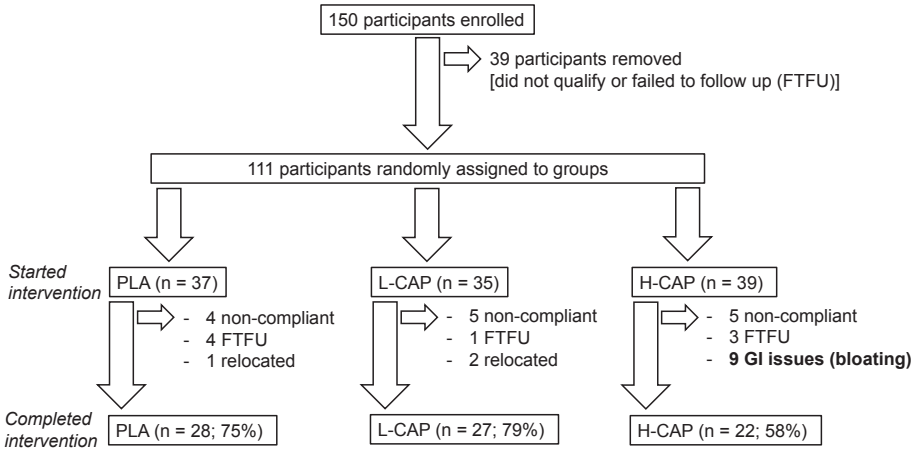

Fig. 1. Consort flow diagram.

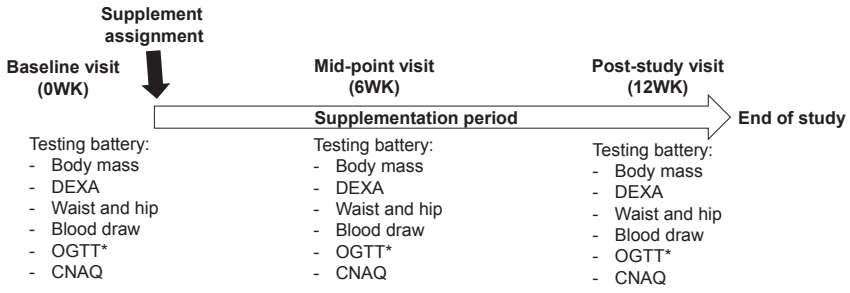

Fig. 2. Study design overview.

one of three supplementation groups. These groups included participants supplementing their diet with either low-dose CAP (L-CAP, 2 mg/d CAP from 200 mg pill; n = 27 total participants, n = 10 males, n = 17 females), high-dose CAP (H-CAP, 4 mg/d CAP from 400 mg pill; n = 22 total participants, n = 9 males, n = 13 females) or a corn-starch placebo (PLA; n = 28 total participants, n = 12 males, n = 16 females) for 12 weeks (PLA and CAP from Capsimax; OmniActive Health Technologies Ltd, Mumbai, India). Notably, dosing was based upon prior work using the same nutritional supplement whereby an acute ingestion of 2 mg increased blood free fatty acids and glycerol at select times up to 4 h post-ingestion (Bloomer, Canale, Shastri, & Suvarnapathki, 2010). Capsules were provided in bottles that were double-blinded to both the research team and participants. Participants were instructed to take pills after breakfast but before lunch (no empty stomach) on a daily basis, and participants were instructed to avoid foods containing chili pepper (i.e., serrano, cayenne, poblano, ancho, jalapeno, etc.) throughout the intervention. Supplementation compliance was monitored by having participants return empty pill bottles to the laboratory at 6 WK and 12 WK. Moreover, 3-d dietary recalls were collected at 0 WK, and participants were informed to not alter his/her diet throughout the 12-week intervention. To ensure that participants did not drastically alter his/her diet, 3-d dietary recalls were also collected at 6 WK and 12 WK. It should finally be noted that dietary recalls were analyzed for daily Calories consumed as well as macronutrient intakes using commercially-available software (ESHA; Salem, OR).

2.4. Statistics

For all 0 WK variables, one-way ANOVAs with Tukey *post hoc* tests were performed to ensure that there were no baseline differences between treatments. For 0 WK and 12 WK OGTT serum glucose and insulin responses, within-group responses were relative to pre-test drink consumption were measured using dependent samples t-tests with a Bonferroni correction factor applied whereby a significant change was accepted at $p < 0.0125$.

For all other dependent variables over time, two-way (treatment*time) ANOVAs were utilized. In the event there were main treatment effects, pairwise comparisons were performed using Tukey *post hoc* tests. In the event there were main time effects, we further decomposed the model by performing within-group

Table 1
Adjusted Council on Nutrition Appetite Questionnaire (CNAQ) surveys administered to participants.

