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Paleolithic nutrition improves plasma lipid concentrations of hypercholesterolemic adults to a greater extent than traditional heart-healthy dietary recommendations

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FOOTNOTES

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ABBREVIATIONS

HDL; high-density lipoprotein

LDL; low-density lipoprotein

TG; triacylglycerols

TC; total cholesterol

AHA; American Heart Association

ANOVA; analysis of variance

CRP; C-reactive protein

CVD; cardiovascular disease

hr; hour

ABSTRACT

Recent research suggests that traditional grain-based heart healthy diet recommendations, which replace dietary saturated fat with carbohydrate and reduce total fat intake, may result in unfavorable plasma lipid ratios, with reduced high-density lipoprotein (HDL) and an elevation of low-density lipoprotein (LDL) and triacylglycerols (TG). The current study tested the hypothesis that a grain-free Paleolithic diet would induce weight loss and improve plasma total cholesterol (TC), HDL, LDL and TG concentrations in non-diabetic adults with hyperlipidemia to a greater extent than a grain-based heart healthy diet, based on the recommendations of the American Heart Association. Twenty volunteers (10 male, 10 female) aged 40 to 62 years were selected based on diagnosis of hypercholesterolemia. Volunteers were not taking any cholesterol-lowering medications and adhered to a traditional heart healthy diet for four months, followed by a Paleolithic diet for four months. Regression analysis was used to determine whether change in body weight contributed to observed changes in plasma lipid concentrations. Differences in dietary intakes and plasma lipid measures were assessed using repeated measures ANOVA. Four months of Paleolithic nutrition significantly lowered ($P < 0.001$) mean TC, LDL, and TG and increased ($P < 0.001$) HDL, independent of changes in body weight, relative to both baseline and the traditional heart healthy diet. Paleolithic nutrition offers promising potential for nutritional management of hyperlipidemia in adults whose lipid profiles have not improved after following more traditional heart healthy dietary recommendations.

Key words: Paleolithic nutrition; heart healthy diet; hyperlipidemia; cholesterol; humans

1. INTRODUCTION

Recent estimates suggest that 17% of US adults have hyperlipidemia [1] and 71 million American adults have high low-density lipoprotein (LDL) [2]. The 2010 Dietary Guidelines for Americans and current American Heart Association (AHA) general recommendations for the dietary management of hypercholesterolemia are to limit dietary saturated fat, with the majority of energy intake derived from carbohydrate, in a calorically appropriate diet for the individual [3-5]. There is evidence, however, that such a macronutrient shift may result in increased atherosclerotic risk, with reduced high-density lipoprotein (HDL) and an elevation of C-reactive protein (CRP), triacylglycerols (TG), very low-density lipoprotein, smaller LDL, and oxidized-LDL [6-11].

Paleolithic nutrition, an eating pattern based on meats, fruits, and vegetables, and devoid of grains and dairy, has been successfully employed to improve biomarkers of cardiovascular disease (CVD) in higher-risk groups (e.g., type 2 diabetes, obesity, metabolic syndrome), with significant reductions in body weight, total cholesterol (TC), TG and blood pressure, as well as increased HDL and glucose tolerance [12-15]. Similarly, plasma lipid improvements have also been reported in non-obese, sedentary individuals following ten days of a Paleolithic diet [16]. Hunter-gatherer populations from five continents, with dietary practices that are the foundation of Paleolithic nutrition, regularly live well into their sixties with no sign of CVD and mean TC levels of 2.6-3.6 mmol/L (100-140 mg/dL) and mean LDL of 1.3-1.8 mmol/L (50-70 mg/dL) [17]. Such LDL levels are associated with atheroma regression in CVD patients following aggressive pharmaceutical management [18].

Relative to traditional diabetic and Mediterranean diets, a Paleolithic diet is more satiating per calorie consumed [19, 20]. This effect can lead to an overall lower caloric intake in the absence of defined energy restrictions [12]. In 14 healthy subjects, three weeks of a Paleolithic diet drove mean caloric intake down 36%, relative to baseline [21]. Similarly, caloric intake was significantly reduced in patients with ischemic heart disease following a Paleolithic diet, compared to a Mediterranean diet [19].

The current study was designed to evaluate the effects of four months of Paleolithic nutrition on dietary intake and plasma lipids in hypercholesterolemic adults who had previously adhered to four months of AHA heart healthy dietary recommendations. We hypothesized that the Paleolithic diet would lead to greater weight loss and improve volunteers' lipid profiles to a larger extent than following a traditional grain-based heart healthy diet.

