

ORIGINAL ARTICLE

Metabolic and physiologic effects from consuming a hunter-gatherer (Paleolithic)-type diet in type 2 diabetes

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BACKGROUND/OBJECTIVES: The contemporary American diet figures centrally in the pathogenesis of numerous chronic diseases—'diseases of civilization'—such as obesity and diabetes. We investigated in type 2 diabetes whether a diet similar to that consumed by our pre-agricultural hunter-gatherer ancestors ('Paleolithic' type diet) confers health benefits.

SUBJECTS/METHODS: We performed an outpatient, metabolically controlled diet study in type 2 diabetes patients. We compared the findings in 14 participants consuming a Paleo diet comprising lean meat, fruits, vegetables and nuts, and excluding added salt, and non-Paleolithic-type foods comprising cereal grains, dairy or legumes, with 10 participants on a diet based on recommendations by the American Diabetes Association (ADA) containing moderate salt intake, low-fat dairy, whole grains and legumes. There were three ramp-up diets for 7 days, then 14 days of the test diet. Outcomes included the following: mean arterial blood pressure; 24-h urine electrolytes; hemoglobin A1c and fructosamine levels; insulin resistance by euglycemic hyperinsulinemic clamp and lipid levels.

RESULTS: Both groups had improvements in metabolic measures, but the Paleo diet group had greater benefits on glucose control and lipid profiles. Also, on the Paleo diet, the most insulin-resistant subjects had a significant improvement in insulin sensitivity ($r=0.40$, $P=0.02$), but no such effect was seen in the most insulin-resistant subjects on the ADA diet ($r=0.39$, $P=0.3$).

CONCLUSIONS: Even short-term consumption of a Paleolithic-type diet improved glucose control and lipid profiles in people with type 2 diabetes compared with a conventional diet containing moderate salt intake, low-fat dairy, whole grains and legumes.

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INTRODUCTION

Patients with type 2 diabetes frequently have a number of metabolic abnormalities including insulin resistance, hypertension, dyslipidemia, hyperuricemia and coagulopathy. The underlying mechanisms that lead to the clustering of these abnormalities are not well understood. Genetic factors are implicated, but environmental factors such as diet are also important.^{1–3} Diet can impact the metabolic abnormalities in a number of ways. First, excess caloric intake increases adiposity and insulin resistance. Second, dietary components (for example, fructose, saturated fats, carbohydrates, vitamins and minerals) *per se* can affect metabolic processes.^{4–8} Population and migration studies and analysis of dietary trends indicate that the typical western diet (rich in processed meat, high-fat dairy products and refined grains) is associated with the increased incidence of type 2 diabetes, hypertension and dyslipidemia.⁹ Diets metabolically more attuned to human evolution¹⁰—composed of meats, fish, fruits, vegetables and nuts and excluding processed foods, dairy products and refined grains, the so-called Paleolithic (Paleo-) type diets—could potentially prevent or reverse these disorders.¹¹ Paleo diets typically are also lower in sodium and very much higher in potassium, antioxidants, micronutrients and fiber and with a much lower diet acid content.^{11,12}

In a short-term study administering an *ad libitum* outpatient Paleo diet to healthy volunteers, Osterdahl *et al.*¹³ noted improvements in blood pressure (BP) and weight loss, but no significant improvement in carbohydrate and lipid metabolism.

In another study, Lindeberg and colleagues placed 29 non-hypertensive patients with either glucose intolerance or type 2 diabetes and ischemic heart disease on 12 weeks of either a Paleo diet or a Mediterranean-type diet. They reported lower glucose excursions with oral glucose tolerance tests on the former compared with the latter diet.¹⁴ These two studies did not attempt to control what subjects actually ate nor for improvements related to weight changes.

