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A multicomponent nutrient bar promotes weight loss and improves dyslipidemia and insulin resistance in the overweight/obese: chronic inflammation blunts these improvements

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ABSTRACT This study determined if twice-daily consumption of a nutrient-dense bar intended to fill gaps in Western diets, without other dietary/lifestyle requirements, favorably shifted metabolic/anthropometric indicators of dysregulation in a healthy direction. Three 8-wk clinical trials in 43 healthy lean and overweight/obese (OW/OB) adults, who served as their own controls, were pooled for analysis. In less inflamed OW/OB [high-sensitivity C-reactive protein (hsCRP) <1.5], statistically significant decreases occurred in weight (-1.1 ± 0.5 kg), waist circumference (-3.1 ± 1.4 cm), diastolic blood pressure (-4.1 ± 1.6 mmHg), heart rate [HR; -4.0 ± 1.7 beats per minute (bpm)], triglycerides (-72 ± 38.2 mg/dl), insulin resistance (homeostatic model of insulin resistance) (-0.72 ± 0.3), and insulin (-2.8 ± 1.3 mU/L); an increase in HDL-2b ($+303 \pm 116$ nM) and realignment of LDL lipid subfractions toward a less atherogenic profile [decreased small LDL IIIb (-44 ± 23.5 nM), LDL IIIa (-99 ± 43.7 nM), and increased large LDLI ($+66 \pm 28.0$ nM)]. In the more inflamed OW/OB (hsCRP >1.5), inflammation was reduced at 2 wk (-0.66 mg/L), and HR at 8 wk (-3.4 ± 1.3 bpm). The large HDL subfraction (10.5–14.5 nm) increased at 8 wk ($+346 \pm 126$ nM). Metabolic improvements were also observed in lean participants. Thus, favorable changes in measures of cardiovascular health, insulin resistance, inflammation, and obesity were initiated within 8 wk in the OW/OB by replacing deficiencies in Western diets without requiring other dietary or lifestyle modifications; chronic inflammation blunted most improvements.—McCann, J. C., Shigenaga, M. K., Mietus-Snyder, M. L., Lal, A., Suh, J. H., Krauss, R. M., Gildengorin, G. L., Goldrich, A. M., Block, D. S.,

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Key Words: cardiovascular · dietary intervention · nutritional supplements · lipid particles · HDL cholesterol

OVERCONSUMPTION OF WESTERN DIETS high in calories, sugar, salt, and unhealthy fats, but low in micronutrients [many essential vitamins and minerals (Vs/Ms) and ω -3 fatty acids], fiber, and plant polyphenolics (1–4), is a major cause of the increasing prevalence of obesity worldwide (5–7). Such diets directly contribute to the metabolic dysregulation that usually accompanies obesity (8–11) and is also present in ~25% of lean individuals (12, 13). Metabolic dysregulation includes chronic inflammation, insulin resistance, dyslipidemia, and oxidative stress (14, 15). Several metabolic abnormalities, together with visceral adiposity and high blood pressure (BP), are collectively termed “the metabolic syndrome” (11, 16). Various aspects of metabolic dysregulation have been shown to be independent risk factors for cardiovascular disease (CVD) and type 2 diabetes, and putative risk factors for the many other obesity-associated diseases including cancer, autoimmune disorders, asthma, and neurodegenerative conditions (17–22).

Because poor diets are a root cause of these health problems, an obvious approach to the obesity epidemic would be to improve dietary habits. However, changing dietary patterns is difficult for many people to initiate and sustain (23–25).

Abbreviations: aka, also known as; BMI, body mass index; BP, blood pressure; bpm, beats per minute; CVD, cardiovascular disease; DBP, diastolic blood pressure; DHA, docosahexaenoic acid; HDL-L, large HDL subfraction; HDLs, total HDL subfractions; HOMA-IR, homeostatic model of insulin resistance; HPMC, hydroxypropylmethylcellulose; HR, heart rate;

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We have developed, guided by 18 small clinical trials conducted over the last 10 years, a low-calorie, fruit-based bar fortified with micronutrients, fiber, and other dietary components inadequate in a typical Western diet (26). This approach was based on the hypothesis that metabolic dysregulation common in the obese (with consequent increased disease risk) is due in large part to what is missing or inadequate in Western diets, and might be improved by increasing intake of these food components.

In addition to the bar having practical application as a nutritional supplement to attenuate the adverse metabolic impact of obesity and hopefully encouraging transition to healthier eating habits, a major goal was to use the nutrient mixture as a scientific tool to investigate mechanisms by which individual dietary components in a complex dietary mixture interact with each other and with human metabolism. Because the composition of the bar is defined and easily manipulated, deconstruction studies aimed at understanding mechanisms are quite feasible, whereas this type of mechanistic detective work would be virtually impossible to do in human trials with a complete diet.

A great deal of evidence points to the impact of dietary deficiencies on metabolic health. For example, low intake of fruits, vegetables, and fish by the great majority of the population in the United States (1, 27), with consequent inadequate intake of many essential V/Ms (28), results in low V/M status, which is particularly apparent in obese people (29–33). Triage theory (34–37) provides a mechanistic rationale for why essential V/M inadequacies common in Western diets increase future chronic disease risk. Research also links other dietary deficiencies common in typical Western diets to increased risk for chronic disease or metabolic dysregulation. Examples include low intake of dietary fiber (38–40) and its fermentation products [short-chain fatty acids (41, 42) and glutamine (43–45)], plant polyphenolics (46–49) and ω -3 fatty acids (50).

Throughout development of the nutrient mixture, formulation modifications to improve palatability and efficacy were guided by small clinical trials that examined effects of formulation modifications on a range of clinical biochemical and anthropometric measures [(51); unpublished results]. A simple and economical experimental design was used for these trials. Participants acted as their own control subjects and were not asked to modify their existing diets during the course of the trial, consistent with our hypothesis that adding back inadequate dietary components would be sufficient to result in positive change. For further discussion on development of the nutrient bar, see our earlier paper (51).

Background/rationale for the current report

Early clinical trials were of short duration (2 wk) and included healthy, predominantly lean, or only slightly overweight adults. Our previous report (51) indicated that twice-daily consumption of the nutrient bar for 2 wk

resulted in a striking increase in most participants in HDL-cholesterol (HDL-c), particularly the large HDL subfraction [designated HDL-L or HDL-2b (10.5–14.5 nm)]. HDL-2b is generally considered to be associated with less future CVD risk (52, 53) and may reflect increased reverse cholesterol transport (RCT), an antiatherogenic function of HDL (54).