Question	Score	
My appetite is	**a) Very poor (1)**	**d) Good (4)**
	b) Poor (2)	**e) Very good (5)**
	c) Average (3)	
When I eat	**a) I feel full after eating only a few mouthfuls (1)**	
	b) I feel full after eating about 1/3 of a meal (2)	
	c) I feel full after eating over 1/2 of a meal (3)	
	d) I feel full after eating most of a meal (4)	
	e) I hardly ever feel full (5)	
I feel hungry	**a) rarely (1)**	**d) most of the time (4)**
	b) occasionally (2)	**e) all of the time (5)**
	c) some of the time (3)	
Food tastes	**a) very bad (1)**	**d) good (4)**
	b) bad (2)	**e) very good (5)**
	c) average (3)	
Compared to when I was younger, food tastes	a) much worse (1)	d) better (4)
	b) worse (2)	e) much better (5)
	c) just as good (3)	
Normally I eat	**a) <1 meal per day (1)**	**d) 3 meals per day (4)**
	b) 1 meal per day (2)	**e) >3 meals per day (5)**
	c) 2 meals per day (3)	
I feel sick or nauseated when I eat	a) most times (1)	d) rarely (4)
	b) often (2)	e) never (5)
	c) sometimes (3)	
Most of my time my mood is	a) very sad (1)	d) happy (4)
	b) sad (2)	e) very happy (5)
	c) neither sad nor happy (3)	

Notes: this questionnaire was adopted from the work of Wilson et al. (Wilson et al., 2005), and participants scores were only tallied from bold-faced questions; higher scores generally indicate a greater appetite.

dependent samples t-tests (i.e., 6 WK to 0 WK and 12 WK to 0 WK). In the event there were treatment*time interactions, we further decomposed the model with the following statistics: a) within-group dependent samples t-tests were performed, and b) one-way ANOVAs at 6 WK and 12 WK were performed between groups and between-treatment significance was further determined using Tukey *post hoc* tests.

Finally, it should be noted that 0 WK and 12 WK OGTT serum glucose and insulin responses were statistically examined the methods of Matsuda and DeFronzo (Matsuda & DeFronzo, 1999). Specifically, the homeostatic model assessment of estimated insulin resistance (HOMA-IR) was derived whereby low HOMA-IR values indicate high insulin sensitivity and high HOMA-IR values indicate low insulin sensitivity (Bonora et al., 2002), and this variable was analyzed using a two-way (treatment*time) ANOVA. Moreover, the Matsuda index was also derived; this metric indicates the rate of glucose disappearance whereby higher values indicate greater insulin sensitivity and lower values indicate greater insulin resistance (Kernan et al., 2003), and this variable was analyzed using two-way (treatment*time) ANOVAs. Finally, integrated areas under the curve (AUCs) for 0 WK and 12 WK serum glucose and insulin were calculated using the trapezoidal method, and this variable was analyzed using two-way (treatment*time) ANOVAs.

All data herein are presented in figures and tables as means ± standard error values, all statistical analyses were performed using SPSS v22.0 (IBM, Armonk, NY), and statistical significance was set at $p < 0.05$.

3. Results

3.1. Participant characteristics

There were no baseline (0 WK) differences between treatments regarding age, gender distribution, ethnicity distribution, body composition variables (total body mass, DEXA lean mass, DEXA fat mass, waist circumference, hip circumference, waist: hip ratio), CNAQ score, Calories consumed per day from 3-d recalls, blood pressure variables, or serum health markers (glucose, insulin, triglycerides, HDL cholesterol, LDL cholesterol) (Table 2).

3.2. CAP supplementation did not affect body mass and body composition

The effects of each treatment on body mass and DEXA body composition variables are presented in Fig. 1. For body mass, there was no treatment effect ($p = 0.62$), time effect ($p = 0.69$) or treatment*time interaction ($p = 0.89$) (Fig. 3a). For DEXA lean body mass, there was no treatment effect ($p = 0.57$), time effect ($p = 0.41$) or treatment*time interaction ($p = 0.97$) (Fig. 3b). For DEXA fat mass, there was no treatment effect ($p = 0.92$), time effect ($p = 0.10$) or treatment*time interaction ($p = 0.63$) (Fig. 3c).

3.3. L-CAP supplementation improved waist: hip ratio

The effects of each treatment on waist circumference, hip circumference and waist: hip ratio are presented in Fig. 2. For waist circumference, there was no treatment effect ($p = 0.31$), time effect ($p = 0.77$) or treatment*time interaction ($p = 0.50$) (Fig. 4a). For hip circumference, there was no treatment effect ($p = 0.63$), time effect ($p = 0.39$) or treatment*time interaction ($p = 0.28$) (Fig. 4b). For waist: hip ratio, there was a time effect ($p < 0.05$), but no treatment effect ($p = 0.22$) or treatment*time interaction ($p = 0.83$) (Fig. 4c). Within-treatment analyses indicated that waist: hip ratio decreased by 2.4% in the L-CAP group from 0 WK to 6 WK.

3.4. Effects of CAP supplementation on appetite and caloric intake

The effects of each treatment on Caloric intakes and adjusted CNAQ scores are presented in Fig. 3. For Caloric intake, there was no treatment effect ($p = 0.74$), time effect ($p = 0.36$) or treatment*time interaction ($p = 0.08$). However, given our trend for an interaction effect, we performed additional *post hoc* analyses (significance not denoted on Fig. 5a). Interestingly, H-CAP participants reported consuming less Calories from 0 WK to 12 WK (difference = 284 kcal/d or 15%, $p < 0.05$). Furthermore, H-CAP

Table 2
Baseline (0 WK) participant characteristics.

