

ORIGINAL ARTICLE

Metabolic and physiologic improvements from consuming a paleolithic, hunter-gatherer type diet

LA Frassetto, M Schloetter, M Mietus-Synder, RC Morris Jr and A Sebastian

Department of Medicine, University of California San Francisco School of Medicine, San Francisco, CA, USA

Background: The contemporary American diet figures centrally in the pathogenesis of numerous chronic diseases—'diseases of civilization'. We investigated in humans whether a diet similar to that consumed by our preagricultural hunter-gatherer ancestors (that is, a paleolithic type diet) confers health benefits.

Methods: We performed an outpatient, metabolically controlled study, in nine nonobese sedentary healthy volunteers, ensuring no weight loss by daily weight. We compared the findings when the participants consumed their usual diet with those when they consumed a paleolithic type diet. The participants consumed their usual diet for 3 days, three ramp-up diets of increasing potassium and fiber for 7 days, then a paleolithic type diet comprising lean meat, fruits, vegetables and nuts, and excluding nonpaleolithic type foods, such as cereal grains, dairy or legumes, for 10 days. Outcomes included arterial blood pressure (BP); 24-h urine sodium and potassium excretion; plasma glucose and insulin areas under the curve (AUC) during a 2 h oral glucose tolerance test (OGTT); insulin sensitivity; plasma lipid concentrations; and brachial artery reactivity in response to ischemia.

Results: Compared with the baseline (usual) diet, we observed (a) significant reductions in BP associated with improved arterial distensibility (-3.1 ± 2.9 , $P=0.01$ and $+0.19 \pm 0.23$, $P=0.05$); (b) significant reduction in plasma insulin vs time AUC, during the OGTT ($P=0.006$); and (c) large significant reductions in total cholesterol, low-density lipoproteins (LDL) and triglycerides (-0.8 ± 0.6 ($P=0.007$), -0.7 ± 0.5 ($P=0.003$) and -0.3 ± 0.3 ($P=0.01$) mmol/l respectively). In all these measured variables, either eight or all nine participants had identical directional responses when switched to paleolithic type diet, that is, near consistently improved status of circulatory, carbohydrate and lipid metabolism/physiology.

Conclusions: Even short-term consumption of a paleolithic type diet improves BP and glucose tolerance, decreases insulin secretion, increases insulin sensitivity and improves lipid profiles without weight loss in healthy sedentary humans.

European Journal of Clinical Nutrition (2009) **63**, 947–955; doi:10.1038/ejcn.2009.4; published online 11 February 2009

Keywords: paleolithic diet; blood pressure; glucose tolerance; insulin sensitivity; lipids

Introduction

In 1985, anthropologists Eaton and Konner (1985) introduced the general medical community in 'paleolithic nutrition'. A consideration of its nature and current implications'. 'Paleolithic' refers to the period of history of the genus *Homo*, beginning more than 2 million years ago and continuing until about 10 000 years ago (10 kya, when the neolithic period began) when humans began to cultivate

plants (predominantly cereal grains) and domesticate animals (Brandt, 2007). During that interval (more than 2-million year), culminating in the emergence of today's sole *Homo* species, *Homo sapiens*, about 200 kya (McDougall *et al.*, 2005), our ancestors, including *Homo sapiens*, lived as hunter-gatherers, eating wild animal-source foods (lean meats, internal organs, bone marrow, but no dairy) and uncultivated plant-source foods (mostly fruits, nongrain, vegetables, nuts, but no legumes). As the 10 000 or so years since the beginning of the agriculture and animal domestication began, that is less than 1% of *Homo* evolutionary time—leaves little time for evolutionary forces to redesign the core metabolic and physiological processes in a major way in response to the major dietary changes introduced by the agricultural revolution and food animal domestication,

Correspondence: Dr LA Frassetto, San Francisco School of Medicine, Campus box 0126 505 Parnassus Avenue, room 1202M San Francisco, CA 94143, USA
E-mail: frassetto@gcrc.ucsf.edu

Received 25 July 2008; revised 20 November 2008; accepted 30 December 2008; published online 11 February 2009

the genetic makeup of contemporary humans may more closely optimize core metabolism and physiology when they consume a diet more closely resembling our ancestral hunter-gatherer's preagricultural diet (Eaton *et al.*, 1988; Cohen, 1989; Jansson, 1990; Eaton and Cordain, 1997; Neel, 1999; Simopoulos, 1999; Eaton and Eaton, 2000; Sebastian *et al.*, 2002, 2006; Lindeberg *et al.*, 2003b, 2007; Mann, 2004; O'Keefe and Cordain, 2004; Cordain *et al.*, 2005).

The contemporary American diet differs from paleolithic-type diets not only as a consequence of the agricultural and husbandry revolutions, but also as a consequence of the industrial revolution and, more recently, the fast food revolution. As detailed by many investigators (Eaton *et al.*, 1988; ; Cohen, 1989; Jansson, 1990; Eaton and Cordain, 1997; Mann, 2004; O'Keefe and Cordain, 2004; Cordain *et al.*, 2005; Sebastian *et al.*, 2006; Lindeberg *et al.*, 2007), these revolutions have introduced foods that were absent or negligible in the paleolithic diet: refined cereal grains and their products, nonhuman mammalian milk and its products, energy-dense nutrient-poor foods (refined carbohydrates of wide variety, readily available and inexpensive; separated fats and oils of wide variety also) and legumes. In acquiring substantial amounts of food energy (kilojoules) from these novel foods, Americans have marginalized one of the mainstays of paleolithic-type diets, namely, noncereal grain and nonleguminous plant foods: vegetables and fruits. These marginalized foods appeal less to the human built-in appetite for sugar and fat, honed during human evolution. Other recognized dietary consequences of the three 'revolutions' include a reduction in the consumption of lean animal-source protein and a great increase in the consumption of sodium chloride and a decrease in potassium salts of organic acids (Eaton and Konner, 1985; Sebastian *et al.*, 2002).