We report here a controlled study of a Paleo diet in type 2 diabetes addressing a number of these confounding factors. We provided all the food with well-defined composition, and we confirmed dietary compliance by composition analyses of several 24-h urine collections. We adjusted caloric intake so as to minimize any weight loss. We compared the Paleo diet with a standard diet based on nutrition recommendations of the American Diabetes Association (ADA diet)¹⁵

MATERIALS AND METHODS

Participants

Twenty-five patients with type 2 diabetes (aged 50–69 years) were recruited from the San Francisco Bay area. Those who passed a telephone screening by the study investigators were invited for a screening visit. Exclusion criteria included the following: diagnosis of type 1 diabetes; inability to consume the provided diet; pregnancy; hemoglobin < 10 g/dl, body mass index (BMI) > 40 kg/m² or on treatments that could affect insulin sensitivity such as thiazolidinediones and glucocorticoids. The study was approved by the UCSF committee on human research, clinicaltrial.gov

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NCT 00548782, and all subjects signed the informed consent. Subjects initially randomized to the ADA diet had the option of participating in the Paleo diet arm after a washout interval of 3 months (five subjects).

Procedures

Baseline data (urine collections; electrolytes, lipids profile, hemoglobin A1c (HbA1c), fructosamine, insulin sensitivity, BP) were collected while patients were on their usual diets (days -2 to 0). Then, subjects were randomized either to the Paleo diet or to the ADA diet. There were three ramp-up diets for 7 days, then 14 days of the test diet. All the initial tests were repeated at days 19 to 21. Subjects were also invited to return 1 month after completing the study for repeat testing to determine whether there was a sustained effect of the diet.

Diet. Participants were interviewed by the Clinical Research Center's (CRC's) dietician using a 5-pass, 24-h diet recall on their usual diet. Diet recalls were analyzed using Food Processor SQL (Version 10.0.0) Nutrition Software (ESHA Research Inc., Salem, OR, USA).

All study diets were developed using ProNutra Nutrition Software (Version 3.1.0.13, Princeton Multimedia Technologies Corporation, Princeton, NJ, USA). We used a 2-day alternating menu to avoid boredom with the diets.

The Paleo diet consisted of meat, fish, poultry, eggs, fruit, vegetables, tree nuts, canola oil, mayonnaise and honey. 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 pre-agricultural foods. The nutrient composition was verified by composite analysis performed by Covance Laboratories (Covance Labs, Madison, WI, USA; Table 1).

The diets were divided into three meals and three snacks, all prepared by the research center kitchen staff. Participants ate some of the meals 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. To prevent weight loss, body weight was measured every 2 days, and if a deviation of three pounds from the third day's weight in the study occurred calorie intake was adjusted.

To allow for adaptation of the subjects' intestinal tract and potassium handling systems to adjust to the markedly higher dietary content of the fiber and potassium in the Paleo diet, a series of ramp diets (with increasing levels of potassium and fiber) were developed. Ramp 1 diet was 1 day, ramp 2 for 3 days and ramp 3 for 3 days and then the Paleo diets were eaten for the remainder of the study. There was no ramp up for the ADA diet.

Blood tests. Fasting blood tests were conducted in triplicate (days -2 to 0 and +19 to 21).

Urine collections. Twenty-four-hour urinary sodium and potassium excretion were carried out in triplicate (days -2 to 0, and +19 to 21) and used as a marker for dietary compliance.

BP measurements. BPs were measured in the upper arm after 10 min of the patients' sitting, at 1 min intervals for 3 min using an automated BP measuring system (Dinamap, GE Healthcare, Little Chalfont, UK).

Euglycemic hyperinsulinemic clamp. Medications were withheld the morning of the procedure. Insulin was given as an IV bolus (0.1 U × kg body weight × desired plasma insulin concentration of 100 mU/l) over 10 min followed by a continuous infusion at 80 mU/min per m² for 120 min. Plasma glucose concentration was maintained at 5 mmol/l by a variable infusion of 20% glucose. Glucose disposal values (M/LBM/l) were calculated as mg glucose infused per min per kg lean body mass (M/LBM) divided by steady-state insulin levels (in μU/ml × 100).^{16,17}

Body composition. Total body water and extracellular water volumes, surrogate markers for fat and fat-free mass, were determined by bioimpedance spectroscopy (Intermed Inc, Melbourne, VIC, Australia). Subjects were measured supine after resting for ~10 min, using electrodes applied to the hands and feet. Fat-free mass by bioimpedance spectroscopy was used as an estimate of LBM.