Variable	PLA (n = 28)	L-CAP (n = 27)	H-CAP (n = 22)	ANOVA p-value
General characteristics				
Age (years)	29 ± 2	31 ± 2	29 ± 2	0.75
Gender				
Male				0.86*
Female				
Total body mass (kg)	83.5 ± 3.7	79.0 ± 3.9	80.2 ± 3.6	0.66
DEXA lean mass (kg)	54.1 ± 2.6	50.2 ± 2.7	52.2 ± 2.6	0.57
DEXA fat mass (kg)	21.0 ± 2.2	25.1 ± 4.7	19.9 ± 2.0	0.52
Waist circumference (cm)	94.6 ± 3.6	86.8 ± 3.5	89.9 ± 2.7	0.24
Hip circumference (cm)	107.4 ± 2.6	102.4 ± 3.5	106.8 ± 2.2	0.37
Waist: hip ratio	0.88 ± 0.02	0.85 ± 0.01	0.84 ± 0.02	0.29
Appetite and Caloric intake				
CNAQ score	31.1 ± 0.5	31.3 ± 0.6	32.0 ± 0.6	0.45
Kcal/d	1826 ± 120	1654 ± 101	1860 ± 146	0.44
Blood pressure parameters				
Systolic (mm Hg)	119 ± 2	115 ± 3	118 ± 2	0.48
Diastolic (mm Hg)	72 ± 2	70 ± 2	73 ± 2	0.49
Serum health markers				
Glucose (mg/dl)	86.7 ± 1.8	90.6 ± 4.1	86.3 ± 1.7	0.52
Insulin (μU/ml)	9.1 ± 4.0	6.1 ± 0.8	4.2 ± 0.5	0.37
Triglycerides (mg/dl)	85.5 ± 9.1	100.6 ± 8.9	86.2 ± 10.1	0.47
HDL cholesterol (mg/dl)	54.3 ± 2.7	52.3 ± 2.6	56.6 ± 3.7	0.60
LDL cholesterol (mg/dl)	107.6 ± 7.4	100.4 ± 5.7	91.5 ± 6.3	0.33

Legend: Measures were obtained at week 0 (0 WK) and compared using one-way ANOVAs to ensure that baseline differences did not exist between treatments. Abbreviations: DEXA, dual-energy x-ray absorptiometry; CNAQ, Council on Nutrition appetite questionnaire. Symbols: *, indicates that statistical analyses were performed on the relative proportion of males to females.

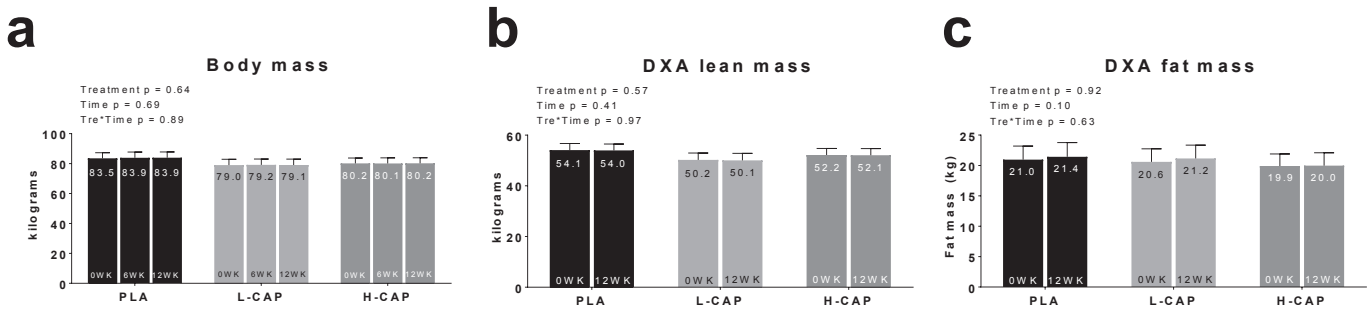

Fig. 3. Effects of treatments on body composition.

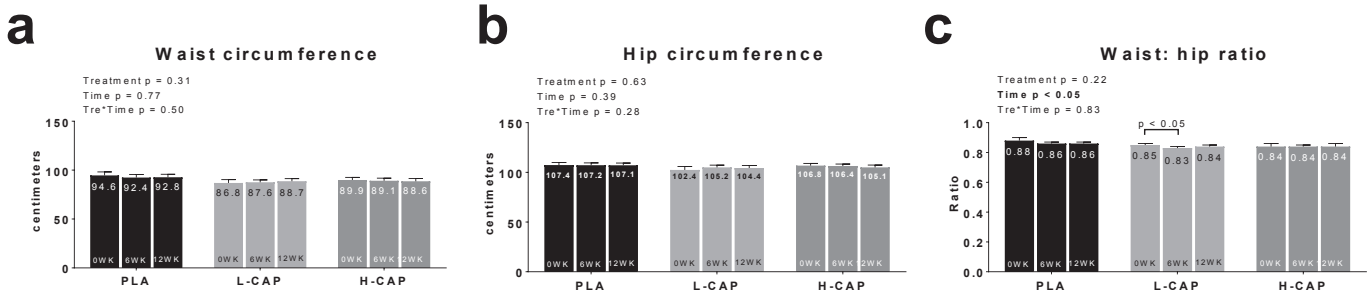

Fig. 4. Effects of treatments on anthropometric measurements.