Subsequent trials included both 2 wk and 2 month time points and approximately equal numbers of lean and overweight/obese (OW/OB) adults. This report presents results of 3 of these 2 month trials using bars of comparable fiber and nutrient composition. The major goal of the analysis was to test whether bar consumption without other lifestyle modifications could shift metabolic dysregulation in the OW/OB toward a “leaner” profile, and to confirm, and extend to 2 months, results of earlier 2 wk trials in predominantly lean individuals (51). Plasma concentrations of standard clinical metabolic and anthropometric measures, lipid protein subfractions, the adipokine measures, lipoprotein subfractions, the adipokine adiponectin (55), and the acute phase protein serum amyloid A (SAA) (56) were quantified at baseline, and after 2 and 8 wk of twice-daily consumption of the nutrient bar.

MATERIALS AND METHODS

Composition of the nutrient bars

The nutrient bars used in this study were similar to the prototype bar described previously (51). The major difference in the bars utilized in this study compared to the prototype bar (51) is the substitution of half of the soluble fiber with hydroxypropylmethylcellulose (HPMC), a highly viscous, nonfermentable soluble fiber (57). Bars used in the 3 trials presented here were identical except in amounts of some vitamins (vitamins A, D₃, and K₁ and folate) and some fruits with high polyphenol (anthocyanin) content, though these differences did not affect outcome distributions (see “Statistical analysis”). Each trial used a different bar. Nutrient profiles of the 3 bars are in **Table 1**.

Study cohort

A total of 43 generally healthy adults participated in ≥ 1 of 3 identical 2-month trials conducted over a period of 4 years. There were 10 participants in 2 trials; 5 were in 3 trials. Each trial was separated by >1 year. There were 2 participants excluded from the analysis because their baseline fasting blood glucose was >126 mg/dl, indicating diabetes. One participant was excluded from analysis because high-sensitivity C-reactive protein (hsCRP) values for all 3 time points were >10 mg/L, indicating probable infection (60). There were 4 individual hsCRP data points >10 (in 4 participants) also excluded. All but one of these high values were supported by documentation of either a cold or allergy at the time of the clinical research center visit. Data points corresponding to these 4 excluded values were also removed for all non-hsCRP parameters analyzed. A single outlier baseline value was also removed from the SAA data set that was 5 sds greater than the mean. The trials were identical in design and involved twice-daily intake of the nutrient bar. Characteristics of the study cohort are shown in **Table 2**. Exclusion criteria were intercurrent infectious disease, untreated stage II hypertension, and medication for diabetes or dyslipidemia. Clinical trials were approved by the institutional review board of Children’s Hospital and Research Center Oakland. All participants signed informed consent forms prior to enrollment.

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hsCRP, high-sensitivity C-reactive protein; IDL, intermediate-density lipoprotein; OW/OB, overweight/obese; PPAR, peroxisome proliferator-activated receptor; RCT, reverse cholesterol transport; SAA, serum amyloid A; TC, total cholesterol; TG, triglyceride; V/M, vitamins and minerals

TABLE 1. *Composition of bars*

Bar components	Bar 1	Bar 2	Bar 3
Total calories (kcal)	107	124	107
Total fat (g)	5.04	5.09	5.04
Saturated fat (g)	2.52	2.54	2.52
Trans fat (g)	0.0	0.0	0.0
Cholesterol (mg)	0.0	0.0	0.0
DHA, 22:6 n-3 (mg)	200	200	200
Sodium (mg)	2.71	3.002	2.71
Potassium (mg)	142	158	142
Total carbohydrate (g)	19.7	25.4	19.7
Fiber, total dietary (g)	7.31	8.79	7.31
Sugars (g)	7.58	11.0	7.58
Total protein (g)	3.78	3.91	3.78
Vitamin A (retinol activity equivalents)	71.9	35.6	71.9
β -Carotene (μ g)	201	180	201
Calcium (mg)	287	362	287
Vitamin D3 (IU)	0.0	2300	200
Vitamin K1 (μ g)	45	36	45
Riboflavin (mg)	0.63	0.65	0.63
Vitamin B6 (mg)	0.69	0.71	0.69
Vitamin B12 (μ g)	0.80	0.80	0.80
Pantothenic acid (mg)	1.39	1.35	1.39
Zinc (mg)	2.8	2.84	2.8
Copper (μ g)	283	287	283
Chromium (μ g)	33	33	33
Vitamin C (mg)	105	106	105
Iron (mg)	1.89	1.98	1.89
Vitamin E (α , γ tocopherols) (mg)	6.63	6.70	6.63
Thiamine (vitamin B1) (mg)	0.43	0.44	0.43
Niacin (mg)	7.77	7.90	7.77
Folate (μ g)	316	558	316
Biotin (μ g)	7.5	7.5	7.5
Phosphorus (mg)	42.2	45.1	42.2
Magnesium (mg)	179	180	179
Selenium (μ g)	6.24	6.20	6.24
Manganese (mg)	0.36	0.36	0.36
Choline (mg)	127	128	127
Glutamine (g)	1.0	1.0	1.0
Lactate (mg)	0.0	326	0.0
Glycerine (g)	1.00	1.50	1.00
Total polyphenols (mg)	473	515	473
Monomeric polyphenols (mg)	87.8	157	87.8

Values are amounts contained in 1 bar; dosage is 2 bars per day. Values were calculated from U.S. Department of Agriculture (USDA) tables (58) and individually added nutrients. Fruit concentrate polyphenol concentrations are derived from the USDA Database for the Flavonoid Content of Selected Foods, Release 2.1 (59). The Nutrient Database numbers are 09050, 09078, 97074, and 09279. Polyphenol content of blueberry powder was provided by the Highbush Blueberry Council. The patent is pending (26).

Intervention

The study design was an open label, nonrandomized 8 wk clinical trial in which participants acted as their own control subjects. Participants were advised to discontinue all vitamin, mineral, and fiber supplements and any other nutraceuticals 2 wk before the initiation of each trial. Compliance with these guidelines as well as absence of intercurrent infectious disease was assessed by self-report. Consumption of 2 bars each day was advised, with the first to be eaten before noon and the second in either the afternoon or evening. Participants were advised to drink a minimum of 8 ounces of water with each bar. No guidelines as to whether to use the bar as a meal replacement or a supplement were given. Baseline, 2 and 8 wk visits to the clinical research center included measurements of height, weight, and waist circumference taken at the umbilicus. Compliance with bar consumption

averaged 95%, as assessed by questionnaire at each visit to the clinical research center. Each physical measurement was taken twice and averaged. BP and heart rate (HR; Dinamap, GE Healthcare, Wauwatosa, WI, USA) were assessed in triplicate and averaged. Fasting venous blood samples were taken in EDTA-containing tubes and immediately processed.