Power calculations. The primary outcomes for this study were change in insulin sensitivity and improvements in lipid profiles (total cholesterol, triglycerides and high-density lipoprotein (HDL) cholesterol). The sample size estimate was determined on the basis of our previous study that observed significant improvements in lipid profiles and insulin sensitivity (changes in insulin area under the curve from an oral glucose tolerance test) with nine healthy subjects who were of average fitness by VO₂ max treadmill testing fed a metabolic balance Paleo diet for 2 weeks.¹⁰ This study documented a change in fasting insulin levels with an approximate standard deviation of 15%. For this study, we wanted to detect a minimum difference of 20% between-group fasting insulin levels with a 5% error (that is, $P < 0.05$). The power analysis indicated that each group should have 10 patients per group (2 groups) in order to give a power of 0.8 (that is, an 80% chance to determine a 20% difference between treatments).

Sample analyses

All of the initial testing was repeated on days 19–21. Repeated test (that is, blood or urine) results for day -2 to 0 and days 19 to 21 were averaged. Blood and urine samples were sent to Quest Diagnostics (San Jose, CA, USA) for sample analysis.

Statistics

Repeated measures analysis of variance with *post hoc* paired *T*-tests or regression analyses were used to evaluate most of the data (Sigmaplot, San Rafael, CA, USA). Unpaired *T*-tests were used for comparisons between groups. The data in tables are mean ± s.d.

RESULTS

Baseline characteristics

Twenty-five subjects enrolled (Table 2) in the study—two subjects decided not to participate after screening; one subject was dropped after being diagnosed with type 1 diabetes; three subjects were lost to follow-up during the trial. Five subjects who initially completed the ADA diet were recruited for the Paleo diet after a washout period of 3 months.

Ten subjects completed ADA diet and fourteen subjects completed the Paleo diet. Table 2 summarizes the baseline demographics. Fifteen (62.5%) of the participants identified their

Table 1. Diet composition

2-Day alternating menus	kcal	Pro, g	Fat, g	CHO, g	SFA, g	MFA, g	PFA, g	Na, mmol	K, mmol	Ca, mg
Paleo 1	3002	146	99	405	11	53	28	64.7	336.0	977
Paleo 2	3001	131	81	469	13	46	14	72.7	292.1	887
Average	3001.5	138.5	90	437	12	49.5	21	68.7	314.0	932
ADA 1	3005	123	102	422	24	52	17	4088	6574	2044
ADA 2	2996	182	90	394	19	40	24	4136	6100	1952
Average	3000.5	152.5	96	408	21.5	46	20.5	4112	6337	1998
% calories										
	Paleo	18.5	27.0	58.2	3.6	14.8	6.3			
	ADA	20.3	28.8	54.4	6.4	13.8	6.1			

Abbreviations: CHO, carbohydrate; MFA, monounsaturated fatty acid; PFA, polyunsaturated fatty acid; Pro, protein; SFA, saturated fatty acid. Bolded are averages. Paleo diet significantly different from ADA with respect to SFA, Na, K, Ca ($P < 0.05$).

Table 2. Baseline characteristics

	ADA diet (n = 10)	Paleo diet (n = 14)	P value
Age (years)	56 ± 13	58 ± 8	0.7
BMI (kg/m ²)	34 ± 7	31 ± 5	0.4
Systolic BP (mmHg)	125 ± 11	121 ± 16	0.5
Diastolic BP (mmHg)	68 ± 7	68 ± 9	0.9
MAP (mmHg)	87 ± 7	86 ± 10	0.7
<i>Blood</i>			
Fasting plasma glucose (mmol/l)	7.7 ± 2.5	8.4 ± 4.2	0.6
HbA1c (%)	7.0 ± 1.5	7.3 ± 2.1	0.8
Fructosamine (mg/dl)	264 ± 49	294 ± 108	0.4
Insulin sensitivity M/LBM/l	6.0 ± 1.8	7.1 ± 2.3	0.3
Total cholesterol (mg/dl)	176 ± 50	192 ± 52	0.4
Triglycerides (mg/dl)	149 ± 73	149 ± 75	0.9
HDL cholesterol (mg/dl)	46 ± 13	51 ± 12	0.3
LDL cholesterol (mg/dl)	92 ± 40	114 ± 41	0.2
<i>Urine</i>			
Creatinine clearance (ml/min/24 h)	142 ± 35	173 ± 65	0.2
Urine K/Na mmol/mmol	0.4 ± 0.2	0.5 ± 0.3	0.3
Urine pH (U)	5.8 ± 0.4	5.9 ± 0.5	0.4
Urine Ca/Creat (mg/g)	91 ± 29	93 ± 23	0.8