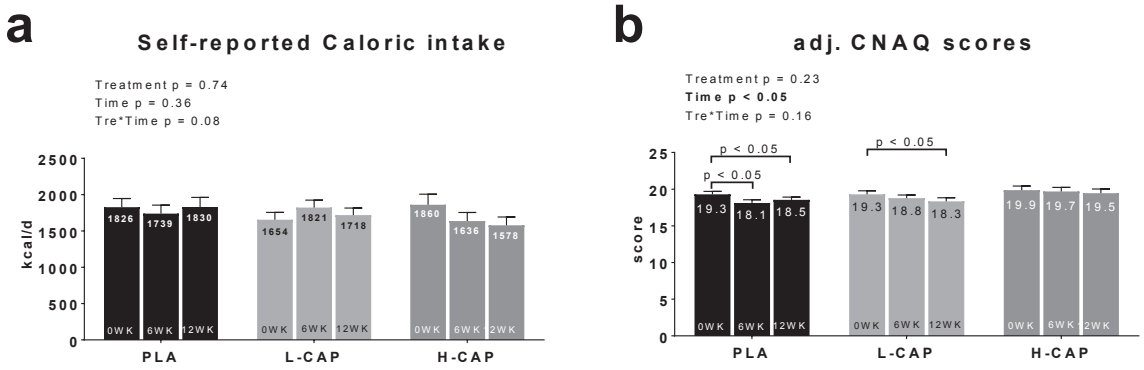

Fig. 5. Effects of treatments on self-reported Caloric intake and appetite.

participants consumed less Calories compared to PLA participants at 12 WK (difference = 252 kcal/d or 14%, $p < 0.05$) and L-CAP participants at 12 WK (difference = 142 kcal/d or 8%, $p < 0.05$).

For adjusted CNAQ scores, there was a time effect ($p < 0.05$), but no treatment effect ($p = 0.23$) or treatment*time interaction ($p = 0.16$) (Fig. 5b). Within-treatment analyses indicated that adjusted CNAQ scores: a) decreased in the PLA group from 0 WK to 6 WK by 6.1% ($p < 0.05$) and 0 to 12 WK by 3.9% ($p < 0.05$), b) decreased in L-CAP group from 0 WK to 12 WK by 5.0%, and c) did not significantly change in the H-CAP group.

3.5. CAP supplementation increased fasting insulin and reduced fasting HDL cholesterol levels

The effects of each treatment on serum health markers are presented in Table 3. There was a significant time effect for insulin ($p < 0.05$); specifically, insulin increased in the H-CAP group from 0 WK to 12 WK from 5.3 ± 0.5 μU/ml to 6.0 ± 0.9 μU/ml. There was a significant time effect for HDL cholesterol ($p < 0.05$); specifically, HDL cholesterol decreased in the H-CAP group from 0 WK to 12 WK from 54.5 ± 2.7 to 52.4 ± 3.1 mg/dl. There were no other treatment effects, time effects or treatment*time interactions for other serum health markers.

3.6. CAP supplementation does not affect serum glucose and insulin responses to an OGTT

The effects of each treatment on the serum glucose and insulin responses to the WK0 and WK12 OGTT tests are presented in Fig. 4. All groups (PLA, L-CAP and H-CAP) presented significant increases in serum glucose 30 min and 60 min post-test drink consumption at 0 WK ($p < 0.0125$; Fig. 6a) and 12 WK ($p < 0.0125$; Fig. 6b). Moreover all groups presented significant increases in serum insulin 30–120 min post-test drink consumption at 0 WK ($p < 0.0125$; Fig 6c) and 12 WK ($p < 0.0125$; Fig. 6d). Regarding glucose AUC values over the intervention, there was no treatment

Table 3
Effects of treatments on serum health markers. * P < 0.05.

Biomarker	Group	Week 0	Week 12	p-value
General metabolic health markers				
Insulin	PLA	9.1 ± 4.0	5.3 ± 0.5	Treatment p = 0.10
(μU/ml)	L-CAP	6.1 ± 0.8	9.3 ± 1.8	**Time p < 0.05**
	H-CAP	4.2 ± 0.5	**6.0 ± 0.9***	Tre*time p = 0.41
Glucose	PLA	86.7 ± 1.8	84.1 ± 1.9	Treatment p = 0.81
(mg/dl)	L-CAP	90.6 ± 4.1	91.8 ± 4.9	Time p = 0.34
	H-CAP	86.3 ± 1.7	87.0 ± 1.1	Tre*time p = 0.23
Triglycerides (mg/dl)	PLA	85.5 ± 9.1	81.4 ± 6.4	Treatment p = 0.10
	L-CAP	100.6 ± 8.9	116.7 ± 12.2	Time p = 0.25
	H-CAP	86.2 ± 10.1	91.4 ± 7.4	Tre*time p = 0.20
HDL cholesterol (mg/dl)	PLA	54.3 ± 2.7	54.5 ± 2.7	Treatment p = 0.59
	L-CAP	52.3 ± 2.6	49.3 ± 2.3	**Time p < 0.05**
	H-CAP	56.6 ± 3.7	**52.4 ± 3.1***	Tre*time p = 0.18
LDL cholesterol (mg/dl)	PLA	107.6 ± 7.4	101.7 ± 6.6	Treatment p = 0.33
	L-CAP	100.9 ± 4.7	100.4 ± 5.7	Time p = 0.33
	H-CAP	94.5 ± 6.8	91.5 ± 6.3	Tre*time p = 0.76

Legend: Measures were obtained at week 0 (0 WK) and week 12 (12 WK). Symbols: *, 12 WK is significantly different from 0 WK in a particular treatment.

(p = 0.09), time (p = 0.50) or treatment*time interaction (p = 0.97) (Fig. 6e). Regarding insulin AUC values over the intervention, there was no treatment (p = 0.28), time (p = 0.98) or treatment*time interaction (p = 0.91) (Fig. 6f). Regarding HOMA-IR index values over the intervention, there was no treatment (p = 0.71), time (p = 0.12) or treatment*time interaction (p = 0.14) (Fig. 6g). Regarding Matsuma index values over the intervention, there was no treatment (p = 0.19), time (p = 0.80) or treatment*time interaction (p = 0.74) (Fig. 6h).

