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Original Research

A Short-Term Paleolithic Dietary Intervention Does Not Alter Adipokines Linked to Adiposity

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ABSTRACT

International Journal of Exercise Science 14(2): 113-122, 2021. The Paleolithic diet, characterized by an emphasis on hunter-gatherer type foods accompanied by an exclusion of grains, dairy products, and highly processed food items, is often promoted for weight loss and a reduction in cardiometabolic disease risk factors. Specific adipokines, such as adiponectin, omentin, nesfatin, and vaspin are reported to be dysregulated with obesity and may respond favorably to diet-induced fat loss. We aimed to evaluate the effects of an eight-week Paleolithic dietary intervention on circulating adiponectin, omentin, nesfatin, and vaspin in a cohort of physically inactive, but otherwise healthy adults. Methods: Seven inactive adults participated in eight weeks of adherence to the Paleolithic Diet. Fasting blood samples, anthropometric, and body composition data were collected from each participant pre- and post-intervention. Serum adiponectin, omentin, nesfatin, and vaspin were measured. Results: After eight weeks of following the Paleolithic diet, there were reductions (p<0.05) in relative body fat (-4.4%), waist circumference (-5.9 cm), and sum of skinfolds (-36.8 mm). No changes were observed in waist to hip ratio (WHR), or in adiponectin, omentin, and nesfatin (p>0.05), while serum vaspin levels for all participants were undetectable. Conclusions: It is possible that although eight weeks resulted in modest body composition changes, short-term fat loss will not induce changes in adiponectin, omentin, and nesfatin in apparently healthy adults. Larger, long-term intervention studies that examine Paleolithic diet-induced changes across sex, body composition, and in populations with metabolic dysregulation are warranted.

KEY WORDS: young adults, nutrition, macronutrients, eating pattern

INTRODUCTION

The Paleolithic diet is a very popular dietary eating pattern (33). Characterized by an emphasis on hunter-gatherer type foods (i.e. fruits, vegetables, and meat) and accompanied by an exclusion of grains, dairy products, and highly processed food items, the diet is often promoted for weight loss and a reduction in cardiometabolic disease risk factors (27). Nevertheless, the body of scientific research concerning the Paleolithic diet remains relatively

small, especially in regard to intervention studies (27). More research is warranted to clarify if the diet's promoted effectiveness in weight loss and improvements in metabolic health is accurate.

Effective weight loss methods that reduce both adiposity and its associated comorbidities are of paramount importance, especially in the US, where over 60% of adults and 30% of children are classified as overweight (23). Indeed, the links between obesity and cardiovascular disease (23, 28), type 2 diabetes (13), cancer (20), metabolic syndrome (13, 28) and other inflammatory/autoimmune conditions (35) are well established. It has been suggested that the modern global shift towards increased consumption of processed foods serves as a major contributor to increases in the prevalence of obesity and these obesity-related complications (40). Indeed, Hall et al.(15) reported greater energy intake (i.e. carbohydrate and fat) and weight gain while participants followed an ultra-processed diet when compared to an unprocessed diet even when presented with meals that were initially matched for calories and macronutrients. Participants followed each diet for two weeks and were instructed to consume the foods *ad libitum*. The authors suggest that limiting processed food consumption may be a useful strategy for the prevention of obesity (15). Thus, obesity is a key link between lifestyle and chronic disease, and the Paleolithic diet may serve as a means for encouraging weight loss and eating fewer processed foods, thereby reducing the risk of chronic disease.

Adipokines are considered a class of biomarkers indicative of health and metabolic disease. They are secreted from adipose tissue and act in an autocrine, paracrine, or endocrine manner and have been implicated in the regulation of metabolic health and eating behaviors (6). Specific adipokines have been shown to be dysregulated with obesity. For example, the adipokines adiponectin, omentin, and nesfatin generally appear to be inversely proportional to adiposity (12, 31, 34), although levels of adiponectin may instead be elevated with extreme obesity (25). Adiponectin, especially high molecular weight (HMW) adiponectin, offers cardioprotective and anti-inflammatory effects (31). Low levels of omentin have been associated with impaired glucose tolerance, dyslipidemia, high blood pressure, and markers of atherosclerosis (29). Nesfatin may be secreted by the brain and gut tissue in addition to adipose tissue and assists with appetite regulation (3, 10, 34). However, the relationship between nesfatin and obesity in humans and the role it plays in regulating metabolic health remains controversial (32). Conversely, levels of the adipokine vaspin positively correlate with body weight, BMI, and visceral adipose tissue, particularly in patients with insulin resistance (7, 12). Importantly, levels of vaspin appear to be responsive to weight loss, as lifestyle-induced reduction in adiposity has been found to result in significantly lower levels of circulating vaspin (7). Thus, levels of circulating adipokines may be important biomarkers to understand particular obesity-related health risks.