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; BP, blood pressure; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAP, mean arterial pressure.

race as European American/White, three (12.5%) as African American, three (12.5%) as Asian and three (12.5%) as Hispanic. The average BMI was 33.8 ± 8.6 in the ADA group and 32.5 ± 6.0 in the Paleo group. Patients in the ADA group and Paleo group did not statistically differ on any patient characteristics at baseline (Table 2). Both groups had well-controlled diabetes with HbA1c around 7% and fructosamine levels close to normal.

Medications

Four subjects were controlled with diet, fourteen were on metformin alone, five were on a combination of metformin and sulfonylurea and one patient was on sulphonylurea and long acting once daily insulin. The subjects remained on the same doses of diabetes medicines for the duration of the study. Nine subjects were on HMG CoA reductase inhibitors ('statin'); two were on statins and fibrates; five subjects were on an angiotensin-converting enzyme inhibitor and one on angiotensin receptor blocker (ARB); one on calcium channel blocker; two were on an ARB and thiazide diuretic; one on β-blocker and ARB; one on ARB, β-blocker and thiazide diuretic; and one on angiotensin-converting enzyme inhibitor, β-blocker and loop diuretic. These subjects remained on these drugs at the same doses for the duration of the study. Subjects were asked to stop other diet supplements including fish oils and multivitamins at the time of recruitment.

The usual diet was obtained from 24-h dietary recalls by an experienced research dietitian. The ADA and Paleo groups were not different at baseline in terms of sodium and potassium intake.

Changes while on diet

Weight changes. The average weight changes were similar in both groups, -2.1 ± 1.9 vs -2.4 ± 0.7 kg in the ADA and Paleo diets, respectively, *P* = 0.7.

Urinary changes. We would expect changes in urinary electrolytes to reflect the diets. The Paleo diet sodium and potassium contents were 69 and 314 mmol/3000 kcal, respectively, and the ADA diet sodium and potassium contents were estimated to be

179 and 162 mmol/3000 Kcal, respectively. We observed that, while on the diets, the ratio of urinary potassium to sodium (K/Na) excretion increased by 0.6 ± 0.3 in the ADA group and by 2.0 ± 0.8 in the Paleo group. As expected, patients on the Paleo diet had greater decreases in the urinary sodium levels and increase in potassium levels and an increase in K/Na ratio compared with the ADA group. Calculation of potassium to sodium ratio confirmed that all the patients, except for one, on the Paleo diet were compliant with the diet. In the Paleo diet group but not the ADA group, there was a decline in urinary calcium/creatinine ratio by 45 ± 43 (mg/g) and an increase in urine pH by +0.8 ± 0.5. The Paleo diet was significantly different compared with the ADA diet group in terms of causing changes in urine pH and urine calcium excretion. (Table 3)

Lipid control. Baseline lipid concentrations are listed in Table 2. There were statistically significant reductions in total cholesterol, HDL cholesterol and low-density lipoprotein (LDL) cholesterol on the Paleo diet (Table 3). The total cholesterol, HDL cholesterol and LDL cholesterol trended downward on the ADA diet, but only the decline in HDL cholesterol reached statistical significance. The triglycerides trended downward to a greater degree on the Paleo diet than on the ADA diet.

Glucose control and changes in insulin resistance. The patients remained on the same medications for the duration of the study. In the Paleo group, the HbA1c declined by 0.3% over the 3 weeks of the study (*P* = 0.04) and 0.2% in the ADA group (*P* = 0.04). Fructosamine, which is a shorter-term marker of glycemic control, declined by 34 μmol/l in the Paleo group (*P* = 0.01) and only by 3 μmol/l in the ADA group.