3.7. CAP supplementation minimally affects blood clinical safety markers

The effects of each treatment on blood clinical safety markers are presented in Table 4. There was a significant time effect for albumin (p < 0.05); specifically, albumin decreased in the all groups from 0 WK to 12 WK. There was also a treatment*time interaction for whole blood neutrophil counts (p < 0.05), whereby neutrophil number increased by 21% in the L-CAP group from 0 WK to 12 WK. There were no other treatment effects, time effects or treatment*time interactions for other blood clinical safety markers (i.e., blood urea nitrogen, serum creatinine, serum globulin, aspartate transaminase, alanine transaminase, red blood cell counts, white blood cell counts, lymphocyte counts, or monocyte counts). Moreover, no adverse effects (anxiety, GI distress or restlessness) were reported in the PLA, L-CAP or H-CAP groups (*data not shown*).

4. Discussion

Herein, we sought to examine the effects of 12 weeks of low- and high-dose capsaicinoid supplementation on appetite and body composition in apparently healthy men and women, and the effects of supplementation on serum health markers was a secondary aim. While only main effects for time existed, we did observe that waist: hip ratio measurements decreased 2.4% in the L-CAP from week 0 to week 6, albeit no difference existed in this group when comparing WK0 to WK12. Moreover, adjusted CNAQ questionnaires indicated that L-CAP participants experienced a within-group decrease in subjective appetite 12 weeks into the intervention (−5%, p < 0.05), albeit this effect also existed within the placebo group. From week 0 to week 12, H-CAP participants presented significant increases in serum insulin as well as a significant decrease in serum HDL cholesterol levels. It is also notable that 23% (9/39) of the originally-enrolled H-CAP participants reported GI distress, although no participants in the L-CAP group reported such adverse events. These findings are discussed in greater detail below.

4.1. The effects of capsaicinoid supplementation on body composition

As mentioned previously, human studies have reported that long-term capsaicinoid supplementation can facilitate body mass maintenance after weight loss (Lejeune et al., 2003) and even potentially promote weight loss (Whiting et al., 2012). Rodent studies have also determined that capsaicinoid consumption affects the expression of lipogenic genes in adipose tissue (Joo, Kim, Choi, & Yun, 2010) and decreases visceral adipose tissue mass (Leung, 2008). While we did observe a decrease in waist: hip ratio measurements in the L-CAP group from 0 WK to 6 WK, we report that low- and high-dose capsaicinoid supplementation in the current study did not affect body mass or body composition. Our findings of improvements in waist: hip ratio is in agreement with Snitker et al. (Snitker et al., 2009) who reported that 12 weeks of 6 mg/d capsaicinoid supplementation in overweight men and women significantly reduced abdominal adiposity by 1.1% compared to a placebo group (0.2% reduction). Notwithstanding, our findings that capsaicinoid supplementation did not improve overall body composition (i.e., reduced total body adiposity) conflicts with the aforementioned anthropometric improvements. Indeed, the abovementioned Snitker et al. study also reported no improvements in overall body composition despite the capsaicinoid-induced improvements in waist: hip ratio. A recent meta-analysis by Ludy et al (Ludy, Moore, & Mattes, 2012) also reported that only one of 12 studies demonstrated that capsaicinoid supplementation was capable of increasing thermogenesis. Specifically, this particular study (Lejeune et al., 2003), the authors had participants consume a relatively high dose of capsaicin (135 mg/d) for 3 months during a weight maintenance period following weight loss. Although the authors reported that fat oxidation after weight maintenance was higher in the capsaicin group compared with placebo, weight maintenance did not differ compared to the placebo group. Hence, while rodent studies have determined that capsaicinoid supplementation possesses anti-obesigenic properties, our study is in agreement with Ludy et al. which reports that most human studies show no overall body composition effect with low-dose capsaicinoid supplementation. Notwithstanding, our data on improvements in waist: hip ratio demonstrate potential promising effects of capsaicinoid supplementation on metabolic