Numerous authors have argued that a discordance between our contemporary diets and the paleolithic-type diets to which evolutionary forces adapted our core metabolism and physiology over a period of millions of years of hominin evolution contributes in a major or critical way to the pathogenesis of the so-called diseases of civilization: atherosclerotic cardiovascular disease and its sequelae, insulin resistance and type 2 diabetes, metabolic syndrome, age-related sarcopenia and osteoporosis, hypertension and its sequelae, some types of cancers and many others (Eaton *et al.*, 1988; Cohen, 1989; Jansson, 1990; Eaton and Cordain, 1997; Cordain, 1999; Neel, 1999; Simopoulos, 1999; Eaton and Eaton, 2000; Sebastian *et al.*, 2002, 2006; Lindeberg *et al.*, 2003b, 2007; Mann, 2004; O'Keefe and Cordain, 2004; Cordain *et al.*, 2005).

Lindeberg *et al.* (2003a) provided support for the above argument from an extensive review of the literature on dietary modifications, as they affect those diseases of glucose tolerance in patients with IHD (ischemic heart disease) who had impaired glucose tolerance or type 2 diabetes mellitus. After advising on the consumption of a paleolithic-type diet or a typical mediterranean-type diet, they found '*...marked improvement of glucose tolerance in IHD patients who had*

increased blood glucose or diabetes after advice to follow a Paleolithic diet compared with a healthy Western diet (Lindeberg *et al.*, 2007).' They interpreted their results *in toto* as suggesting '*...that avoiding Western foods is more important than counting calories, fat, carbohydrate or protein*' in effecting such improvement in glucose metabolism. In a short-term study administering an *ad libitum* outpatient paleolithic-type diet to healthy volunteers, Osterdahl *et al.* (2007) noted an improvement in blood pressure (BP) and weight loss, but no significant apparent improvement in carbohydrate and lipid metabolism.

In this metabolically controlled study, we compared the effects of a usual diet with that of a paleolithic-type diet on normal adult Americans based on multiple metabolic and physiological variables: glucose tolerance, insulin sensitivity, blood lipid profiles, BP, vascular reactivity and electrolyte excretion rates.

Materials and methods

Healthy nonobese men and women over 18 years of age reporting minimal regular physical activity were recruited from the San Francisco Bay area. Those who passed a telephone screening by the study investigators underwent a graded maximal exercise treadmill test and qualified if they were at or below the fitness exercise standards of their age and sex (by VO_2max). Subjects were excluded if they had any medical problems as determined by history and physical examination and laboratory testing (complete blood count, liver and kidney function, fasting blood sugar, urinalysis and pregnancy testing), or were taking any medications, including over-the-counter and herbal medications. The participants were instructed to continue their usual activity pattern during the study.

On each of the first 3 days (days -2 to 0), participants ate their usual diet and underwent baseline 24-h urine collections, fasting blood samples for electrolytes, glucose and lipid profiles and BP measurements. Participants were interviewed by the dietician of the clinical research center (using a five-pass, 24-h diet recall on their usual diet, and underwent one 2-h oral glucose tolerance test (OGTT). Diet recalls were analyzed using Food Processor SQL (Version 10.0.0) Nutrition Software (ESHA Research, Salem, OR, USA).

For the intervention phase, beginning day 1, for adaptation purposes, a series of 1-day cycle diets with gradually increasing levels of potassium and fiber were developed by the research dietitians. This was to allow the subjects' intestinal tract and potassium handling systems to adjust to the markedly higher dietary content of fiber and potassium. 'Ramp 1' diet was given for 1 day, 'Ramp 2' diet for 3 days, 'Ramp 3' diet for 3 days and finally the 'Paleo diet' for the remainder of the study. All diets were developed using ProNutra Nutrition Software (Version 3.1.0.13, Princeton Multimedia Technologies Corp, Princeton, NJ, USA). The nutrient composition of the Paleo diet was verified by a

composite analysis carried out by Covance Laboratories (Covance Labs, Madison, WI, USA). Meat, fish, poultry, eggs, fruits, vegetables, tree nuts, canola oil, mayonnaise and honey were included in the Ramp and Paleo phases of the diet. We excluded dairy products, legumes, cereals, grains, potatoes and products containing potassium chloride (some foods, such as mayonnaise, carrot juice and domestic meat were not consumed by hunter-gatherers, but contain the general nutritional characteristics of preagricultural foods).

The Paleo diet was divided into three meals and three snacks, all prepared by the clinical research center kitchen staff. The same diet was consumed every day. Participants ate one meal a day in the Research Center and the rest of the meals were packed for take-out. Maintenance energy needs were calculated for each individual based on their weight and daily activity levels. Body weight was measured daily, and if a deviation of three pounds from the third day's weight in the study occurred, calorie intake was adjusted (see below). We wanted to eliminate weight loss, as weight loss itself can affect the targeted outcome variables. Few adjustments were required. The 24-h urinary sodium and potassium excretion was used as a marker for dietary compliance. Bioimpedance spectroscopy (Impedimed, Sydney, Australia) was used to evaluate the total body and intracellular water content.