The ADA group and Paleo group were not statistically different in terms of insulin resistance at baseline (M/LBM/l), 6 ± 1.8 vs 7.1 ± 2.3 (*P* = 0.3). After the diet, the mean change in M/LBM/l was 1.0 mg/min/kg/mU insulin (*P* = 0.1) in the ADA group and 1.3 in the Paleo group (*P* = 0.09). Weight change could not explain the mean change in insulin resistance. In a bivariate analysis with group allocation and weight change as explanatory variables, the change in insulin resistance was independent of weight change (ADA group, *P* = 0.7; Paleo group, *P* = 0.1). We did observe that, within the Paleo diet subjects, those who were the most insulin resistant (M/LBM/l) at baseline had the greatest improvement in insulin resistance with the diet (Δ M/LBM/l; *r* = 0.63, *P* = 0.02). In contrast, baseline M/LBM/l did not predict the response to the ADA diet (Figure 1).

Blood pressure. BP data are given in Table 3. The mean arterial pressure did not significantly change in any of the two groups—mean arterial pressure declined by -2 ± 7 mm Hg in the Paleo diet group (*P* = 0.3) and by -1 ± 7 mm Hg on the ADA diet.

One-month follow-up data. We also wanted to determine whether having been on an experimental diet had a sustained benefit, and hence we asked patients to return for metabolic testing 1 month after completing the diet protocol. At the end of the study period, subjects were sent out with information about their respective diets. Twenty-two of twenty-four subjects returned for the follow-up urine studies, lipid profile and euglycemic clamp. The urine studies indicated that patients had returned to their pre-existing diet in terms of sodium and potassium intake. Glucose control and lipid profiles reverted toward baseline in both groups (Figure 2).

DISCUSSION

Obese patients with type 2 diabetes were randomly assigned to a Paleo-type diet or a standard diet based on the nutrition recommendations of the ADA. We observed greater effects on

Table 3. Changes in blood and urine parameters within each diet and between diets

	ADA	P value for changes within ADA group	Paleo	P value for changes within Paleo group	P value for differences between groups
Weight (kg)	-2.1 ± 1.9	0.004	-2.4 ± 0.7	< 0.001	0.7
Systolic BP (mmHg)	-2 ± 13	0.7	-4 ± 12	0.2	0.6
Diastolic BP (mmHg)	0 ± 12	0.9	-1 ± 6	0.4	0.6
MAP (mmHg)	-1 ± 7	0.8	-2 ± 7	0.3	0.6
Blood					
HbA1c (%)	-0.18 ± 0.24	0.04	-0.3 ± 0.49	0.04	0.5
Fasting plasma glucose (mmol/l)	+0.6 ± 1.8	0.4	-1.3 ± 1.4	0.008	0.3
Fructosamine (mg/dl)	-3 ± 28	0.7	-34 ± 41	0.009	0.06
Insulin sensitivity M/LBM/l	+1.0 ± 1.9	0.1	+1.3 ± 2.6	0.09	0.8
Total cholesterol (mg/dl)	-9 ± 25	0.2	-26 ± 27	0.003	0.2
Triglycerides (mg/dl)	-5 ± 63	0.8	-23 ± 46	0.08	0.5
HDL cholesterol (mg/dl)	-6 ± 8	0.03	-8 ± 7	0.001	0.5
LDL cholesterol (mg/dl)	-7 ± 17	0.2	-15 ± 22	0.02	0.4
Urine					
CrCl	-16 ± 29	0.1	-3 ± 29	0.9	0.2
Urine K/Na	+0.6 ± 0.3	< 0.0001	+2.0 ± 0.8	< 0.0001	0.001
Urine pH	0.1 ± 0.3	0.7	+0.8 ± 0.5	< 0.0001	< 0.001
Urine Ca/Creat	-2 ± 33	0.9	-45 ± 43	0.002	0.008

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; BP, blood pressure; CrCl, creatinine clearance; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAP, mean arterial pressure.