2. METHODS AND MATERIALS

2.1 Participants

Following approval by the Eastern Michigan University Human Subjects Review Committee, 46 non-diabetic men and women were screened for participation in this two-phase (AHA and Paleolithic) diet intervention study. Of those, 10 men (9 Caucasian, 1 Hispanic) and 10 women (8 Caucasian, 2 Hispanic) met the inclusionary criteria of a diagnosis of hypercholesterolemia within the past 14 months and abstinence from medications known to influence blood lipid concentrations (Table 1). All subjects gave informed consent.

2.2 Experimental Design

The study was designed and conducted as a two-phase diet intervention, with volunteers serving as their own controls. Baseline blood samples were collected and analyzed for TC, LDL, HDL, and TG concentrations to confirm hypercholesterolemia. Volunteers then adhered to AHA heart healthy dietary guidelines for four months (phase one), followed by four months of Paleolithic dietary adherence (phase two). Blood samples were collected and analyzed at the completion of each phase.

2.3 Dietary Interventions

All volunteers received diet education and sample meal plans prior to each phase of the study. Specific dietary guidelines are included in Table 2. Additionally, the AHA guidelines emphasized a diet rich in fruits and vegetables, choosing whole-grain, high-fiber foods, foods prepared with little or no salt, and fish consumption at least twice per week, while minimizing the consumption of foods and beverages with added sugars [4, 5]. The Paleolithic diet was based on vegetables, lean animal protein, eggs, nuts, and fruit, but excluded all dairy, grains, and legumes [12]. No caloric limitations were implemented for the Paleolithic diet phase. Similarly, no limitations were implemented for the AHA diet phase, with the exception of providing a caloric maximum – based on current AHA recommendations for each volunteer's age, gender, height, and weight [22] – to allow for adherence to AHA dietary recommendations that are expressed relative to total energy intake (e.g., < 7% daily energy derived from saturated fats). Volunteers did not consume any dietary supplements for the duration of the study, except for vitamin D and calcium. Women and men consumed 800 IU/d vitamin D_3; women also consumed 500mg/d calcium citrate. Similarly, volunteers were not taking any prescription medications throughout the study and pharmaceutical use was limited to occasional ibuprofen for headache and skeletomuscular pain relief.

Compliance with dietary guidelines was monitored via bi-weekly review of daily diet journals and fortified with monthly nutrition counseling sessions. Energy and macronutrient intakes were determined from a series of ten 24hr diet recalls recorded at Baseline and during each diet phase. Volunteers were instructed to maintain baseline physical activity levels throughout the duration of the study, with physical activity monitored via bi-weekly review of daily activity journals. Energy expenditure via physical activity remained constant, relative to Baseline, for all volunteers throughout the duration of the study.

2.4 Measurement of Body Weight

Body weight was measured following an overnight fast at Baseline and every month throughout the study. Wearing similar clothing for all measures, volunteers removed shoes, belts, jewelry, and emptied pockets before mounting a balance-beam scale (Detecto 2371S; Webb City, MO). Weight was recorded to the nearest tenth of a pound. Body weight data are presented as *kg*.

2.5 Assessment of Plasma Lipids

Plasma lipid concentrations were determined at Baseline and subsequent to each 4-month diet intervention phase. Following an overnight fast, venous blood was collected and plasma TC, HDL, LDL, and TG concentrations were measured from EDTA- and lithium-heparin-processed plasma samples and standard enzymatic techniques, conducted by Laboratory Corporation of America (Labcorp; New York, NY). Plasma lipid data are presented as *mmol/L*.

2.6 Statistical Analyses

Baseline volunteer characteristics are described using common descriptive statistics. A multivariate ANOVA was used to determine differences in baseline volunteer characteristics across sex (i.e., men vs. women). Regression analysis was used to determine whether change in body weight contributed to observed changes in plasma lipid concentrations. Differences in dietary intakes and plasma lipid measures were assessed using repeated measures ANOVA with diet (Baseline vs. AHA vs. Paleolithic) as a within-subjects factor and sex (men vs. women) as a between-subjects factor. The level for statistical significance was set at $P < 0.05$. When a significant interaction was observed, pairwise comparisons were made using the Bonferroni correction. Marginal means are reported for all main and interaction effects: diet, sex, or diet-by-sex. Data were analyzed using IBM SPSS Statistics for Windows (version 22; IBM Corp.) and are presented as means ± SD. Effect sizes for observed changes in plasma lipid concentrations were determined using Cohen's d, with the following thresholds: *small*, d = 0.2; *medium*, d = 0.5; *large*, d = 0.8; *very large*, d = 1.3.