Blood pressure was measured after 10 min of the patients' sitting, at 1-min intervals for 3 min using an automated BP measuring system (DinaMap@PRO, GE Healthcare Worldwide, Inc., www.gehealthcare.com/). On one of those days, brachial artery diameter (BAD) and blood flow were measured at baseline and after 5 min of cuff occlusion by ultrasound (brachial artery reactivity). Subjects rested supine in a darkened room for 5–10 min before the first vascular images were recorded, and remained supine throughout the study. Longitudinal images of the brachial artery were taken with a 15-MHz linear array vascular transducer and a Sequoia C256 system (Acuson, Mountain View, CA, USA). After basal scans for velocity and diameter, a pneumatic tourniquet was inflated for 5 min; during the fifth minute of cuff inflation, a scan of the brachial artery was recorded for the 'prerelease' diameter. At the moment of cuff release, the image was shifted to a velocity measurement to document the increase in blood flow. Within 30 s, DICOM data were stored continuously for 120 s after cuff release.

All of the initial testings were repeated for days 15 to 17, and the results for days –2 to 0 and 15 to 17 were averaged. This study was approved by the University of California San Francisco Institutional Review Board (UCSF IRB), and all subjects signed a written informed consent before starting the study. This study was registered at www.clinicaltrials.gov, ID number NCT00360516. Blood and urine samples were sent to Quest Diagnostics (San Jose, CA, USA) for sample analysis.

For the calculation of the sample size, not knowing what effect size to expect, we ran one participant through the study first. We used triplicate measurements during each of

the two test diets (days –2, –1 and 0; days 15, 16 and 17), and for BP, we carried out daily triplicate measurements, each daily measure representing the average of three BP measurements taken 1 min apart after sitting for 10 min in the morning. As we had multiple measurements for each variable, we used repeated measures analysis of variance to determine the significance of each variable and estimate the sample size based on each variable.

In that participant, total cholesterol decreased by 1.8 ± 0.2 mmol/l (32% decrease) and LDL (low-density lipoprotein) cholesterol decreased by 1.6 ± 0.2 mmol/l (39% decrease); based on an effect-size of half of the observed change, 0.9 mmol/l with an s.d. of 0.2 mg per 100 ml, the sample size was two subjects. Mean arterial pressure decreased by 15 ± 9 mm Hg and diastolic BP decreased by 18 ± 9 mm Hg. On the basis of an effect size of 15 mm Hg with an s.d. of 9 mm Hg, the sample size was five subjects. To allow for more intersubject variability, we chose to study 10 subjects.

Repeated measures analysis of variance with *post hoc* paired *t*-tests or regression analyses were used to evaluate most of the data (Sigmastat, San Rafael, CA, USA). For some parameters, median and range data were also calculated. We also evaluated the consistency of the directional changes in the outcome variable. Electrolyte and lipid profiles were averaged for days –2 to 0 and 15 to 17 for each subject, and these mean values were compared before and after the diet. The three BP measures were averaged for each participant for each day, then for days –2 to 0 and for days 15 to 17, and then the resultant means were compared.

In the 2-h OGTT, blood samples were drawn at 0 (fasting), 30, 60 and 120 min. The insulin area under the curve (AUC) from the 2-h OGTT was calculated using the trapezoidal method. Insulin sensitivity was tested by the homeostatic assessment model (HOMA), calculated as $\text{HOMA} = (\text{fasting insulin} \times \text{fasting glucose}) / 22.4$, where a value of < 2.1 is considered to be insulin-sensitive and a value > 4.2 is considered to be insulin-resistant. Statistics are reported as mean \pm s.d.

Subjects

Eleven participants enrolled in this study; two were medical students and declined to continue because of the amount of time required for the study procedures. Nine participants (six male, three female; age: 38 ± 12 years, body mass index: 27.8 ± 2.4 kg/m²) completed the study. There was no significant change in weight during the study, or in total body or intracellular water content by bioimpedance spectroscopy (BIS) between days –2 to 0 (the 'usual' diet) and 15 to 17 (the Paleo diet). There was no change in mean creatinine clearance 0.07 ± 0.55 ml/s).

Urinary sodium content decreased by 89 ± 73 mmol/day ($P = 0.007$) and chloride content decreased by 76 ± 64 mmol/day ($P = 0.007$); a decrease occurred in all nine participants. Urinary potassium content increased by 71 ± 54 mmol/day

($P=0.004$), an increase observed in eight of the nine participants. The ratio of urinary potassium to sodium (K/Na) excretion increased from 0.5 ± 0.1 to 2.2 ± 0.6 ($P<0.001$), and all nine participants showed an increase. Urinary calcium/creatinine excretion decreased by 10 ± 5 mmol Ca/88400 mmol Cr/day, $P=0.001$, a consistent decrease in all nine participants. There was no significant change in the urine pH.

Nutrient comparisons between paleolithic and usual diets

The usual diet was obtained from one or two 24-h food recalls by an experienced research dietician. Comparison between the usual and Paleo diet intakes and 24-h urine excretion is shown in Table 1, whereas Table 2 lists the menus for the actual foods consumed during the metabolic diet phases of the study. The usual diet had a calculated K/Na intake ratio of 0.6 ± 0.3 and averaged 18% of calories from protein, 44% from carbohydrates and 38% from fats. An analyzed paleolithic diet composite had a K/Na intake ratio of 4.3 ($P<0.0001$) and contained 30% of calories from proteins, 32% from fat (mainly unsaturated) and 38% from carbohydrates.