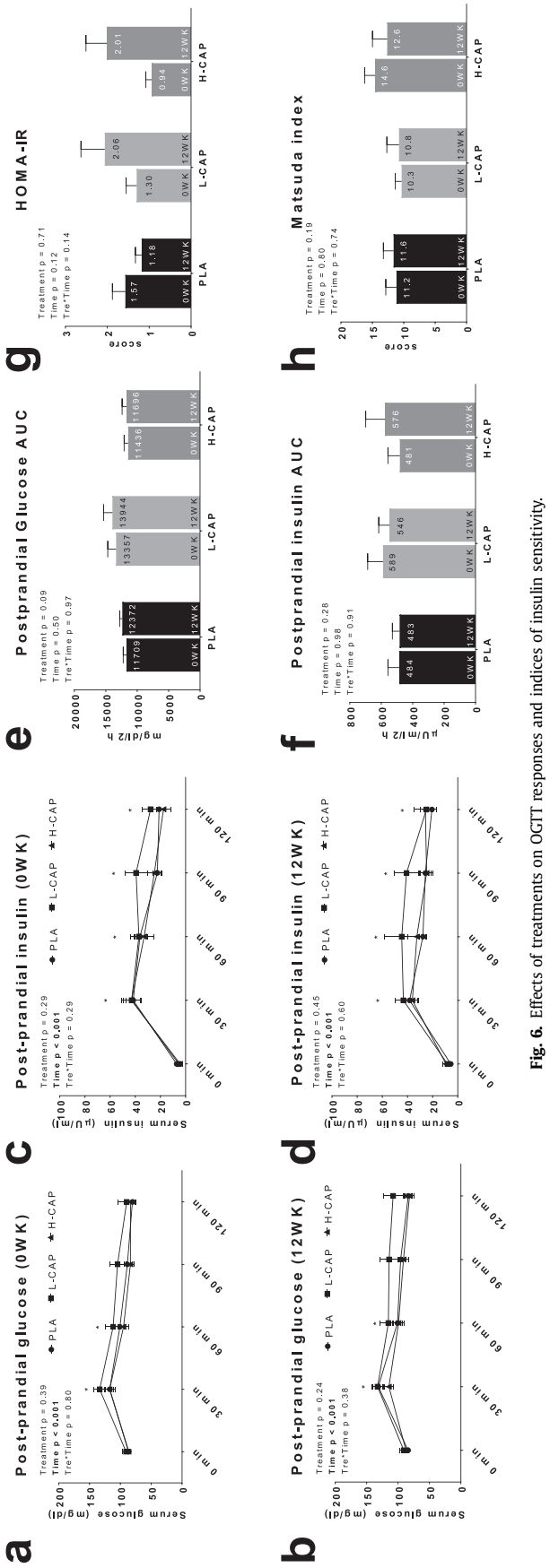

Fig. 6. Effects of treatments on OGTT responses and indices of insulin sensitivity.

Table 4
Effects of treatments on blood clinical safety markers.* P < 0.05.

Biomarker	Group	Week 0	Week 12	p-value
Kidney health markers				
BUN	PLA	14.1 ± 0.8	13.7 ± 0.6	Treatment p = 0.31
(mg/dl)	L-CAP	14.9 ± 0.7	13.7 ± 0.8	Time p = 0.18
	H-CAP	15.1 ± 1.0	15.8 ± 1.0	Tre*time p = 0.09
Creatinine (mg/dl)	PLA	0.93 ± 0.03	0.91 ± 0.03	Treatment p = 0.51
	L-CAP	0.92 ± 0.04	0.92 ± 0.04	Time p = 0.18
	H-CAP	0.95 ± 0.04	0.95 ± 0.04	Tre*time p = 0.63
Liver health markers				
Albumin	PLA	4.39 ± 0.06	**4.25 ± 0.06***	Treatment p = 0.65
(mg/dl)	L-CAP	4.35 ± 0.06	**4.22 ± 0.06***	**Time p < 0.05**
	H-CAP	4.29 ± 0.07	**4.18 ± 0.07***	Tre*time p = 0.95
Globulin	PLA	2.55 ± 0.07	2.55 ± 0.08	Treatment p = 0.60
(mg/dl)	L-CAP	2.64 ± 0.06	2.64 ± 0.06	Time p = 0.39
	H-CAP	2.54 ± 0.07	2.59 ± 0.07	Tre*time p = 0.81
AST	PLA	26.5 ± 2.3	21.5 ± 1.3	Treatment p = 0.71
(U/L)	L-CAP	27.4 ± 4.7	21.2 ± 1.8	Time p = 0.12
	H-CAP	21.2 ± 1.2	22.2 ± 3.0	Tre*time p = 0.39
ALT	PLA	25.5 ± 3.9	23.7 ± 5.2	Treatment p = 0.57
(U/L)	L-CAP	23.9 ± 3.3	21.9 ± 3.2	Time p = 0.54
	H-CAP	18.5 ± 1.6	18.7 ± 2.0	Tre*time p = 0.81
Blood cell differentials				
RBCs	PLA	4.63 ± 0.09	4.53 ± 0.11	Treatment p = 0.90
($*10^6$/μl)	L-CAP	4.53 ± 0.09	4.57 ± 0.08	Time p = 0.87
	H-CAP	4.47 ± 0.11	4.55 ± 0.10	Tre*time p = 0.11
WBCs	PLA	6.22 ± 0.35	5.87 ± 0.28	Treatment p = 0.41
($*10^3$/μl)	L-CAP	6.16 ± 0.37	6.87 ± 0.40	Time p = 0.26
	H-CAP	5.80 ± 0.34	6.04 ± 0.33	Tre*time p = 0.07
Neutrophils	PLA	3541 ± 326	3171 ± 208	Treatment p = 0.43
($*10^3$/μl)	L-CAP	3227 ± 247	**3895 ± 328***	Time p = 0.17
	H-CAP	2875 ± 253	3267 ± 278	**Tre*time p < 0.05**
Lymphocytes	PLA	2023 ± 119	2111 ± 134	Treatment p = 0.13
($*10^3$/μl)	L-CAP	2500 ± 155	2354 ± 179	Time p = 0.40
	H-CAP	2249 ± 159	2089 ± 129	Tre*time p = 0.29
Monocytes	PLA	396 ± 33	370 ± 28	Treatment p = 0.21
($*10^3$/μl)	L-CAP	474 ± 39	404 ± 36	Time p = 0.51
	H-CAP	418 ± 37	456 ± 30	Tre*time p = 0.17

Legend: Measures were obtained at week 0 (0 WK) and week 12 (12 WK). Abbreviations: BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase. Symbols: *, 12 WK is significantly different from 0 WK in a particular treatment.

outcomes, and this finding (along with the aforementioned Snitker et al. study) warrant more research regarding how capsaicinoid supplementation mechanistically affects visceral adipose tissue.