Biochemical analyses

Lipid profiles

Plasma samples prepared within 15 min of collection were kept at 4°C throughout processing. For 1 of the 3 trials analyzed, the basic lipid panel [total cholesterol (TC), triglycerides (TGs), HDL-c, and LDL cholesterol (LDL-c)] was determined as follows. Plasma TC and TG concentrations were determined by enzymatic

TABLE 2. Baseline metabolic and anthropometric characteristics of OW/OB and lean participants

Characteristics	BMI <25	BMI ≥25
Mean clinical measures (sd)	(n = 29)	(n = 30)
Age (years)*	43.4 (14.3)	52.7 (12.6)
Female sex (%) ^a	86.7	40
Physical		
BMI*	22.6 (1.7)	29.7 (3.4)
Weight (kg)*	62.3 (8.4)	92.0 (16.8)
Waist circumference (cm)*	80.5 (6.5)	104.0 (11.5)
Systolic BP (mmHg)*	112.2 (11.0)	120.8 (9.7)
Diastolic BP (mmHg)*	70.7 (7.5)	77.8 (8.3)
HR (bpm)	64.7 (11.9)	67.0 (6.9)
Lipids		
HDL-c (mg/dl)*	68.7 (20.8)	49.8 (12.5)
LDL-c (mg/dl) [†]	101.3 (34.0)	124.4 (36.6)
TC (mg/dl)	186.1 (35.6)	201.9 (36.6)
Non-HDL-c (mg/dl)*	115.0 (37.9)	149.2 (36.6)
TGs (mg/dl)*	80.7 (41.2)	157.4 (118.9)
VLDL-c (mg/dl)*	16.1 (8.2)	31.5 (23.8)
TG/HDL-c*	1.4 (1.2)	3.9 (4.7)
Insulin resistance		
Glucose (mg/dl)*	93.3 (7.7)	102.8 (7.5)
Insulin (mU/L)*	6.4 (3.9)	13.3 (6.9)
HOMA-IR*	1.4 (0.8)	3.4 (1.7)
Inflammation related		
hsCRP(mg/L)*	0.87 (1.3)	2.1 (1.6)
Adiponectin (ng/ml)*	6797 (5895)	3179 (2858)
SAA (ng/ml)	918.4 (667.7)	3887 (8526)
Mean lipoprotein particle measurements (sd)	(n = 28)	(n = 30)
HDL particles		
HDL-2b (nM)*	3187 (1959)	1467 (967.1)
HDL3_2a (nM)	5548 (1788)	5686 (1391)
Total (nM) [†]	8736 (2704)	7152 (1747)
LDL particles		
Peak diameter (Å)*	224.7 (6.1)	219.8 (6.2)
LDL I (nM)	346.3 (128.3)	346.0 (145.6)
LDL IIa (nM) [†]	210.0 (98.1)	267.2 (92.4)
LDL IIb (nM)*	205.2 (103.1)	297.2 (110.9)
LDL IIIa (nM) [†]	147.7 (121.3)	248.2 (172.0)
LDL IIIb (nM)	52.5 (48.0)	88.4 (82.7)
LDL IVa (nM)	57.3 (30.9)	76.0 (48.1)
LDL IVb (nM)	52.6 (23.3)	65.9 (26.9)
LDL IVc (nM)	32.8 (10.2)	37.0 (15.1)
Total (nM)*	1105 (354.4)	1426 (313.8)
VLDL and IDL particles		
IDL I (nM)	170.8 (65.3)	188.3 (58.5)
IDL II (nM) [†]	277.7 (131.7)	204.8 (76.4)
VLDL small (nM)	72.7 (31.9)	72.7 (24.6)
VLDL intermediate (nM)*	49.6 (26.6)	65.8 (24.1)
VLDL large (nM)*	15.0 (12.3)	25.7 (14.5)

n refers to the number of observations measured, not the number of participants (see Materials and Methods). The number of observations averaged for each measure is indicated at the head of each column unless otherwise indicated. BMI <25: *n* = 23 (non-HDL), *n* = 27 (adiponectin), and *n* = 5 (SAA). BMI ≥25: *n* = 28 (LDL-c), *n* = 22 (non-HDL), *n* = 30 (adiponectin), and *n* = 18 (SAA). The differences in this table are not intended to represent a definitive comparison because the lean and OW/OB groups were not matched for age, sex, or ethnicity, which are known to affect the metabolic profile. Ethnicities were BMI <25 (48% Caucasian, 31% Asian-American, 7% Hispanic, 7% unknown, 3% African American, and 3% other) and BMI ≥25 (58% Caucasian, 10% Asian-American, 16% Hispanic, 10% unknown, and 6% African American). HDL3_2a, small HDL (7.6–10.5 nm). For HDL, LDL, and other particle definitions, see Abbreviations. ^aNo significant difference by χ^2 analysis. **P* < 0.01; [†]*P* < 0.05.

procedures on an Express 550 Plus analyzer (Ciba Corning, Oberlin, OH, USA) controlled by the U.S. Centers for Disease Control and Prevention-U.S. National Institutes of Health National Heart, Lung, and Blood Institute standardization monitoring program. HDL-c was measured after dextran sulfate

precipitation of plasma. LDL-c was calculated using a standard formula (61) for all samples with TG concentrations <400 mg/dl. For the other 2 trials analyzed, the basic lipid panel (TC, TGs, HDL-c, and LDL-c) was determined by a commercial provider (ARUP Laboratories, Salt Lake City, UT, USA). Ion mobility

analysis was used to measure concentrations of lipoprotein subfractions in all 3 trials, as previously described (62).

Other measures

Plasma fasting glucose, insulin, and hsCRP were measured using standard procedures by a commercial provider (ARUP Laboratories). Insulin resistance was estimated using the homeostatic model of insulin resistance (HOMA-IR) calculated as fasting glucose (milligrams per deciliter) \times fasting insulin (milli-international units per liter) \div 405. High molecular weight adiponectin was measured by solid-phase sandwich ELISA (Quantikine; R&D Systems, Minneapolis, MN, USA). SAA was measured using detection antibodies that emit light upon electrochemical stimulation (Meso Scale Discovery, Rockville, MD, USA).