Many of these adipokines are relatively new, and thus the number of published human participant intervention research studies examining these adipokines is extremely limited. As of yet, none of these markers have been examined in the context of a Paleolithic dietary intervention. Therefore, the purpose of this study was to evaluate the effects of an eight-week Paleolithic dietary intervention on HMW adiponectin, omentin, nesfatin, and vaspin in a

cohort of physically inactive, but otherwise apparently healthy adults. We hypothesized that reductions in adiposity achieved through the Paleolithic diet would result in favorable alterations in these obesity-related adipokines. Specifically, we hypothesized that levels of HMW adiponectin, omentin, and nesfatin would increase with a decrease in adiposity, and that vaspin levels would decrease with decreased adiposity.

METHODS

Participants

This study is a part of a larger project that investigated the effectiveness of a self-administered Paleolithic diet on improving cardiometabolic disease risk factors (21). All participants provided a signed written statement of informed consent prior to participation in the study, and this study was approved by the Institutional Review Boards at both Chatham University and the University of Houston. The research was carried out fully in accordance to the ethical standards of the International Journal of Exercise Science (24). Potential participants completed health history and a physical activity [International Physical Activity Questionnaire (IPAQ)] questionnaires. Potential participants were excluded if they reported cardiovascular, metabolic (i.e. type 1 or type 2 diabetes), or respiratory disease; tobacco use; or pregnancy. Preliminary eligible participants then proceeded to complete a 3-day dietary recall recorded over 2 weekdays and 1 weekend day that was used to confirm the consumption of a Western diet and to determine average baseline total daily energy intake (TDEI) and macronutrient distribution.

As previously reported, 21 participants met the initial eligibility but only seven (males = 4, females = 3; age: 32.4 ± 4.9 years; BMI: 29.4 ± 2.4 kg/m^2) completed the intervention and all study measures (21). The seven participants were considered physically inactive, according to the criteria outlined by the IPAQ. All participants were consuming a typical Western diet, characterized by the high consumption of dairy products, cereal grains, added salt, and refined sugars and vegetable oils (9). This was confirmed following completion of the three-day dietary recall.

Protocol

Pre- and post-intervention testing occurred before and after the eight-weeks of adherence to the Paleolithic diet. For both testing sessions, participants reported to the laboratory after a 12-hour overnight fast. Following a 15-minute rest in the seated position, each participant's heart rate (HR) and blood pressure (BP) were measured. Thereafter, a tourniquet was applied to the subject's preferred arm and the antecubital space was sterilized using an alcohol swab with time provided to air dry. A 21 gauge needle was used to collect a venous blood sample into a 10 ml red top SST vacutainer tube. Samples were chilled, allotted 30 minutes for clotting, and centrifuged at 1370 x g (4^{o}C) for 10 minutes. Serum was then aliquoted into cryovials and stored at -80°C until batch analysis.

Height and weight were then measured, using a mechanical beam scale with a height rod (Health o meter® Professional Scales, McCook, IL, USA). Body composition was also measured using the 7-site skin fold method (1) at the following sites: chest, abdomen, thigh, triceps,

subscapular, suprailliac, and midaxilla. Each measurement was taken to the nearest 0.1 mm, and two measurements were taken at each site in a rotational manner to ensure that each measurement was within 2 mm of each other. If the measurements differed by more than 2 mm, a third was taken. All measurements were then averaged for each site. Skinfolds were all performed by the same researcher using a Lange skinfold caliper (Beta Technology, Santa Cruz, CA, USA). Body density and body composition were calculated from the sum of skinfolds across all sites (SS) using the sex-specific formulas for 7-site skin folds (1).