3. RESULTS

3.1 Dietary Intake

Throughout the study, men consumed significantly more energy and absolute amounts of each macronutrient than women ($P < 0.001$; Table 3). Mean energy intake was significantly lower during the AHA diet phase, relative to Baseline, with Paleolithic energy intake significantly lower than both Baseline and AHA ($P < 0.001$). Mean carbohydrate intake was not different between Baseline and AHA, but was significantly lower during the Paleolithic diet phase ($P < 0.001$). In contrast, mean protein intake did not differ between Baseline and AHA, but was significantly higher during the Paleolithic phase (P < 0.001). Mean fat intake was significantly different between each diet phase, with the highest intake at Baseline and the lowest during the AHA diet phase (P < 0.001).

3.2 Body Weight

Mean body weight was greater for men than women at all measures (P < 0.05). A diet-by-sex interaction (P < 0.05) was observed for the reduction in body weight over the course of the two diet phases. Four months of adhering to AHA heart healthy dietary recommendations reduced mean body weight by 3.3 ± 2.7 kg for men, relative to baseline (P < 0.001), with an additional 10.4 ± 4.4 kg reduction following four months of Paleolithic dietary guideline adherence (P < 0.001). Mean body weight did not significantly change for women following the AHA diet phase, relative to Baseline (P > 0.05), although the Paleolithic diet induced a significant 8.1 ± 5.9 kg weight loss compared to AHA (P < 0.001).

3.3 Plasma Lipid Concentrations

TC, LDL, and TG concentrations were not significantly different between men and women at any measurement point (P > 0.05). Additionally, body weight change across diet phase was not significantly correlated to change in TC, LDL, HDL or TG (P > 0.05) from Baseline-to-AHA (r^2 = 0.001, 0.007, 0.060, and 0.018, respectively) nor from AHA-to-Paleolithic (r^2 = 0.032, 0.022, 0.002, and 0.002, respectively).

Mean TC experienced a *small* decrease of 3% (d = 0.3; P < 0.001) from Baseline-to-AHA, followed by a *very large* decrease of 20% (d = 1.9; P < 0.001), from AHA-to-Paleolithic (Table 5). Similarly, mean LDL underwent a *small* decrease of 3% (d = 0.2; P < 0.001) from Baseline-to-AHA, followed by a *very large* decrease of 36% (d = 2.1; P <

0.001) from AHA-to-Paleolithic (Table 5). Mean TG did not change from Baseline-to-AHA, but had a *very large* decrease of 44% (d = 1.3; $P < 0.001$) from AHA-to-Paleolithic (Table 5). As expected, mean HDL was higher ($P < 0.05$) for women than men. Mean HDL concentrations did not significantly change from Baseline-to-AHA, but experienced an overall *large* increase of 35% (d = 1.2; $P < 0.001$) from AHA-to-Paleolithic (Table 5).

4. DISCUSSION

The primary findings from this two-phase diet intervention study are significant improvements in plasma TC, LDL, HDL, and TG concentrations of hypercholesterolemic adults, independent of changes in body weight, following four months of a Paleolithic diet, relative to four months of traditional heart healthy dietary guidelines. These results confirm the original research hypothesis and are similar to observed improvements in lipid profiles following both 10-day [16] and 3-month [12] Paleolithic diet interventions.

The Paleolithic diet has increased in popularity in recent years, as evidenced by an escalating prevalence of websites, blogs, books, celebrity endorsements, and its general adoption by the CrossFit community [23]. The diet has also received criticism, particularly over the potential for increased atherogenic risk due to higher fat and meat intakes [24]. When compared to a typical American/Western diet, however, a Paleolithic diet contains three-fold more fiber and potassium, 2-fold more polyunsaturated and monounsaturated fats, four-fold more omega-3 fatty acids, and four-fold less sodium [25-27]. A Paleolithic diet generally contains 12.5-fold more potassium than sodium and provides sufficient nutrient density to easily exceed current Recommended Dietary Allowances for vitamins A, B1, B2, B3, B6, B9, B12, C, and E, as well as phosphorous, magnesium, iron, and zinc [28].