Statistical analysis

Prior to pooling data from the 3 trials, quantitative measures and changes from baseline to 2 and 8 wk were assessed by ANOVA within each trial. Outcome distributions were similar in all 3 trials, and results were pooled. All statistical analyses were performed using SAS (version 9.3; SAS Institute, Cary, NC, USA). Variables included standard clinical metabolic and anthropometric measures and lipoprotein subfraction concentrations. Means \pm SE were calculated for the various subgroups and time points. Correlations were computed using Spearman's nonparametric estimates. Data were examined for assumptions of normality using measures of skewness and kurtosis, plots, and the Anderson-Darling test. Log transformations were performed for highly skewed data (HOMA-IR, insulin, hsCRP, TGs, SAA, and adiponectin). Initial bivariate analysis using Student's *t* test was conducted to compare baseline values between lean and OW/OB. Linear regression models were constructed on the continuous outcomes and on changes from baseline. Bar-induced changes were examined over time in the OW/OB and in the 2 OW/OB subgroups using general linear models with time treated as repeated measures. The generalized estimating equation approach, with an exchangeable working correlation structure, was used to account for the within-person correlation in outcomes at different time points (*i.e.*, statistical analysis included adjustment for participants who were in >1 trial). A significance level of 0.05 was used for all statistical tests. Because multiple statistical tests were conducted, some false positives may have occurred.

RESULTS

Baseline characteristics of lean and OW/OB participants

Baseline metabolic characteristics of lean and OW/OB participants are shown in Table 2 and reflect recognized differences between these groups (63–68). As shown, HDL-c is significantly lower in the OW/OB, and BP, LDL-c, TGs, insulin resistance (as measured by HOMA-IR), insulin, glucose, and inflammation (as measured by hsCRP) are all significantly higher. Adiponectin and SAA also reflect known differences between the OW/OB and lean. Adiponectin is significantly higher in the lean (55, 69), and SAA is higher in the OW/OB (70).

Significant lipoprotein subfraction differences between the OW/OB and lean groups are 1) higher concentrations of HDL-2b and intermediate-density lipoprotein (IDL) II in the lean, 2) greater LDL peak diameter in the lean, and 3) lower concentrations of LDL IIb and large VLDL (very LDL) in the lean. In addition, as expected (71), across all

OW/OB and lean participants, concentrations of small LDL subfractions are strongly and positively correlated with TG concentration and strongly and negatively correlated with HDL-c. The correlation coefficient of the sum of the 2 most atherogenic small subfractions (LDL IIb and IIIa) (72) with HDL-c is -0.74 ($P < 0.001$; $n = 60$) and with TGs is $+0.71$ ($P < 0.001$; $n = 60$).

Effects of 2 and 8 wk twice-daily consumption of 2 nutrient bars in lean and OW/OB healthy adults

Effects of nutrient bar consumption in the lean

Previously, we reported that consumption of 2 nutrient bars a day for 2 wk by healthy, predominantly lean [body mass index (BMI) <25] or slightly overweight adults significantly increased HDL-c, particularly the HDL-2b [also known as (aka) HDL-L] (51). Similar results were observed at 2 wk for lean participants in this study and persisted at 8 wk, as shown in **Fig. 1**. HDL-c increased in 76% of participants, with an overall average increase of 4.1 ± 1.0 mg/dl ($P < 0.001$), and HDL-2b increased 492 ± 148 nM ($P < 0.007$). The additional major change observed in this study was a large increase in the adipokine adiponectin, not measured in our earlier study (51), which also increased very significantly at 2 wk ($+1026 \pm 405$ ng/ml; $P < 0.002$) and 8 wk ($+1475$ ng/ml; $P = 0.005$).

Additional parameters for which changes were statistically significant at 8 wk included total HDL subfractions (HDLps) ($+859 \pm 296$ nM; $P = 0.0040$) and TC ($+9.5 \pm 3.2$ mg/dl; $P = 0.0029$), not unexpected given the robust increases in HDL measures, and several other statistically significant changes: non-HDL cholesterol ($+6.6 \pm 3.1$ mg/dl; $P = 0.044$), waist circumference ($+1.1 \pm 0.6$ cm; $P = 0.042$), and LDL IIa ($+20.4 \pm 9.2$ nM; $P = 0.047$). There were no statistically significant changes

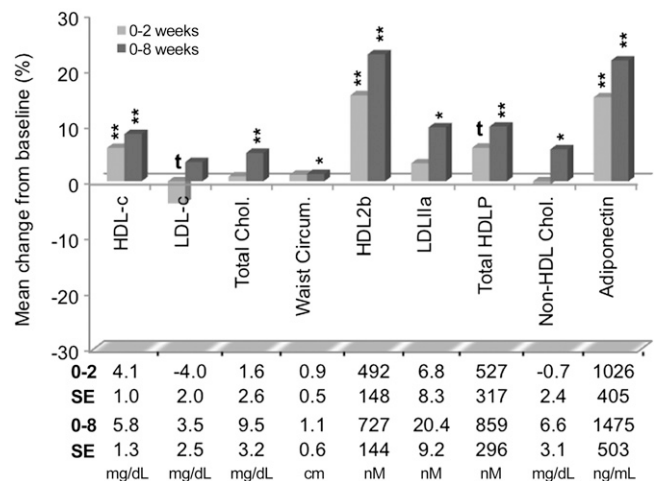


Figure 1. Effects of the nutrient bar in the lean (BMI <25) after 2 and 8 wk consumption of 2 nutrient bars each day. Chol., cholesterol; Circum., circumference. Values plotted are changes from baseline, averaged across all participants and plotted as percentage of the overall baseline mean for each endpoint. Average changes and SE are specified below the figure. HDL-2b is one of the 2 classes of HDL subfractions identified by the lipid particle-sizing assay and is defined in Abbreviations. * $P < 0.05$; ** $P < 0.01$; † $P < 0.10$.

in any other biochemical or anthropometric measures at 8 wk in the lean group (data not shown).