Lipid profiles

Mean lipid concentrations and insulin and glucose are reported in Table 3. Total cholesterol decreased by 0.8 ± 0.6 mmol/l (16%), $P=0.007$; LDL cholesterol decreased by 0.7 ± 0.5 mmol/l (22%), $P=0.003$. Eight of the nine

Table 1 Usual vs Paleo diet intake and urine output comparisons (mean \pm s.d.)

Diet factors	Usual diet	delta	P-value
Energy (Kcal)	2372 \pm 886	+ 329 \pm 840	NS
Protein (g)	107 \pm 49	+ 91 \pm 50	0.0006
Carbohydrates (g)	254 \pm 128	- 5 \pm 126	NS
Total fat (g)	99 \pm 56	- 3 \pm 53	NS
Saturated fat (g)	32 \pm 22	- 16 \pm 21	0.05
Monounsaturated fat (g)	33 \pm 22	+ 13 \pm 20	NS
Polyunsaturated fat (g)	10 \pm 4	+ 20 \pm 5	<0.0001
Cholesterol (mg)	498 \pm 290	- 187 \pm 275	NS
Calcium (mmol)	22 \pm 10	- 2 \pm 10	NS
Sodium (mmol)	156 \pm 84	- 92 \pm 82	0.01
Potassium (mmol)	81 \pm 29	+ 193 \pm 42	<0.0001
Phosphate (mmol)	56 \pm 21	+ 22 \pm 19	0.01
Magnesium (mmol)	15 \pm 4	+ 14 \pm 6	<0.0001
24-h urine (n = 9)			
pH ^a	6.20 \pm 0.17	+ 0.34 \pm 0.46	NS
UNaV (mmol)	151 \pm 66	- 89 \pm 73	0.007
UCIV (mmol)	142 \pm 63	- 76 \pm 63	0.007
UKV (mmol)	66 \pm 20	+ 71 \pm 56	0.004
UKV/UNaV (mmol)	0.5 \pm 0.1	+ 1.8 \pm 0.6	<0.0001
CrCl (ml/min)	115 \pm 27	+ 4 \pm 33	NS
UCa/CrV (mg/100 mg)	100 \pm 40	- 40 \pm 30	0.0009

Abbreviations: NS, not significant; Na, sodium; K, potassium; CrCl, creatinine clearance; Ca/Cr, calcium/creatinine ratio.

^an = 5 for pH.

participants showed the decrease in these two variables. Very low density lipoproteins (VLDL) cholesterol decreased by 0.2 ± 0.1 mmol/l (35%) and triglycerides decreased by 0.3 ± 0.3 mmol/l (35%). All nine participants showed the decrease in these two variables. No significant change occurred in HDL (high-density lipoprotein).

Glucose and insulin profiles

Results of the 2-h OGTTs are also given in Table 3. Mean fasting glucose decreased by 0.3 ± 0.4 mmol/l (5%), which was not significant. Fasting insulin decreased by 48 ± 62 pmol/l (68%), from baseline ($P=0.07$). During the 2-h OGTT, insulin AUC decreased by 181 ± 132 pmol, $P=0.006$. The decrease in insulin AUC correlated inversely with the magnitude of change in urinary potassium excretion among the subjects (Figure 1b), the highest decreases in insulin AUC occurring in those subjects with the highest increases in the intake of dietary potassium (Figure 1a). Reductions in fasting plasma insulin and in the 2-h plasma insulin AUC occurred in eight of the nine subjects. The integrated value of plasma insulin concentration over the period of the oral GTT (viz, the insulin AUC) relative to the corresponding integrated value of plasma glucose concentration was significantly lower during the paleolithic diet period than during the usual diet period. Specifically, insulin/glucose AUC of the usual diet vs the Paleo diet decreased from 20 ± 10 to 12 ± 9 mg/M, $P=0.005$. All nine participants showed a decrease in the ratio of plasma insulin AUC to plasma glucose AUC.

Blood pressure and vascular reactivity

Blood pressure and vascular reactivity data, as measured by brachial artery reactivity are given in Table 4. There was a significant decrease in the mean diastolic BP, -3 ± 3 mm Hg ($P=0.006$), and the mean value of mean arterial pressure, -3 ± 3 mm Hg ($P=0.01$), both occurring in eight of the nine participants. There was only a trend toward a decrease in systolic BP -3 ± 5 mm Hg.

Table 4 shows the BP measures and vascular diameter and blood flows before and after arterial occlusion for days -2 to 0 and 15 to 17. The mean diastolic BP decreased by 3.4 ± 2.7 mm Hg ($P=0.006$), a decrease seen in eight of the nine participants. The mean arterial pressure also decreased significantly ($P=0.01$), with a decrease seen in the same eight participants. The peak BAD during hyperemia increased significantly. There was no significant difference before or on the Paleo diet for baseline BAD. After 5 min of brachial artery occlusion, just before releasing the BP cuff, BAD tended to be slightly smaller during the Paleo diet, -0.15 ± 0.20 mm, $P=0.07$. Immediately after cuff release, the peak BAD during the compensatory hyperemia following blood flow occlusion (pkFMD) was significantly greater on the Paleo diet, $+0.19 \pm 0.23$ mm, $P=0.05$. The Paleolithic diet-related increases in baseline BAD, in precuff release BAD