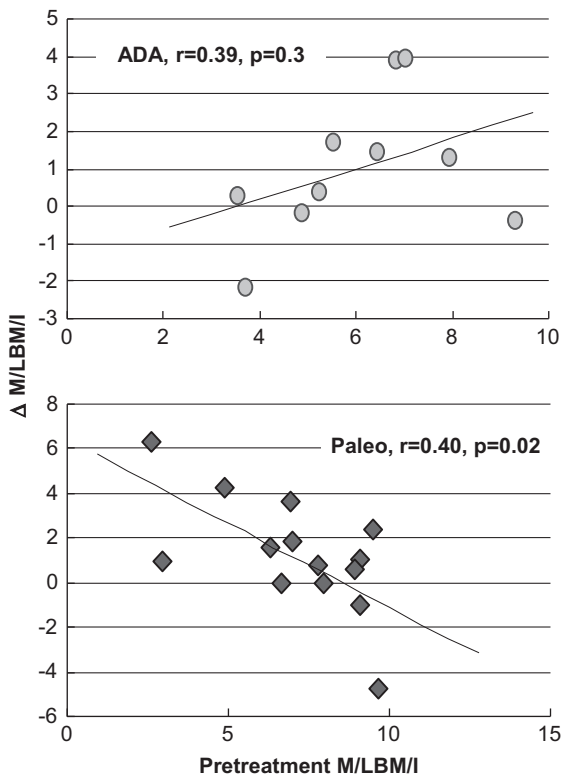


Figure 1. Scatterplot of change in insulin sensitivity as measured by euglycemic hyperinsulinemic clamp (change in mg glucose/min/kg/mU insulin, Δ M/LBM/l) against baseline M/LBM/l. The most insulin-resistant subjects had a significant improvement in insulin sensitivity on the Paleo diet ($r=0.40$, $P=0.02$) but not on the ADA diet ($r=0.39$, $P=0.3$).

metabolic parameters while on the Paleo diet than on the ADA diet just after 3 weeks. The Paleo diet group had improvement in glucose levels—declines in HbA1c of 0.3% ($P=0.04$) and fructosamine by 34 μ mol/l ($P=0.009$). The ADA group had a

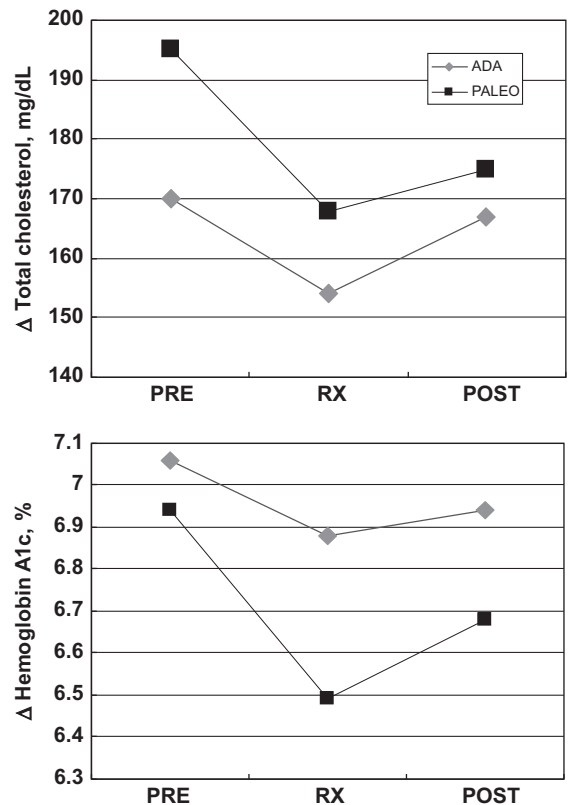


Figure 2. Metabolic testing was performed immediately before and after the diets and then 1 month after completion of test diets. The glucose and lipid changes were not sustained and reverted toward baseline in both groups at the 1-month time-point.