4.2. The effects of capsaicinoid supplementation on appetite and caloric intake

In the current study, we report that the L-CAP group reported lower subjective appetite scores on the adjusted CNAQ questionnaires from 0 WK to 12 WK. Moreover, while the treatment*time interaction for self-reported Calorie intake only approached statistical significance ($p = 0.08$), the H-CAP participants reduced their Calorie intakes from 1860 kcal/d at 0 WK to 1578 kcal/d at 12 WK, and a 'forced' post hoc analysis within this group yielded a significant decrease from 0 WK to 12 WK ($p < 0.05$). However, our findings are limited given that the placebo group also reported a significant reduction in subjective appetite from 0 WK to 6 WK and 12 WK.

Other studies have reported that capsaicinoid consumption reduces appetite (Castonguay & Bellinger, 1987; Ludy & Mattes, 2011; Westerterp-Plantenga, Smeets, & Lejeune, 2005; Yoshioka et al., 1999), although equivocal data exists (Smeets & Westerterp-Plantenga, 2009). In rodents, Castonguay and Bellinger (Castonguay & Bellinger, 1987) reported capsaicin injections reduced the intake of sweetened condensed milk. In humans,

Westerterp-Plantenga et al (Westerterp-Plantenga et al., 2005) reported that consumption with tomato juice or pill-form consumption of 225 mg of capsaicin 30 min prior to meal consumption reduced Calorie consumption and perceived satiety. Yoshika et al (Yoshioka et al., 1999) reported in humans that the consumption of 10 g of red pepper with breakfast decreased food intake during a subsequent lunch meal, and the authors attributed this to the capsaicinoid content of the peppers. Similarly, Ludy and Mattes (Ludy & Mattes, 2011) reported that naïve red pepper consumers who consumed 1 g of red pepper exhibited a reduced preoccupation with their desire to consume fatty/salty/sweet foods. Regarding potential appetite-reducing mechanisms of capsaicin, prior rodent research has reported that peripheral gut sensory neurons that are capsaicin-sensitive can regulate food intake (Gomez et al., 2002). Moreover, recent human data suggests that capsaicin administration does not affect the secretion of anorectic gastrointestinal (GI) peptides (i.e., glucagon-like peptide or peptide YY), but instead promotes satiety through increased GI distress and bloating sensation (van Avesaat et al., 2016); again, this being possibly mediated through capsaicin-sensitive afferent gut neurons which relay satiety signals to appetite control mechanisms in the brain. Thus, future research should continue to examine how graded doses of capsaicin administration affect appetite, and whether longer-term capsaicin-induced decreases in food intake can facilitate appreciable weight loss without promoting a negative GI response.

4.3. The effects of capsaicinoid supplementation on serum health markers and OGTT responses

Interestingly, there were time effects for serum insulin, HDL cholesterol and albumin and *post hoc* analyses indicated that serum insulin increased and serum HDL cholesterol decreased from 0 WK to 12 WK. While the research is limited, some studies have examined how capsaicinoids affect serum health markers. For instance, capsaicin supplemented in the daily feed of hypercholesterolemic rats (0.015%) has been found to lower serum cholesterol levels (Manjunatha & Srinivasan, 2007). Hence, our finding that capsaicinoid supplementation lowered HDL cholesterol in the H-CAP group is somewhat in agreement with these findings. However, equivocal findings also exist. For instance, Babu and Srinivasan (Babu & Srinivasan, 1997) reported that diabetic rats fed 15 mg/d of capsacin for 8 weeks did not experience any alterations in serum cholesterol. Moreover, in obese patients, Mohammadi et al (Mohammadi et al., 2013) reported that 1 g/d of capsaicinoid supplementation did not affect serum cholesterol levels. Thus, our findings require more research with regards to elucidating how capsaicinoid supplementation affects different cholesterol species and liver cholesterol synthesis. It is important to note, however, that capsaicinoid supplementation did not cause a drastic reduction in HDL cholesterol levels and we posit that this effect should not be a cause for concern when supplementing with capsaicinoids.

The capsaicinoid-induced increase in insulin at 12 WK was also unexpected albeit this, again, was not a treatment*time interaction. Moreover, the OGTT tests and 0 WK and 12 WK indicated that capsaicinoid supplementation did not augment the insulinogenic response to a glucose test drink solution. It should be noted that the L-CAP and H-CAP participants did not present greater basal glucose levels at 12 WK, nor did they present significant increases in HOMA-IR or significant decreases in Matsuda index values which may be suggestive of insulin resistance. Again, there is a lack of literature that has studied the effects of capsaicinoid ingestion on insulin, although one study exists to our knowledge whereby this was a specific aim of the study. Specifically, 8 weeks of capsaicin supplemented in the diet of diabetic rats has been shown to increase insulin secretion during hyperglycemic clamp (Kwon et al., 2013). Thus, the greater insulin levels in our study may be reflective of the ability of capsaicinoids to potentiate insulin secretion, and this should be studied in greater detail in models of impaired insulin secretion.