Table 2 Menu: 1 week of increasing fiber and potassium diets ('ramp' diets) and Paleo diet (per 3000 kcal)

Diet	Ramp 1	Ramp 2	Ramp 3	Paleo diet
Potassium content	125 mmol	180 mmol	259 mmol	339 mmol
Breakfast	Honey Fresh pineapple Scrambled eggs	Honey Orange juice Fresh pineapple Pork tenderloin	Honey Orange juice Fresh pineapple Pork tenderloin	Honey Carrot Juice Fresh pineapple Pork tenderloin
AM snack	Lettuce, cucumber, celery and tomatoes with oil and vinegar dressing Carrot juice	Celery, cucumber, red peppers and tomatoes with oil and vinegar dressing	Low salt tomato soup	Almonds Carrot juice
Lunch	Stir-fried fresh zucchini Tuna salad (tuna, radish, shallots, mayo) on lettuce Applesauce Honey	Carrot juice Tuna salad/mayo on lettuce	Carrot juice Tuna salad/mayo on lettuce Honey	Carrot juice Tuna Salad (mayo, radishes, shallots) on lettuce Low-salt tomato soup with chopped tomatoes
Day Snack	Lettuce, carrot and peppers with oil and vinegar dressing Canned pears Honey	Turkey/mayo in lettuce wrap Carrots and tomatoes with oil and vinegar dressing	Turkey/mayo with lettuce wrap Carrots and tomatoes with oil and vinegar dressing Tomato juice	Turkey, guacamole and tomato lettuce roll-ups
Dinner	Chicken breast stir-fry with broccoli and garlic Mandarin oranges	Chicken breast stir-fry with fresh spinach, garlic and broccoli Mandarin oranges Honey	Chicken breast stir-fry with fresh spinach, broccoli and garlic Mandarin oranges Tomato juice	Chicken breast stir-fry with fresh spinach, garlic and broccoli Roasted parsnips and mushrooms with thyme Low salt tomato soup
PM Snack	Turkey and tomatoes with mayo in lettuce wrap	Cantaloupe Carrot juice	Cantaloupe Carrot juice Honey	Cantaloupe Carrot juice

Table 3 Effect of the paleolithic diet on metabolic variables

Category	Variable	Usual diet	Paleolithic diet	% Change	P-value
Lipids	Total cholesterol (mmol/l)	4.7 ± 0.9	4.0 ± 0.7	-16	0.007
	HDL (mmol/l)	1.3 ± 0.2	1.3 ± 0.3	+4	NS
	LDL (mmol/l)	3.0 ± 0.7	2.3 ± 0.6	-22	0.003
	VLDL (mmol/l)	0.4 ± 0.2	0.3 ± 0.1	-35	0.01
	Triglycerides (mmol/l)	0.9 ± 0.4	0.6 ± 0.1	-35	0.01
Fasting Insulin and Glucose	Fasting insulin (pmol/l)	69 ± 63	21 ± 7	-68	0.07
	Fasting glucose (mmol/l)	18 ± 3	17 ± 2	-5	NS
OGTT	Insulin AUC (pmol × h/l)	533 ± 222	361 ± 194	-39	0.006
	HOMA ^a	3.2 ± 3.2	1.0 ± 0.4	-72	0.07

Abbreviation: HOMA = homeostatic assessment.

^aEquation for HOMA = (fasting insulin × fasting glucose)/22.4.

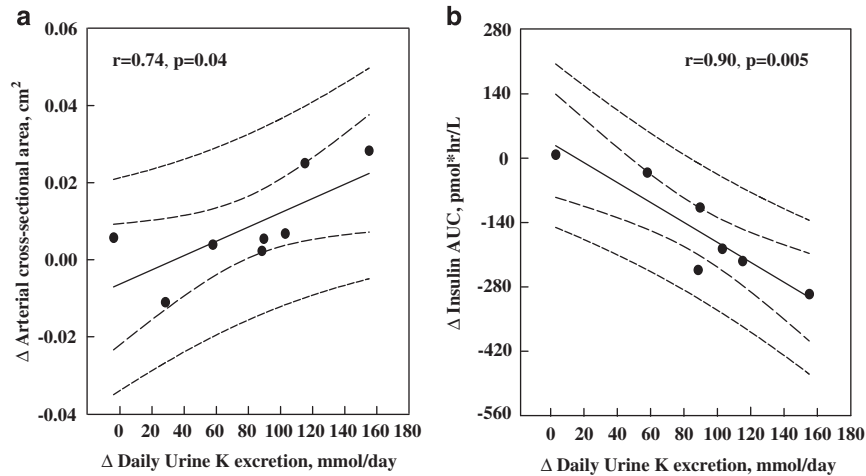


Figure 1 (a and b) Physiological changes correlating with increases in average daily urine potassium excretion (an index of dietary potassium intake). (a) Increasing arterial dilation and (b) decreasing insulin secretion during 2-h oral glucose tolerance test.

Table 4 Resting blood pressure measurements and brachial artery reactivity data

Factor	Days -2 to 0 (usual diet)	Days 15 to 17 (Paleo diet)	P-value
<i>Resting BP</i>			
Systolic BP (mm Hg)	116 ± 10	-2.6 ± 5.1	NS
Diastolic BP (mm Hg)	71 ± 6	-3.4 ± 2.7	0.006
MAP (mm Hg)	86 ± 7	-3.1 ± 2.9	0.01
Brachial artery diameter at baseline (BAD; mm)	3.97 ± 0.88	3.98 ± 0.85	0.14
Peak brachial artery diameter during hyperemia (pkFMD; mm)	4.25 ± 0.83	4.35 ± 0.73	0.05
Absolute difference (pkFMD-BAD; mm)	0.288 ± 0.089	0.371 ± 0.158	0.06

Abbreviations: BAD, brachial artery diameter; BP, blood pressure.

and in the brachial artery cross-sectional area, all are correlated ($r=0.71$, $P=0.047$; $r=0.72$, $P=0.04$; $r=0.74$, $P=0.04$, respectively).