Waist and hip circumference were measured using a tape measure at the level of the umbilicus, and around the largest portion of the buttocks, respectively. Two measurements of each were taken in a rotational manner to ensure that each measurement was within 2 cm of each other. These values were then averaged and the waist-to-hip ratio (WHR) was calculated.

All participants agreed to adhere to the Paleolithic diet for the duration of the eight-week intervention. They were provided with recipes, sample menus, and a list of resources to assist them with food shopping and food preparation (21). Study team members provided contact information and were available to respond to any last-minute questions. Participants met with study personnel weekly to address any study-related concerns, provide encouragement, and to discuss strategic methods for adherence to the Paleolithic diet over the course of the intervention. No caloric restrictions were established, and participants were encouraged to consume Paleolithic diet-appropriate foods *ad libitum*. During week 4 and 8, participants completed a 3-day food diary over the course of 2 weekdays and 1 weekend day that were used to verify adherence to the Paleolithic diet and to quantify caloric intake.

Baseline and final testing serum samples were thawed for each participant and analyzed together. Serum HMW adiponectin (30 kDa adipocyte complement-related protein; intra-assay CV 8.9%) was measured using a commercially available ELISA kit (RayBiotech, Norcross, GA, USA). Serum omentin (intra-assay CV 5.5%), nesfatin (CV 5.3%), and vaspin (CV 3.1%) were measured using commercially available enzyme immunoassay kits according the manufacturer's instructions (EIA's;RayBiotech, Norcross, GA, USA). All samples were run in duplicate on a microplate reader (BioTek; Winooski, VT, USA).

Statistical Analysis

Changes in body composition, anthropometric measures, and serum biomarkers over the course of the intervention were assessed using paired samples *t*-tests. Statistical significance was established *a priori* at $p \leq 0.05$, and all statistical analyses were performed using R version 3.4.

RESULTS

Details related to the 3-day dietary analysis were published elsewhere. In short, the participants significantly decreased total caloric and carbohydrate intake after switching to the Paleolithic diet (21). After eight-weeks of adherence to the Paleolithic diet participants had reductions ($p<0.05$) in relative body fat (-4.4%), waist circumference (-5.9 cm), and sum of skinfolds (-36.8 mm) across all sites when compared to baseline values. No significant differences were observed

in WHR (Table 1). As previously reported, body mass (pre: 87.5 ± 14.0 kg; post: 82.2 ± 12.7 kg) and BMI (pre: 29.4 ± 2.4 kg/m²; post: 27.7 ± 2.2 kg/m²) were also significantly reduced after the intervention, but no changes were observed in both systolic and diastolic blood pressure (21).

Table 1. Body composition data pre- and post-8-week adherence to Paleolithic diet (n=7)

	Pre	Post	*p*-value	95% CI	
	mean ± SE	mean ± SE		lower	upper
Waist circumference (cm)	91.2 ± 7.0	85.3 ± 5.9	0.028	0.9	10.9
Waist to hip ratio	0.856 ± 0.024	0.844 ± 0.027	0.587	-0.036	0.059
Sum of skinfolds (mm)	204.2 ± 23.9	167.4 ± 24.8	0.001	20.6	53.1
Body fat (%)	30.8 ± 2.6	26.4 ± 2.4	0.002	2.4	6.4
Fat mass (kg)	27.1 ± 5.3	22.4 ± 5.1	<0.001	3.7	5.7

p-values and 95% confidence intervals represent pre-to-post comparisons for each variable

There were no pre to post intervention changes in serum adiponectin (p = 0.944; 95% CI -18.92, 20.09), omentin (p = 0.328; 95% CI -5.271125, 2.072268) or nesfatin (p = 0.400; 95% CI -1.2409321, 0.5706464; Figure 1). Serum vaspin levels for all participants were undetectable despite using the smallest possible dilution recommended by the kit manufacturer. The standard curve for vaspin was within expected kit limits. To ensure this result was not due to human error, all samples were run in duplicate a second time, on a separate day from a different frozen serum tube and still yielded undetectable results.