Effects in the OW/OB

Bar-induced changes after 2 and 8 wk in the OW/OB are shown for metabolic (Fig. 2A) and anthropometric (Fig. 2B) measures and in Fig. 3 for lipid subfractions. As shown, after 8 wk consumption of 2 bars a day, statistically significant ($P < 0.05$) or trending significant ($P < 0.10$) changes in the direction of baseline values typical of the lean (Table 2) were observed: HDL-c ($+2.4 \pm 1.2$ mg/dl; $P = 0.078$); TGs (-34.3 ± 21.0 mg/dl; $P = 0.061$); insulin resistance (as measured by HOMA-IR, -0.60 ± 0.2 ; $P = 0.011$); insulin (-2.3 ± 0.90 mU/L; $P = 0.0088$); glucose (-2.2 ± 1.2 mg/dl; $P = 0.054$); and adiponectin ($+743 \pm 431$ ng/ml; $P = 0.079$) (Fig. 2A). Changes in hsCRP (-0.30 ± 0.22 mg/L) and SAA (-204 ± 236 ng/ml) were also in the direction of improvement. Improvements in anthropometric measures were also observed, as shown in Fig. 2B: diastolic blood pressure (DBP) (-2.4 ± 1.3 mmHg; $P = 0.082$); HR [-3.7 ± 1.0 beats per minute (bpm); $P < 0.001$]; weight (-0.80 ± 0.40 kg; $P = 0.039$); and waist circumference (-1.80 ± 0.90 cm; $P = 0.043$).

Changes in lipid subfractions are shown in Fig. 3. Changes in HDL subfractions (HDL-2b and HDL3_2a) indicate that nutrient bar-induced increase in HDL-c in the OW/OB is primarily due to an increase in the HDL-2b (aka HDL-L), as reported previously in predominantly lean individuals (51).

Little change in LDL-c is apparent in Fig. 2A. However, examination of Fig. 3 suggests consistent favorable decreases across the more atherogenic (72) small LDL subfractions (LDL IVa, IVb, and IVc and LDL IIIa and IIIb) and consistent favorable increases in the less atherogenic (72) larger subfractions (LDL I and IIa and IDL 2). Only increases in 2 large subfractions [LDL I ($+40.8 \pm 18.1$ nM) and IDL 2 ($+20.7 \pm 10.5$ nM)] reached statistical significance, and decreases in only 2 small

subfractions trended significant [LDL IIIb (-21.7 ± 12.4 nM; $P = 0.069$) and IIIa (-44.0 ± 24.7 nM; $P = 0.077$)]. However, the consistency of downward movement in the small dense subfractions and upward movement in the larger subfractions is persuasive.

In summary, consumption of 2 bars each day for 2 months resulted in positive changes in indicators of cardiovascular health (HDL and LDL dyslipidemia, DBP, and HR), insulin resistance (HOMA-IR, insulin, and glucose), and obesity itself (weight and waist circumference). The significant increase in adiponectin is also consistent with improved metabolic health (55, 69, 73). There were no gastrointestinal or other adverse effects from bar consumption.

Inflammation blunts responsiveness to bar consumption

In the OW/OB, baseline inflammation (hsCRP) is inversely correlated with early (2-wk) increase in all 4 HDL measures and with later (8-wk) increase in less atherogenic LDL and IDL lipid subfractions

As shown, baseline hsCRP in the OW/OB is inversely correlated with bar-induced change from 0–2 wk (but not 0–8 wk) in all measures of HDL: HDL-c ($r = -0.42$; $P = 0.025$); HDL3_2a ($r = -0.47$; $P = 0.010$); HDL-2b ($r = -0.44$; $P = 0.018$); and HDLP ($r = -0.55$; $P = 0.0021$) (Fig. 4A–D). Baseline hsCRP was also inversely correlated with bar-induced 0–8 wk (but not 0–2 wk) change in the less atherogenic LDL subfractions LDL I ($r = -0.52$; $P = 0.0044$) and IDL 2 ($r = -0.46$; $P = 0.015$). No additional correlations were observed.

In the OW/OB, improvement in almost all measures occurs more robustly in those who are less inflamed at baseline

Baseline hsCRP values in OW/OB participants are illustrated in Fig. 5. As shown, approximately half of the

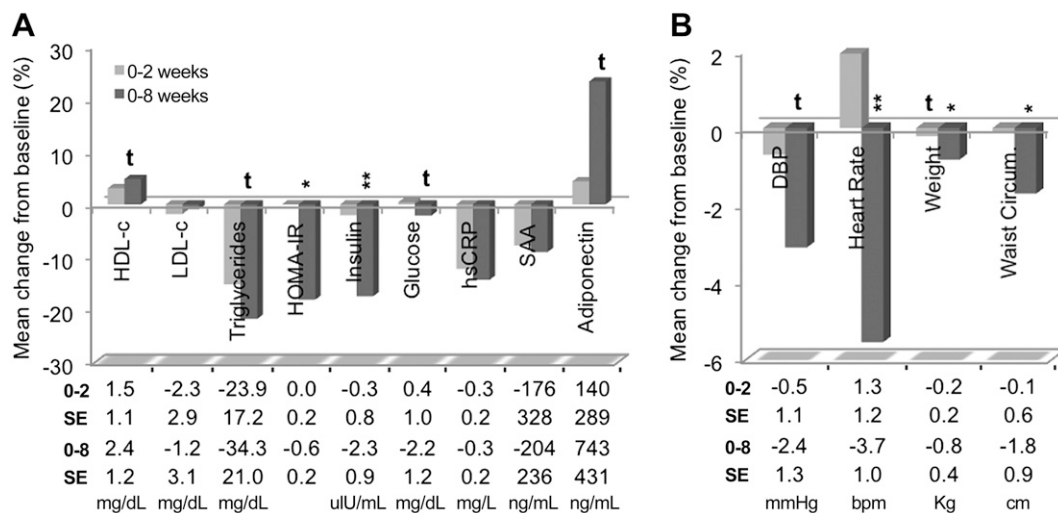


Figure 2. Improvements of measures linked to cardiovascular risk, insulin resistance, inflammation, and obesity in the OW/OB. A) Metabolic. B) Anthropometric. Results after consumption of 2 nutrient bars per day for 2 and 8 wk are shown. * $P < 0.05$, ** $P < 0.01$, ^t $P < 0.10$. See Fig. 1 legend for additional information.