Capsaicinoid supplementation did not negatively affect other kidney or liver function parameters and/or total red blood cell or white blood cell counts suggesting that the tested capsaicinoid source was safe for human consumption over a 12-week period. Neutrophil counts did significantly increase from 0 W K to 12 WK in the L-CAP group. Indeed, animal studies have reported that capsaicinoid treatments can alter the number and function of neutrophils (Franco-Penteado et al., 2006; Zhukova & Makarova, 2002). However, our observations that neutrophils increase in the L-CAP group without functional neutrophil assays precludes us from interpreting how or if neutrophil function is affected.

What is important to note is that 23% of the originally-enrolled participants in the H-CAP group (9/39) did report GI distress and removed themselves from the study. This in not unfounded given recent human research has reported that the intraduodenal infusion of capsaicin significantly increases satiety, but also increases GI pain, nausea, and bloating compared a placebo infusion (van Avesaat et al., 2016). Therefore, this potential negative side effect should be considered prior to individuals ingesting high doses of capsaicin-related supplements.

4.4. Limitations

This study is not without limitations. First, the L-CAP and H-CAP groups were supplemented with 2 mg/d and 4 mg/d of capsaicinoids, and other studies have supplemented participants with much higher doses (i.e., 135 mg/d (Lejeune et al., 2003)). Hence, our not finding treatment*time interactions may be due to relatively low doses administered, albeit it should be noted that the capsaicinoid content of the tested supplement was relatively high compared to other studies. Second, our participants were apparently healthy and were mildly overweight but not obese. Thus, if capsaicinoid supplementation is indeed effective at improving body composition, then more studies need to be performed in participants with greater BMIs.

5. Conclusions

Despite the aforementioned limitations, our data demonstrate that 12 weeks of capsaicinoid supplementation may be effective at reducing appetite and potentially improving select body composition metrics (i.e., waist: hip ratio). Future studies are needed which control for various lifestyle factors (i.e., diet and physical activity) in order to determine if modulating these factors with concomitant CAP supplementation unveils potential synergistic effects. More mechanistic research is also needed in order to determine the mechanisms whereby capsaicinoid supplementation may affect cholesterol production and insulin secretion in diseased populations; specifically, if capsaicinoid supplementation can increase insulin secretion in diabetic patients and/or reduce cholesterol levels in hypercholesterolemic patients then this could be a viable nutraceutical strategy to help improve metabolic outcomes.

Legend: 150 participants were enrolled in the study and 29 participants were removed due to not qualifying or not following up for the initial T1 visit. The remaining 111 participants were randomly assigned to the PLA (n = 37), L-CAP (n = 35) or H-CAP (n = 39) groups. 9 participants in the PLA group did not finish the trial, 8 participants in the L-CAP group did not finish the trial, and 17 participants in the H-CAP group did not finish the trial. Notably, in the H-CAP group only numerous participants (n = 9) complained

about gastrointestinal issues (i.e., bloating).

Legend: Briefly, participants visited the laboratory in an overnight-fasted state prior to the intervention (0 WK), and 6- (6 WK) and 12 weeks (12 WK) following supplementation. The following assessments were performed in order: a) body mass, b) body composition via dual x-ray absorptiometry (DEXA), c) waist and hip circumferences, d) blood was drawn for clinical health marker assessment, d) an oral glucose tolerance test was performed (* indicates that this was done in a subset of participants), and e) appetite levels were assessed via the Council on Nutrition Appetite Questionnaire (CNAQ). It should finally be noted that self-reported 3-day food logs were also collected at each time point (not depicted in figure).

Legend: Effects of placebo (PLA), low-dose capsaicinoid supplementation (2 mg/d; L-CAP) and high-dose capsaicinoid supplementation (4 mg/d; H-CAP) on body mass (A), DEXA lean mass (B) and DEXA fat mass (C) over a 12-week period. Measures were obtained at either week 0 (0 WK), week 6 (6 WK) and week 12 (12 WK), or 0 WK and 12 WK (DEXA data).

Legend: Effects of placebo (PLA), low-dose capsaicinoid supplementation (2 mg/d; L-CAP) and high-dose capsaicinoid supplementation (4 mg/d; H-CAP) on waist circumference (A), hip circumference (B) waist: hip ratio (C) over a 12-week period. Measures were obtained at week 0 (0 WK), week 6 (6 WK) and week 12 (12 WK).

Legend: Effects of placebo (PLA), low-dose capsaicinoid supplementation (2 mg/d; L-CAP) and high-dose capsaicinoid supplementation (4 mg/d; H-CAP) on self-reported Caloric intakes (A) and Council on Nutrition appetite questionnaire (CNAQ) scores (B) over a 12-week period. Reported Caloric intakes were based upon 3-d food recalls at week 0 (0 WK), week 6 (6 WK) and week 12 (12 WK). Council on Nutrition appetite questionnaire (CNAQ) surveys were also administered at 0 WK, 6 WK and 12 WK; notably higher scores generally indicate a greater appetite.

Legend: OGTT serum glucose at week 0 and 12 are presented in panels A and B, respectively. OGTT serum insulin at week 0 and 12 are presented in panels C and D, respectively. Integrated areas under the curve at weeks 0 and 12 for glucose and insulin are presented in panels E and F, respectively. The homeostatic model assessment of estimated insulin resistance (HOMA-IR) at weeks 0 and 12 is presented in panel G; lower HOMA-IR values indicate high insulin sensitivity and higher HOMA-IR values indicate low insulin sensitivity. Finally, the Matsuda index at weeks 0 and 12 is presented in panel H; higher values indicate greater insulin sensitivity and lower values indicate greater insulin resistance.

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