0.2% drop in HbA1c ($P=0.04$) but no decline in fructosamine. This improvement in glycemic control with the Paleo-type diet could not be explained by changes in weight or by group improvements in insulin sensitivity—both diet groups had equivalent changes in

weight and insulin sensitivity. In a bivariate analysis with group allocation and weight change as explanatory variables, the change in insulin resistance was independent of weight loss (ADA group $P=0.7$; Paleo group $P=0.1$). We did observe, however, that those subjects who were the most insulin resistant at baseline demonstrated the greatest improvements in insulin sensitivity on the Paleo diet but not on the ADA diet. This is similar to the effect we saw in our previous study of healthy sedentary volunteers; those who were most insulin resistant at baseline, using the HOMA index, ((fasting insulin x fasting glucose)/22.4) demonstrated the greatest improvement in insulin sensitivity on the Paleo diet.¹⁰ Our Paleo diet was not low in carbohydrates, but the sources of carbohydrates were different—from fruits, vegetables and honey. The ADA group in contrast ate rice, bread and pasta. The Paleo compared with the ADA diet was also high in fiber—about 35 g/2500 kcal vs 12 g/2500 kcal, and it is possible that the fiber attenuated the post-prandial glucose rise and that this was the main driver improving overall glucose control.^{18,19}

The Paleo diet group had statistically significant declines in total cholesterol, HDL cholesterol and calculated LDL cholesterol. The triglycerides trended down but did not reach statistical significance. In contrast, the ADA group only had a decline in HDL cholesterol but not in total cholesterol, calculated LDL cholesterol or triglycerides. Our Paleo diet was lower in saturated fats and higher in mono- and polyunsaturated fats compared with the ADA diet (Table 1), and it is likely that this explains the decline in the total and HDL cholesterol levels.²⁰ The modest decline in the HDL cholesterol on the ADA diet probably also reflects the improved fat composition of the experimental diet compared that which the patients were eating at home. There were no significant changes in systolic or mean arterial pressures with either diet. This is despite both diets being lower in sodium and higher in potassium than the baseline diets consumed by the subjects.

We might have expected, based on our previous study¹⁰ and published studies,^{13,14} to see a more marked within-group effect of the Paleo diet or between-group effect with the ADA diet on the described metabolic variables. A number of factors, however, may have attenuated these effects. First, the patients overall were well controlled at baseline with HbA1c levels around 7%, systolic pressures in the mid 120s and triglycerides around 150 mg/dl, and we kept them on their baseline glucose lowering, antihypertensives and lipid-lowering medicines. We might have seen greater benefits in patients who were not on treatment and less well controlled at baseline.

Second, we wanted to evaluate the impact of the diets in the absence of weight loss, and even though we adjusted the caloric intake to avoid weight loss both the control and test groups lost ~2 kg in weight. We might have seen more marked differences between the diets if there had not been any weight loss. The subjects on the Paleo-type diet did complain that the volume of food that they had to eat was excessive and without our encouragement would likely have lost more weight. Increased satiety has been reported on Paleo-type diets compared with Mediterranean diets.²¹

Third, on the basis of our intake questionnaire and food recall responses, we expected the parameters of the subjects on the ADA recommended diet to remain unchanged from baseline, but in fact they also improved reducing the differences observed with the two diets. This may reflect the poor nutritional characteristics of the subjects' baseline diet and/or the bias effects of being in a non-blinded clinical study.

The metabolic benefits of the diets were not sustained, and both diet groups reverted back toward baseline 1 month after completing the diets. The study, however, was of short duration, and a definitive result on whether the Paleo diet can have sustained metabolic benefits would probably require a prolonged intervention.

In conclusion, we demonstrate in a small randomized, metabolically controlled diet study that patients with type 2

diabetes can benefit from being on a Paleolithic-type diet compared with a conventional diet based on nutritional recommendations of the ADA. The nutritional composition of a Paleo diet—high-fiber content, high antioxidants, high mono- and polyunsaturated fats, low sodium and high potassium—may be particularly beneficial in these patients, even if they are on medicines to control glucose levels, BP and lipids.

CONFLICT OF INTEREST

All the authors were involved in the design of the experiment. UM, PS, MS, SS, AX and LF performed the experiments. UM and LF analyzed the data and wrote the manuscript. The authors declare no conflict of interest.