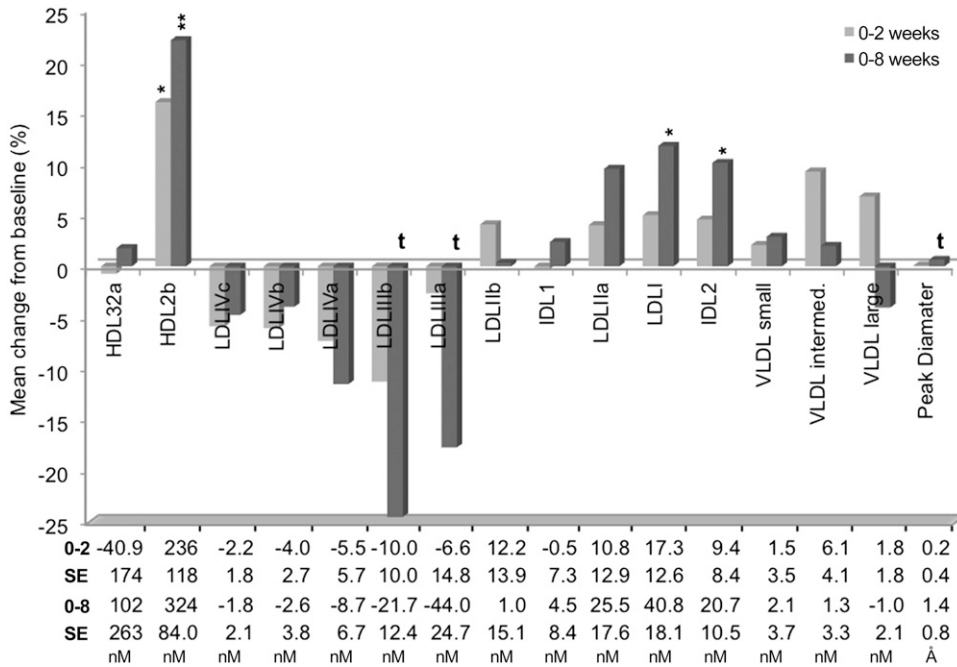


Figure 3. Improvements of lipoprotein subfractions in the OW/OB. HDL, LDL, IDL, and VLDL subfractions are as defined in Abbreviations. intermed., intermediate. * $P < 0.05$, ** $P < 0.01$, † $P < 0.10$. See Fig. 1 legend for additional information.

baseline hsCRP values fall below an informal cutoff of 1.5, which has been used to classify chronic inflammation linked to CVD risk (74).

In Figs. 6, 7, and 8, effects of nutrient bar consumption for 2 and 8 wk are shown for each of these 2 inflammation subgroups for basic clinical measures (Figs. 6 and 7) and lipoprotein subfractions (Fig. 8). All measures with changes that were either statistically significant or trended significant in either the lower- or higher-inflammation subgroup are plotted. As shown in Figs. 6A and 7A, with the

exception of adiponectin, nutrient bar-induced change in the less inflamed subgroup is clearly more robust compared to the more highly inflamed subgroup. As shown in Figs. 6B and 7B, change in the anthropometric measures is also more robust in the less inflamed subgroup, with the exception of decreased HR. In Fig. 8, a similar pattern is seen for the lipid subfractions. HDL-2b increases in both subgroups, but the response is slower in the more inflamed subgroup. The suggestive realignment of less and more atherogenic LDL and IDL subfractions toward a healthier

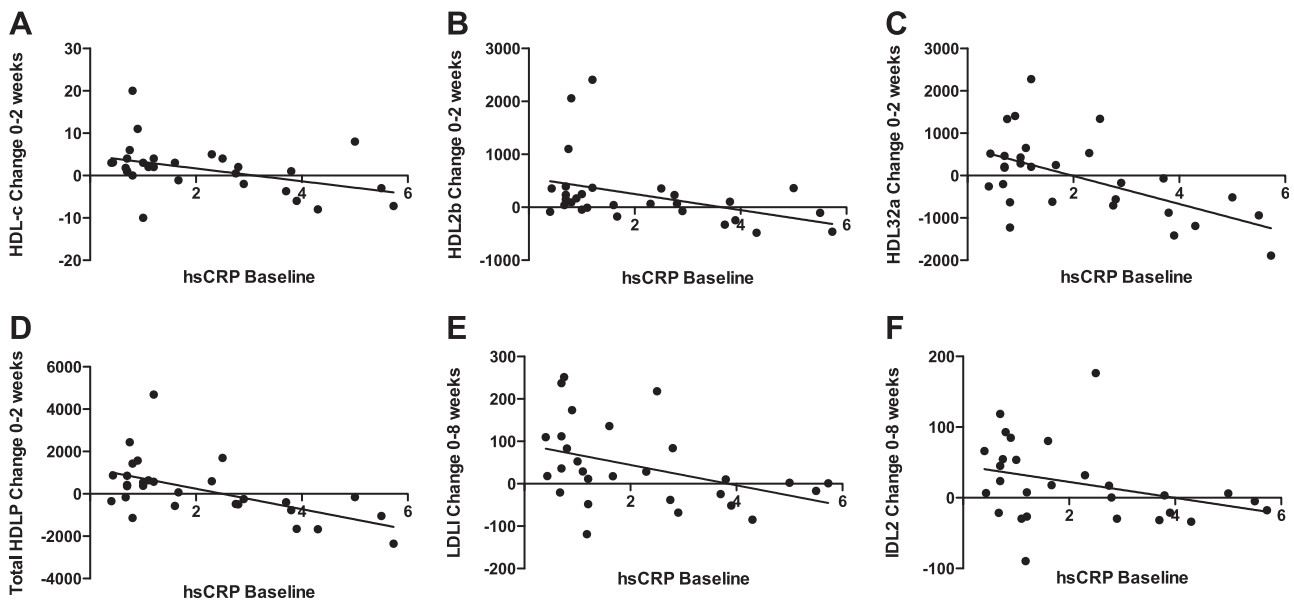
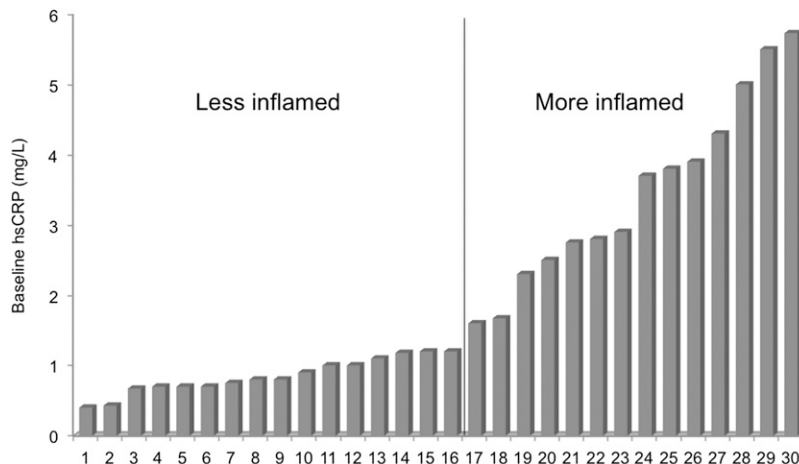