While the current study did not implement caloric limits as a component of the Paleolithic dietary intervention, volunteers lost significantly more weight during the Paleolithic phase than during the AHA phase. One of the demonstrated effects of consuming a Paleolithic diet is a noted increase in satiety [12, 19-21]. We expected that this increased satiety would drive weight loss and contribute to improvements in plasma lipid concentrations [29], but change in body weight was not a significant correlate for any observed changes in lipid concentrations. Frassetto et al. [16] have previously shown comparable lipid improvements in obese individuals, following 10 days of Paleolithic feeding, while controlling energy intake and ensuring no change in body weight. Similarly, 12 weeks of a Paleolithic diet improved glucose tolerance to a greater extent than a Mediterranean diet in glucose intolerant or Type 2 diabetic patients with ischemic heart disease, independent of changes in waist circumference [13]. With no significant relationship between change in body weight and change in plasma lipid concentrations, the current findings similarly suggest that the observed lipid profile improvements were the result of more than just weight loss and that the composition of the two diets may have exerted a significant influence on these parameters.

Intake patterns of present day hunter-gatherer societies, with dietary practices similar to those incorporated into the Paleolithic diet, reveals dietary macronutrient ratios that differ markedly from traditional dietary recommendations for cardiovascular disease prevention and treatment [30]. The foundation of the 2010 Dietary Guidelines for Americans and the AHA's heart healthy guidelines are grains (preferably as whole grains), fruits, vegetables, and low fat or fat-free dairy products [3, 4]. In contrast, hunter-gatherer societies consume the majority of energy (45 to 65%) from animal foods, providing a significant fraction of energy intake from protein (19-35%), balanced by energy from plant carbohydrates (22-40%) [30]. Fat intake on a Paleolithic diet typically exceeds 30% of total energy [17], as was the case in the current study.

Diets centered on lean protein and fish rich in long-chain omega-3 polyunsaturated fatty acids have the potential to alter serum lipids in a manner thought to be protective against atherosclerosis [7, 31, 32]. In contrast, hunter-gatherers who transition to grain-based agricultural diets begin to exhibit cardiovascular disease risk factors, including abnormal lipid profiles, in as little as three months [33-35]. In the present study, moving from a grain-based heart healthy diet to a grain-free Paleolithic diet significantly improved TC, LDL, HDL, and TG, likely indicating decreased CVD risk. Such improvements are most commonly associated with pharmaceutical intervention, with statins as the leading class of pharmaceuticals prescribed for abnormal lipid profiles [36]. In one large retrospective cohort study, however, statins were discontinued, at least temporarily, by 53% of the subjects due to myopathy, nausea, neuropathy, and/or elevated liver enzymes [37]. Moreover, treatment with certain statins has been associated with an increased risk of new onset diabetes [38]. The current findings highlight the cardioprotective potential of a dietary approach for the large number of hypercholesterolemic individuals who have been unsuccessful with traditional dietary management or who have experienced negative side effects associated with pharmaceutical therapy.

The limitations of the current study include the relatively small and homogenous (i.e., predominantly Caucasian) volunteer pool. With CVD accounting for one-third of the mortality difference between African Americans and Caucasians [39], a larger, more diverse study population would allow for a broader understanding of potential findings. Similarly, while the current study implemented a longer Paleolithic diet intervention than some previous reports, an even longer study duration would allow for a better understanding of whether these observed changes can be maintained over time. Findings from a two-year Paleolithic intervention showed an abrogation of 6-month improvements at 24 months [40].

Additionally, the current study design does allow for the opportunity for order bias to influence results, with all volunteers cycling through the traditional heart healthy diet prior to the Paleolithic intervention. While the uniformity of the standard errors of the means for all dependent variables suggests that diet order had a minimal effect upon internal validity, the study could be improved by utilizing a cross-over design with a washout period between diet treatments. Finally, since obesity and CVD have been associated with chronic inflammation [41], it would be beneficial to include assessment of inflammatory markers (e.g., interleukin-6, tumor necrosis factor α, and high sensitivity CRP) in future evaluations of the effects of Paleolithic nutrition on factors related to cardiovascular health in obese individuals.

In summary, adherence to a Paleolithic diet for four months significantly decreased TC, LDL, and TG, while increasing HDL, independent of changes in body weight, relative to a diet based on traditional heart healthy recommendations. These findings suggest the potential for Paleolithic dietary recommendations to mediate cardioprotective benefits in those with established hypercholesterolemia.