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REFERENCES

- Murea M, Ma L, Freedman BI. Genetic and environmental factors associated with type 2 diabetes and diabetic vascular complications. *Rev Diabet Stud* 2012; **9**: 6–22.
- Parillo M, Riccardi G. Diet composition and the risk of type 2 diabetes: epidemiological and clinical evidence. *Br J Nutr* 2004; **92**: 7–19.
- Steyn NP, Mann J, Bennett PH, Temple N, Zimmet P, Tuomilehto J *et al*. Diet, nutrition and the prevention of type 2 diabetes. *Public Health Nutr* 2004; **7**: 147–165.
- Stanhope KL, Schwarz JM, Havel PJ. Adverse metabolic effects of dietary fructose: results from the recent epidemiological, clinical, and mechanistic studies. *Curr Opin Lipidol* 2013; **24**: 198–206.
- Siri PW, Krauss RM. Influence of dietary carbohydrate and fat on LDL and HDL particle distributions. *Curr Atheroscler Rep* 2005; **7**: 455–459.
- Martini LA, Catania AS, Ferreira SR. Role of vitamins and minerals in prevention and management of type 2 diabetes mellitus. *Nutr Rev* 2010; **68**: 341–354.
- Baz-Hecht M, Goldfine AB. The impact of vitamin D deficiency on diabetes and cardiovascular risk. *Curr Opin Endocrinol Diabetes Obes* 2010; **17**: 113–119.
- Weinberger MH. Salt sensitivity of blood pressure in humans. *Hypertension* 1996; **27**: 481–490.
- Eaton SB, Konner M. Paleolithic nutrition. A consideration of its nature and current implications. *N Engl J Med* 1985; **312**: 283–289.
- Frassetto LA, Schloetter M, Mietus-Synder M, Morris Jr RC, Sebastian A. Metabolic and physiologic improvements from consuming a paleolithic, hunter-gatherer type diet. *Eur J Clin Nutr* 2009; **63**: 947–955.
- Cordain L. The nutritional characteristics of a contemporary diet based on Paleolithic food groups. *J Am Nutr Assoc* 2002; **5**: 15–24.
- Strohle A, Hahn A, Sebastian A. Estimation of the diet-dependent net acid load in 229 worldwide historically studied hunter-gatherer societies. *Am J Clin Nutr* 2010; **91**: 406–412.
- Osterdahl M, Kocurk T, Koochek A, Wandell PE. Effects of a short-term intervention with a paleolithic diet in healthy volunteers. *Eur J Clin Nutr* 2008; **62**: 682–685.
- Lindeberg S, Jonsson T, Granfeldt Y, Borgstrand E, Soffman J, Sjostrom K *et al*. A Palaeolithic diet improves glucose tolerance more than a Mediterranean-like diet in individuals with ischaemic heart disease. *Diabetologia* 2007; **50**: 1795–1807.
- Bantle JP, Wylie-Rosett J, Albright AL, Apovian CM, Clark NG, Franz MJ *et al*. Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. *Diabetes Care* 2008; **31**: S61–S78.
- Defronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 1979; **237**: E214–E223.
- Ferrannini E, Mari A. How to measure insulin sensitivity. *J Hypertens* 1998; **16**: 895–906.
- Post RE, Mainous 3rd AG, King DE, Simpson KN. Dietary fiber for the treatment of type 2 diabetes mellitus: a meta-analysis. *J Am Board Fam Med* 2012; **25**: 16–23.
- Robertson MD, Wright JW, Loizon E, Debard C, Vidal H, Shojaaee-Moradie F *et al*. Insulin-sensitizing effects on muscle and adipose tissue after dietary fiber intake in men and women with metabolic syndrome. *The J Clin Endocrinol Metab* 2012; **97**: 3326–3332.
- Mattson FH, Grundy SM. Comparison of effects of dietary saturated, mono-unsaturated, and polyunsaturated fatty acids on plasma lipids and lipoproteins in man. *J Lipid Res* 1985; **26**: 194–202.
- Jonsson T, Granfeldt Y, Erlanson-Albertsson C, Ahren B, Lindeberg S. A paleolithic diet is more satiating per calorie than a mediterranean-like diet in individuals with ischemic heart disease. *Nutr Metab (Lond)* 2010; **7**: 85.