In all the consistency data reported, the Wilcoxon signed-rank test gave significant P -values, ranging from <0.004 to <0.04 .

Discussion

We found, in a small group of sedentary, slightly overweight (body mass index: $27.8 \pm 2.4 \text{ kg/m}^2$), but not obese adult humans, that switching from their usual diet to a paleolithic-type diet, which contained no cereal grains, dairy and legumes, resulted, after only a short period of time and without any weight loss or increase in activity levels, in (a) significant reductions in BP associated with improved arterial distensibility; (b) large significant reductions and increases, respectively, in 24-h urine sodium and potassium excretion; (c) reduced urinary calcium excretion; (d) a significant reduction in fasting plasma insulin concentration; (e) a significant reduction in the plasma insulin vs time AUC, during an OGTT; (f) the highest reductions in plasma

insulin AUC occurring in participants with the highest increase in urinary potassium (index of dietary potassium); (g) a significantly lower integrated value of plasma insulin concentration over the period of the OGTT (that is, the plasma insulin AUC) relative to the corresponding integrated value of plasma glucose concentration (that is, the plasma glucose AUC)—an index of improved insulin sensitivity; (h) improved insulin sensitivity by homeostatic model assessment; (i) improved insulin sensitivity proportional to the degree of baseline insulin resistance; (j) large significant reductions in total cholesterol, LDL and triglycerides; and (k) no significant change in HDL. In addition to the quantitative statistical significance, in all these measured variables, either eight or all of the nine participants had identical directional responses to the switch from the usual diet to the paleolithic-type diet. The direction of change indicated very consistently improved metabolic and physiological status with respect to circulatory, carbohydrate and lipid metabolism/physiology. We did not consider the BP changes surprising, in as much as switching to the paleolithic diet greatly reduced sodium excretion and increased potassium excretion, with a fivefold increase in the urine K/Na ratio—reflecting, presumably, corresponding changes in the BP

variables and the changes in urine sodium, potassium, or the K/Na ratio. On the other hand, as the participants in this study did not have hypertension to begin with ($116 \pm 10/71 \pm 6$), we did not expect large BP changes or strong correlations with the changed electrolyte parameters. In the Dietary Approaches to Stop Hypertension (DASH) sodium diet, nonblack subjects without hypertension also experienced minimal changes in their systolic BP on both the DASH intermediate and the DASH low-sodium diets (Sacks *et al.*, 2001). As calcium intake remained unchanged and urine calcium decreased, the reduction in BP may have related, in part, to a positive calcium balance (Pryer *et al.*, 1995; Bucher *et al.*, 1996).

Recently, Lindeberg *et al.* (2007) compared 29 nonhypertensive patients with either glucose intolerance or type 2 diabetes and ischemic heart disease on 12 weeks of either a paleolithic- or a mediterranean-type diet, and reported no reduction of BP in the study participants consuming a paleolithic diet. In normotensive persons, homeostatic mechanisms to minimize reductions in BP would militate against further lowering of BP. This does not rule out the possibility that with the prolonged consumption of a paleolithic-type diet, homeostasis-set-points may change and maintain 'normal' BP at lower than current 'normotensive' norms.

Our studies in these nondiabetic participants showed no significant decrease in plasma glucose concentration AUC during a 2-h OGTT. What did change was that the same plasma glucose AUC was maintained with a significantly lower amount of insulin secretion, as indicated by significantly lower plasma insulin AUC during the glucose challenge. Indeed, the ratio of the integrated values of plasma insulin to those of plasma glucose (insulin /glucose AUC ratio) during the glucose challenge decreased significantly by about 40% in response to consuming the paleolithic diet. In other words, glucose tolerance could be maintained with less insulin secretion. Confirming an implied increase in insulin sensitivity, the insulin sensitivity measured by HOMA improved, in particular in those individuals who had the least insulin sensitivity when consuming their usual diet (Figure 2).

In Lindeberg *et al.*'s study (2007), the diabetic or hyperglycemic subjects on paleolithic-type diets also showed improvement in both insulin and glucose AUC in 2-h OGTTs to a larger extent than those on the mediterranean-type comparison diet. Subjects in both groups lost about the same amount of weight, approximately 4.5 kg, over the course of this study, compared with baseline, yet those in the paleolithic diet groups showed a reduction in their glucose levels by 36% ($P=0.0003$) compared with 7% in the mediterranean group, and a decrease in their insulin secretion by 30% ($P=0.007$) compared with 13% in the mediterranean group, suggesting additional benefits of the paleolithic diet over the mediterranean diet because of weight loss.