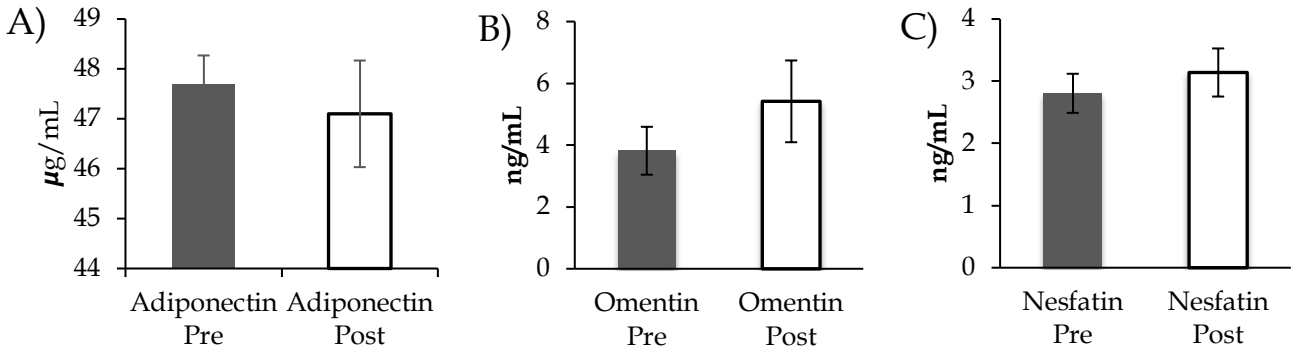

Figure 1. Adiponectin (A), Omentin (B), and Nesfatin (C) concentration (means and SE's) before and following eight weeks of adherence to the Paleolithic diet (n=7)

DISCUSSION

To our knowledge, this is the first study to examine the effects of short-term Paleolithic dieting on HMW adiponectin, omentin, and nesfatin in a cohort of physically inactive, apparently healthy adults. We report a 6.5% decrease in waist circumference, an 18.0% decrease in sum of skinfolds, and significant reductions in body weight and BMI as reported previously (21). We also observed a 17.3% and 14.3% reduction in absolute and relative body fat, respectively, that suggests eight weeks of adherence to the Paleolithic diet by participants accustomed to a Western dietary eating pattern was effective at reducing fat mass. Furthermore, the reported decrease in waist circumference may indicate a reduction in central adiposity that could in turn,

impact adipokine secretion and levels of circulation—especially those related to visceral fat. The main findings of this study were the lack of differences observed in serum adipokine concentrations of adiponectin, omentin, or nesfatin as a result of the Paleolithic dietary intervention despite changes in body composition and fat distribution.

Our findings support other research that has shown improvements in body composition following a Paleolithic dietary intervention (14, 26). For example, Genoni et al. (14) reported a significant decrease in body weight, fat mass, and waist circumference in middle-aged healthy women after only 4-weeks of Paleolithic dieting. In another study, healthy young adults between the ages of 20 and 40 years experienced a significant decrease in body weight, BMI, waist circumference, and systolic blood pressure after a 3-week Paleolithic dietary intervention (26). While the Paleolithic diet appears to be effective in improving body composition, the effects on circulating adipokines is less clear. Following a 6-month Paleolithic dietary intervention, Blomquist et al. (5) reported significant decreases in body weight and waist to hip ratio, but no change in circulating adiponectin among overweight, post-menopausal women. Although the duration of the intervention was only 8-weeks in the current study, our findings are in support of Blomquist et al. (5) as we also found no change in adiponectin and other adipokines despite improved body composition among individuals free from chronic disease.

There are several possible explanations for the lack of change in adipokine levels in this study. While the aforementioned adipokines were reported to have altered levels in obesity and insulin resistance, none of the participants enrolled in the present study had been diagnosed with diabetes or other metabolic abnormalities. Thus, significant changes in adipokine levels may not have occurred due to the relatively healthy status of the study cohort. In support of this, while serum adiponectin levels are lower in individuals with type 2 diabetes and coronary atherosclerosis (16, 37), low levels of adiponectin do not appear to precede the development of coronary atherosclerosis (4, 17). As such, levels of circulating adiponectin are not considered a predictor of cardiovascular diseases (31), potentially due to a delay in the appearance of the relationship between adiponectin and obesity-related diseases until the later stages of disease progression (37). Furthermore, many studies examining the relationship between obesity and adiponectin do not distinguish between HMW adiponectin and its other subtypes, which may be problematic as research suggests that only HMW adiponectin exerts cardioprotective effects, while LMW adiponectin has been associated with inflammation and insulin resistance (31). Less conclusive relationships have been established between serum nesfatin and obesity, with some investigators demonstrating a negative relationship between circulating nesfatin levels and BMI (34), and others showing a positive relationship (32). Li et al. (2010) reported that plasma nesfatin levels were significantly reduced among those who were diagnosed with type 2 diabetes, most of whom were overweight, but that the negative correlation between circulating nesfatin and BMI no longer existed when looking at a mixed population of healthy, type 1, and type 2 diabetic adults (19). These results suggest the relationship between obesity and nesfatin levels may only be apparent among individuals with type 2 diabetes. Collectively, there is evidence to suggest that the relationships between obesity and circulating levels of these adipokines are most readily apparent when obesity-related diseases, such as type 2 diabetes and cardiovascular disease, are