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Table 1. Baseline Volunteer Characteristics

	Total (n=20)	Men (n=10)	Women (n=10)
Age, *y*	53 ± 7	53 ± 7	52 ± 7
Height, *cm*	171 ± 8	176 ± 6	166 ± 6[‡]
Weight, *kg*	85 ± 16	93 ± 11	77 ± 17[‡]
BMI, kg/m^2	28.8 ± 5.0	30.1 ± 4.5	27.6 ± 5.4
Total Cholesterol, *mmol/L*	6.1 ± 0.6	6.0 ± 0.5	6.2 ± 0.7
LDL Cholesterol, *mmol/L*	4.0 ± 0.6	4.2 ± 0.6	3.8 ± 0.5
HDL Cholesterol, *mmol/L*	1.37 ± 0.46	1.16 ± 0.33	1.60 ± 0.48[‡]
Triacylglycerols, *mmol/L*	1.6 ± 0.7	1.5 ± 0.6	1.7 ± 0.8

Note: Values are means ± SD. [‡]Different from Men, $P < 0.05$.

Table 2. Dietary guidelines for each intervention phase

Phase One: American Heart Association [4, 5]

- < 7% daily energy derived from saturated fats
- < 1% daily energy derived from *trans* fats
- < 300mg dietary cholesterol per day
- < 2400mg sodium per day

Phase Two: Paleolithic (adapted from [12])

- abstain from all dairy, grains, and legumes
- no more than ½ cup of potato per day
- no more than 1 ounce of dried fruit per day
- no more than 4 ounces of wine per day
- no limit on egg consumption

Table 3. Energy and Absolute and Relative Macronutrient Intakes during Diet Phases

	Energy (*MJ*)		Carbohydrate (*g*)		Protein (*g*)		Fat (*g*)	
	Men	Women‡	Men	Women‡	Men	Women‡	Men	Women‡
Baseline	13.2 ± 0.9	10.1 ± 1.4	405 ± 29 *51%*	320 ± 61 *53%*	119 ± 34 *15%*	90 ± 20 *15%*	117 ± 12 *33%*	86 ± 16 *32%*
AHA	12.0 ± 1.1*	9.5 ± 1.3*	400 ± 46 *56%*	341 ± 40 *60%*	148 ± 38 *21%*	94 ± 23 *17%*	73 ± 6* *23%*	58 ± 8* *23%*
Paleolithic	8.8 ± 1.6†	7.2 ± 1.1†	121 ± 47† *23%*	97 ± 26† *23%*	197 ± 26† *37%*	160 ± 23† *37%*	93 ± 14† *40%*	76 ± 12† *40%*

Note: Absolute values are means ± SD. Men, n=10; Women, n=10. Italicized values represent percentage of energy derived from each macronutrient. *Different from Baseline, P < 0.001. †Different from Baseline and AHA, P < 0.001. ‡Different from Men, P < 0.001.

Table 4. Body Weight across Diet Phases

	Total (n=20)	Men (n=10)	Women (n=10)‡
Baseline	84.7 ± 16.4	92.8 ± 10.8	76.6 ± 17.4
AHA	82.8 ± 15.5	89.5 ± 9.6*	76.1 ± 17.7
Paleolithic	73.5 ± 11.4	79.1 ± 6.5†	68.0 ± 12.7†

Note: Values are means ± SD. *Different from Baseline, $P < 0.001$. †Different from Baseline and AHA, $P < 0.001$. ‡Different from Men, $P < 0.05$

Table 5. Plasma Lipid Concentrations across Diet Phases

	Total Cholesterol (*mmol/L*)	LDL Cholesterol (*mmol/L*)	Triacylglycerols (*mmol/L*)	HDL Cholesterol (*mmol/L*)	
				Men	Women‡
Baseline	6.1 ± 0.6	4.0 ± 0.6	1.6 ± 0.7	1.17 ± 0.33	1.59 ± 0.48
AHA	5.9 ± 5.9*	3.9 ± 0.6*	1.6 ± 0.6	1.14 ± 0.29	1.52 ± 0.50
Paleolithic	4.7 ± 0.7†	2.5 ± 0.7†	0.9 ± 0.3†	1.62 ± 0.37†	1.97 ± 0.25†

Note: Values are means ± SD. n=20 (10 men, 10 women). *Different from Baseline, P < 0.001. †Different from Baseline and AHA, P < 0.001. ‡Different from Men, P < 0.05.

Highligths

- 2-Phase diet intervention (Heart Healthy vs. Paleolithic) for hypercholesterolemia
- Major improvements in total cholesterol, HDL, LDL, and TG after Paleolithic phase
- Plasma lipid improvements were independent of change in body weight
- Possible diet therapy for those without success following traditional guidelines