Our data also revealed a marked improvement in the lipid profiles of those on the Paleo diet. Lindeberg *et al.* (2007) did

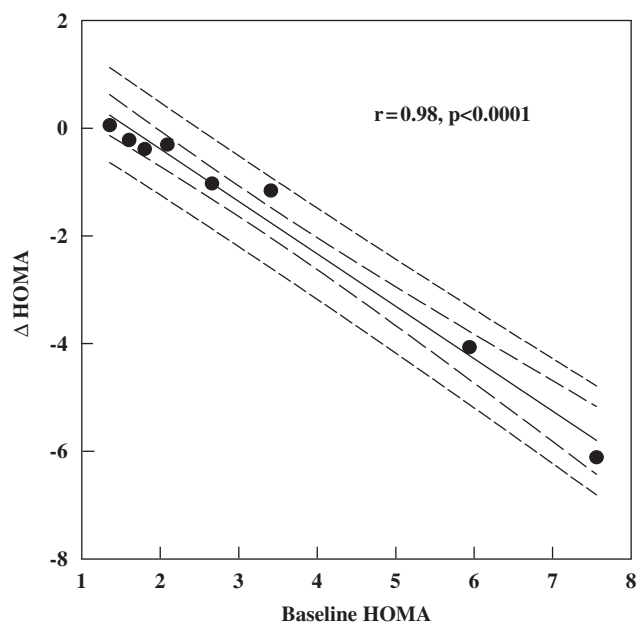


Figure 2 Degree of improvement in HOMA on Paleo diet was greatest in those with the highest baseline HOMA values. HOMA, homeostatic assessment.

not report lipid profile data, but other studies with partial paleolithic-type diets have evaluated diet composition effects on lipid profiles. In the OmniHeart study, 164 adults with pre- or Stage 1 hypertension were randomized to crossover trial of three 6-week periods of a diet rich in carbohydrates from fruits and vegetables, a diet rich in protein or a diet rich in unsaturated fat (Appel *et al.*, 2005). Compared with baseline diet, which was the same for all subjects, on the three intervention diets, total cholesterol decreased by an average of 0.3–0.5 mmol/l (8–13%), LDL cholesterol decreased by 0.3–0.4 mmol/l (9–11%) and triglycerides by 0–0.2 mmol/l (0–16%) over the 6-week intervention period. To put this in perspective, medication therapy, such as statins lowers LDL cholesterol in a dose-dependent fashion, between 25 to 50% over a 3-month period (Davidson and Toth, 2004).

In comparison, the Paleo diet, which could be thought of as a combination of all three of these diets (high fruits and vegetables, high protein and high unsaturated fat), not surprisingly lowered lipid levels even more than these diets did, as shown in Table 3. What is remarkable is how rapidly and dramatically our subjects improved over such a wide range of parameters; lipid profiles, insulin secretion, BP and vascular reactivity, all without losing weight, increasing their activity levels or taking any medication.

One limitation of our study was the small sample size. However, we had an estimate of effect-size and variability from our first subject for both changes in BP and in lipid profiles, and both suggested that 10 subjects would be a reasonable sample size. In addition, the study was tightly

managed in a rigorously applied protocol. The subjects were fed a metabolically prepared diet, and were observed daily for the duration of the study to ensure compliance with the diet, and many of our measurements were made in triplicate, on different days, and the results averaged.

Another limitation was the heterogeneity of the subjects (male, female, African–American, Caucasian, Asian). Undoubtedly a variation exists between both different populations and different subjects. For example, there seems to be genetic differences in the risk of developing type 2 diabetes on a westernized diet. Owing to the small sample size of this study one cannot confidently predict that paleolithic diets induce the same metabolic effects in different populations or different subjects. On the other hand, if our basic hypothesis holds, namely, that humans should be better adapted physiologically to this kind of diet, then we might expect many subjects to improve on this diet, and that is exactly the consistency we saw. Only large clinical trials among diverse groups can settle the issue. With this and two other promising studies (Lindeberg *et al.*, 2007; Osterdahl *et al.*, 2007), perhaps we can justify such trials.

A third limitation could be that we did not have a separate group of participants as a control group. We used the subjects as their own controls and utilized a control period in which the repeatable target variables remained stable, and we ensured compliance with measures of urinary potassium.

Many arguments critical of the contemporary use of paleolithic-type diets have been put forward, and detailed responses have been put forward to counter them (Eaton *et al.*, 2002). Nevertheless, a consensus has not been reached, in particular about the potential disadvantages of the contemporary consumption of a paleolithic-type diet. One argument is that the generous quality of animal-source foods, in the form of livestock, in the paleolithic diet cost more in production-energy and in the generation of greenhouse gases than do plant-source foods, thereby contributing to global warming (Steinfeld *et al.*, 2006).

Many diet regimens have been reported to have health benefits. Several of them (for example, vegetarian and vegan diets) differ in many respects compared with paleolithic-type diets. Further investigation of the short- and long-term effects of such diets compared with paleolithic-type diets will be necessary to determine relative health efficacy. As we discussed earlier, the paleolithic-type we employed showed similar BP effects in non-hypertensive subjects on the DASH low-sodium diet, and better lipid profiles than the Omni-Heart diets (high-carbohydrate from fruits and vegetables; high-protein from animal-source foods; high-unsaturated fats).

This was a preliminary study conducted to see whether future research in larger numbers of subjects would be needed. Because the subjects who were most insulin resistant or had the highest lipid levels improved the most when switched to a paleolithic-type diet, we next plan to study the effect of a paleolithic-type diet in patients with type 2 diabetes. What we can say with this study is that even the

most ‘normal’ of our healthy sedentary subjects showed an improvement in their BP and glucose tolerance, a decrease in insulin secretion and an increase in insulin sensitivity, and a great improvement in their lipid profiles without weight loss in less than 2 weeks on the Paleo diet—all important factors that would be necessary in any potential cure for the metabolic syndrome.