at later stages of development. Therefore, these adipokines may not serve as early detection biomarkers and may be why we did not see changes in the present study.

The length of the intervention in the present study (eight weeks) may also have been too short to induce major physiological changes in markers of metabolic dysfunction. Other, longer (12 weeks – 12 months) dietary interventions in overweight and obese individuals have resulted in significant changes in serum adiponectin (30), serum omentin (22) and serum vaspin (7). Changes in serum adiponectin were observable with greater (> 7%) weight loss (30), and may be more related to visceral fat loss than to subcutaneous fat loss, particularly in non-obese participants (38), similar to some of the participants in the present study. Additionally, a 12-week intervention aimed at reducing body weight in obese participants reported that the strongest correlations between weight reduction and serum vaspin were present among those with insulin resistance (7). In another study, a 12-week low-calorie or 5-week very low-calorie dietary intervention in overweight and obese individuals, also failed to elicit significant changes in circulating vaspin and nesfatin (36). The above studies suggest that adiponectin, omentin, nesfatin, and vaspin are not suitable as early biomarkers to detect weight and/or early metabolic changes, but rather are more late-stage indicators or consequences of metabolic dysfunction.

While the body of literature on these adipokines is still quite limited, particularly among human participants, it appears that weight loss, and specifically fat loss, serve as major contributors to preventing dysregulation of these biomarkers. Thus, in addition to the aforementioned effects of dietary interventions, exercise has also been suggested as a potential, cost-effective lifestyle intervention with beneficial effects. Indeed, a recent meta-analysis supported that exercise training was effective at increasing serum adiponectin levels in overweight and obese individuals (39). Furthermore, 12 weeks of combined aerobic and resistance training elicited a significant increase in omentin (2), and an inverse relationship has been observed between cardiorespiratory fitness level and vaspin concentration (8). This strengthens the idea that habitual exercise may indeed contribute to the restoration of optimal metabolic function in those who have already begun to develop the metabolic syndrome, and would be interesting to investigate in conjunction with dietary interventions. Perhaps, examining a combined exercise and dietary intervention would shorten the intervention length necessary to observe meaningful changes in adipokines related to obesity and metabolic dysfunction.

There are several noteworthy limitations to the present study. First, visceral adipose tissue was not directly measured; instead, waist circumference was used as an anthropometric estimator. Omentin and vaspin are produced in visceral adipose tissue (12), and so a more sensitive body composition method, such as the DEXA, which accounts for visceral fat, should be incorporated into follow-up studies. Furthermore, others have reported sex differences in the expression of adiponectin (18), omentin (11), and vaspin (12), which we were not able to explore in the current study because it was not powered for detecting sex differences. The main limitation to the present study is a small sample size that limits the generalizability of the results and may increase the risk of committing a type II error. Another limitation was the absence of a control group, which could have further confirmed that the results of the present study were due to the dietary change and not other factors. As it was a feasibility study, however, these results indicate

that a Paleolithic dietary intervention is indeed feasible. Additionally, it remains possible that a larger study with a more homogenous sample population may be able to detect changes that are specific to BMI classification, sex, and/or the presence of metabolic dysfunction. We were able to detect changes in our main study variables (relative body fat, waist circumference, leptin, and serum fibroblast growth factor 21 (21)).

In conclusion, we did not observe any significant changes in circulating adiponectin, omentin, or nesfatin following eight weeks of adherence to the Paleolithic diet. Future researchers should aim to strengthen these results by conducting larger, more long-term studies that examine changes across sex, body composition, and in populations with metabolic dysregulation such as morbid obesity, insulin resistance, cardiovascular disease, and type 2 diabetes.

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