Figure 4. Spearman correlations in the OW/OB between baseline hsCRP and change after consumption of 2 nutrient bars each day for 2 wk [(A) HDL-c (milligrams per deciliter), (B) HDL-2b (nanomolar), (C) HDL3_2a (nanomolar), and (D) HDLP (nanomolar)] or change after 8 wk [(E) LDL I (nanomolar), and (F) IDL 2 (nanomolar)]. Correlation coefficients and P values were $r = -0.42$ and $P = 0.025$ (HDL-c), $r = -0.44$ and $P = 0.018$ (HDL-2b), $r = -0.47$ and $P = 0.010$ (HDL3_2a), $r = -0.55$ and $P = 0.0021$ (HDLP), $r = -0.52$ and $P = 0.0044$ (LDL I), and $r = -0.46$ and $P = 0.015$ (IDL 2).

Figure 5. Distribution of baseline hsCRP values among OW/OB participants. Each of the 30 observations in the OW/OB is plotted as baseline hsCRP (milligrams per liter). All participants with baseline hsCRP values <1.5 mg/L were classified as less inflamed, and those with baseline values >1.5 mg/L were classified as more inflamed.



profile after 8 wk of nutrient bar consumption, as observed in the OW/OB group as a whole (Fig. 3), is now clearly shown to be due to bar-induced changes in the less-inflamed subgroup.

Most of the nonsignificant decrease in hsCRP in the OW/OB group (Fig. 2A) occurred in the higher-inflamed subgroup; decrease at 8 wk was statistically significant (-0.78 ± 0.37 mg/L; $P = 0.03$). Changes in SAA were not significant.

DISCUSSION

A nutrient-dense, high-fiber, fruit-based, low-calorie bar intended to restore nutrient adequacy by filling gaps in Western diets was used as a dietary intervention in three 2-month clinical trials in lean and OW/OB healthy adults to examine effects of consuming 2 bars a day on metabolic and anthropometric measures. Metabolic improvements were seen in both lean and OW/OB participants. Striking improvements occurred in the OW/OB (Figs. 2 and 3), primarily in participants with relatively low levels of chronic inflammation (Figs. 4, 5, 6, 7, and 8). These improvements were in major areas that characterize metabolic

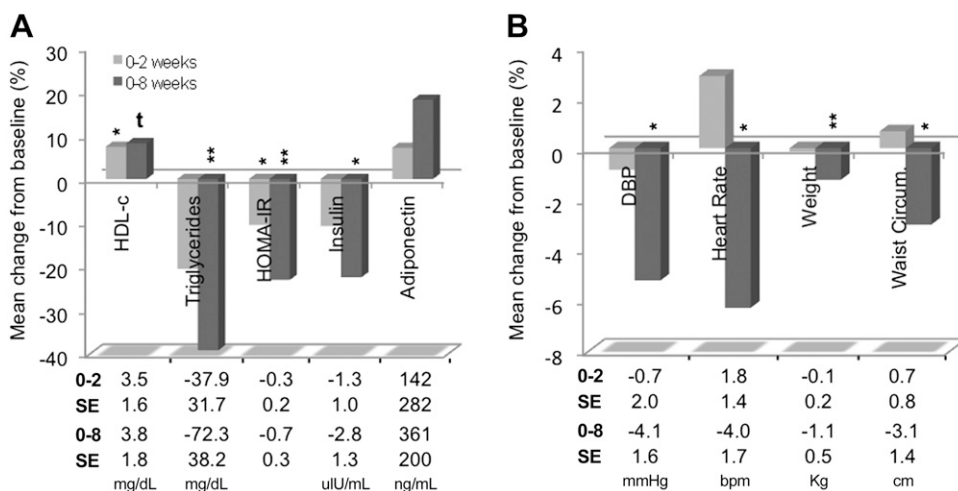
dysregulation associated with obesity: HDL and LDL dyslipidemia, as well as other indicators of cardiovascular health (HR and DBP) and insulin resistance (HOMA-IR).

Statistically significant improvements in weight and waist circumference also occurred primarily in the OW/OB group with lower levels of chronic inflammation (Figs. 2B and 6B). These reductions were small, not unexpected given the relatively short duration of the intervention and the fact that ~220 daily kilocalories were added in the form of the nutrition bar without requirements to adjust baseline diet or otherwise change behavior.

This is the first report of which we are aware that documents the resistance of OW/OB individuals with higher levels of chronic inflammation to dietary-induced improvements in a wide range of metabolic and anthropometric indicators of obesity-associated dysregulation. The adverse effect of chronic inflammation on diet-induced improvements in some lipids was previously observed (75–79), and one study reported that baseline plasma IL-6 concentrations were significantly higher in individuals more resistant to weight loss (80).

It is of interest that bar-induced improvements at 8 wk in HDL-2b and the adipokine adiponectin appeared to be relatively independent of inflammation, occurring in the

Figure 6. Changes in the lower-inflammation OW/OB subgroup after 2 and 8 wk consumption of the nutrient bar. A) Metabolic. B) Anthropometric. Parameters plotted were selected from those with changes that were statistically significant or trending significant in either of the 2 inflammation subgroups over the 8-wk period. Additional significant or trending significant changes not plotted are as follows. BMI: 0–8 = -0.25 , $P = 0.086$; TC: 0–8 = -4.93 mg/dl, $P = 0.079$; TG/HDL-c: 0–8 = -1.35 , $P = 0.046$; and non-HDL cholesterol: 0–8 = -7.10 mg/dl, $P = 0.062$. * $P < 0.05$, ** $P < 0.01$, † $P < 0.10$.