Acknowledgements

We thank the staff of the Clinical Research Center for all the work and support that they provided during this study. This study was supported by the GCRC center Grant M01 RR00027

References

- Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller III ER *et al.* (2005). Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. *J Am Med Assoc* **294**, 2455–2464.
- Brandt Niel. *Evolutionary and Geological Timelines*. http://www.talkorigins.org/origins/geo_timeline.html. 2007.
- Bucher HC, Cook RJ, Guyatt GH, Lang JD, Cook DJ, Hatala R *et al.* (1996). Effects of dietary calcium supplementation on blood pressure. A meta-analysis of randomized controlled trials. *J Am Med Assoc* **275**, 1016–1022.
- Cohen M (1989). *Health and the Rise of Civilization*. Yale University Press: New Haven, pp 131–141.
- Cordain L (1999). Cereal Grains: Humanity's Double-Edged Sword. In: Simopoulos AP (ed). *Evolutionary Aspects of Nutrition and Health: Diet, Exercise, Genetics and Chronic Disease*. S Karger: Switzerland, pp 19–73.
- Cordain L, Eaton SB, Sebastian A, Mann N, Lindeberg S, Watkins BA *et al.* (2005). Origins and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr* **81**, 341–354.
- Davidson MH, Toth PP (2004). Comparative effects of lipid-lowering therapies. *Prog Cardiovasc Dis* **47**, 73–104.
- Eaton SB, Cordain L (1997). Evolutionary aspects of diet: old genes, new fuels. Nutritional changes since agriculture. *World Rev Nutr Diet* **81**, 26–37.
- Eaton SB, Cordain L, Lindeberg S (2002). Evolutionary health promotion: a consideration of common counterarguments. *Prev Med* **34**, 119–123.
- Eaton SB, Eaton III SB (2000). Paleolithic vs modern diets—selected pathophysiological implications. *Eur J Nutr* **39**, 67–70.
- Eaton SB, Konner M (1985). Paleolithic nutrition. A consideration of its nature and current implications. *N Engl J Med* **312**, 283–289.
- Eaton SB, Konner M, Shostak M (1988). Stone agers in the fast lane; chronic degenerative diseases in evolutionary perspective. *Am J Med* **84**, 739–749.
- Jansson B (1990). Dietary, total body, and intracellular potassium-to-sodium ratios and their influence on cancer. *Cancer Detect Prev* **14**, 563–565.
- Lindeberg S, Cordain L, Eaton SB (2003a). The biological and clinical potential of a Palaeolithic diet: review. *J Nutr Environ Med* **13**, 149–160.
- Lindeberg S, Cordain L, Eaton SB (2003b). Biological and clinical potential of a palaeolithic diet. *J Nutr Environ Med* **13**, 149–160.
- Lindeberg S, Jonsson T, Granfeldt Y, Borgstrand E, Soffman J, Sjostrom K *et al.* (2007). A Palaeolithic diet improves glucose tolerance more than a Mediterranean-like diet in individuals with ischaemic heart disease. *Diabetologia* **50**, 1795–1807.
- Mann NJ (2004). Paleolithic nutrition: what can we learn from the past? *Asia Pac J Clin Nutr* **13**, S17.

- McDougall I, Brown FH, Fleagle JG (2005). Stratigraphic placement and age of modern humans from Kibish, Ethiopia. *Nature* **433**, 733–736.
- Neel JV (1999). When Some Fine Old Genes Meet a ‘New’ Environment. In: AP Simopoulos (ed). *Evolutionary Aspects of Nutrition and Health: Diet, Exercise, Genetics and Chronic Disease*. S Karger: Switzerland, pp 1–15.
- O’Keefe Jr JH, Cordain L (2004). Cardiovascular disease resulting from a diet and lifestyle at odds with our Paleolithic genome: how to become a 21st-century hunter-gatherer. *Mayo Clin Proc* **79**, 101–108.
- Osterdahl M, Kocturk T, Koochek A, Wandell PE (2007). Effects of a short-term intervention with a paleolithic diet in healthy volunteers. *Eur J Clin Nutr* **62**, 682–685.
- Pryer J, Cappuccio FP, Elliott P (1995). Dietary calcium and blood pressure: a review of the observational studies. *J Hum Hypertens* **9**, 597–604.
- Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D *et al.* (2001). Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med* **344**, 3–10.
- Sebastian A, Frassetto LA, Sellmeyer DE, Merriam RL, Morris Jr RC (2002). Estimation of the net acid load of the diet of ancestral preagricultural *Homo sapiens* and their hominid ancestors. *Am J Clin Nutr* **76**, 1308–1316.
- Sebastian A, Frassetto LA, Sellmeyer DE, Morris Jr RC (2006). The evolution-informed optimal dietary potassium intake of human beings greatly exceeds current and recommended intakes. *Semin Nephrol* **26**, 447–453.
- Simopoulos AP (1999). The Center for Genetics NaH. In: AP Simopoulos (ed). *Evolutionary Aspects of Nutrition and Health: Diet, Exercise, Genetics and Chronic Disease*. Switzerland: S Karger, pp 1–99.
- Steinfeld H, Gerber P, Wassenaar T, Castel V, Rosales M, de Haan C (2006). *Livestock’s Long Shadow: Environmental Issues and Options*. Food and Agricultural Organization of the United Nations: Rome. <ftp://ftp.fao.org/docrep/fao/010/A0701E/A0701E00.pdf>. ISBN 9789251055717, pp 79–111.