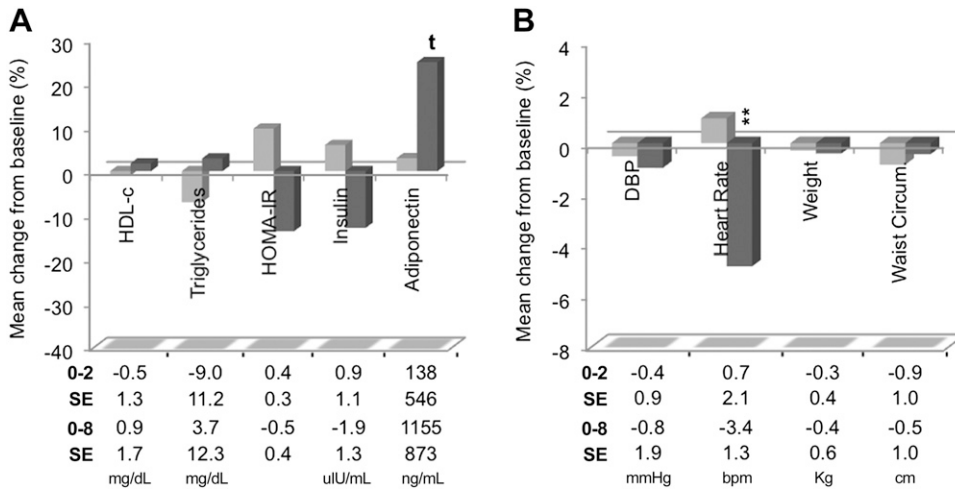


Figure 7. Changes in the higher-inflammation OW/OB subgroup after 2 and 8 wk consumption of the nutrient bar. (A) Metabolic and (B) anthropometric measures. Parameters plotted were selected from those with changes that were statistically significant or trending significant in either of the 2 inflammation subgroups over the 8-wk period. The only additional change not plotted was non-HDL cholesterol: 0–8 = +6.8 mg/dl; $P = 0.075$. ** $P < 0.01$, $^tP < 0.10$.

lean (Fig. 1), in the OW/OB as a whole (Figs. 2A and 3), and in both OW/OB inflammation subgroups (Figs. 6A, 7A, and 8). Higher plasma concentrations of adiponectin have been suggested as an overall biomarker of metabolic health (73) and have been linked to increased HDL-c and decreased inflammation (55, 81). Adiponectin was reported to induce RCT (82, 83), which could help to explain the bar-induced increase in HDL-2b (54) observed here and previously (51).

Effects of the nutrient bar on inflammation

Inflammatory response is a recognized mechanism in the pathogenesis of atherosclerosis and related risk for CVD (18). Among several measures of inflammation (including SAA), hsCRP is preferentially recommended for clinical use in identifying individuals at risk (18). In the OW/OB, both hsCRP and SAA appeared to decrease after bar consumption, but results did not reach statistical significance (Fig. 2A). However, there was a statistically significant reduction in hsCRP (~20%; $P = 0.030$) among participants

who fell into CVD risk categories considered to be high average or high (Fig. 5) (18). Although a causal role of the nutrient bar in improving inflammation cannot be inferred from these results, it is suggested that the initial effect of the bar in the more inflamed OW/OB subgroup may be to decrease inflammation, which would then allow positive changes in metabolic dysregulation to manifest over a longer period than the 8-wk duration of this intervention. In this regard, it is noted that HDL-2b increased after 2 wks of bar consumption in the lower-inflammation groups (lean, Fig. 1; lower-inflammation OW/OB subgroup, Fig. 8A), but not until 8 wk in the higher-inflammation OW/OB subgroup (Fig. 8B).

Possible mechanisms

It is suggested that improvements in such a wide range of metabolic and anthropometric measures in the OW/OB (Figs. 2, 3, 6, and 8) may be the result of the restoration of impaired underlying metabolic processes due to the resupply by the nutrient bar of critical dietary components

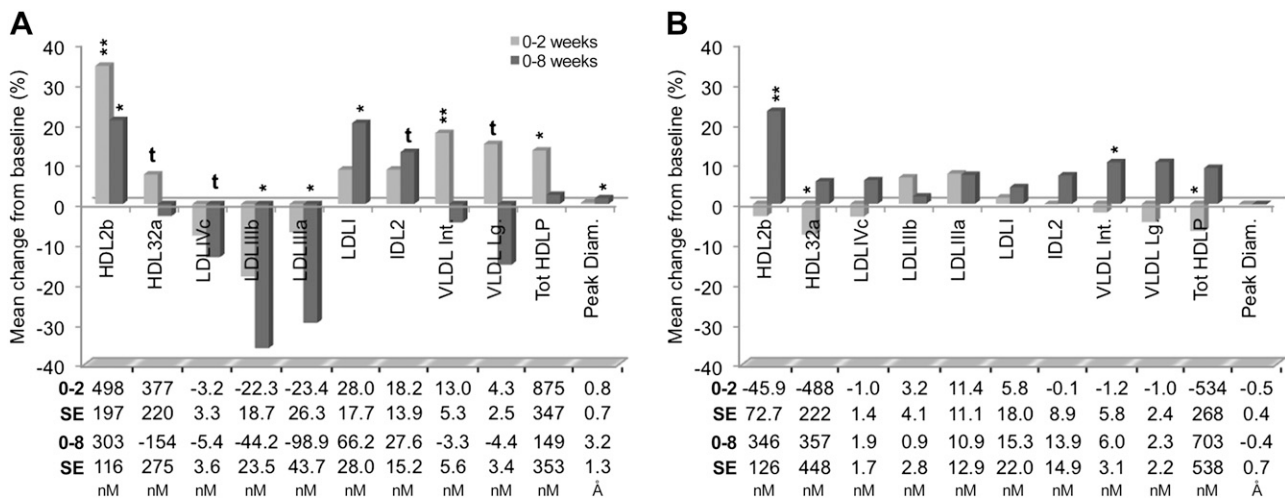


Figure 8. Changes in the lower- and higher-inflammation OW/OB subgroups after 2- and 8-wk consumption of the nutrient bar. A) Lower-inflammation subgroup. B) Higher-inflammation subgroup. Lipid particle subfractions are shown. Parameters plotted were those with statistically significant or trending significant changes in either of the 2 subgroups over the 8-wk period. Int., intermediate; Lg., large; Diam., diameter. * $P < 0.05$, ** $P < 0.01$, $^tP < 0.10$.

deficient in Western diets. Mitochondrial stress and impaired gut wall integrity are candidate underlying processes that may be improved by bar consumption. Both of these conditions are common in the obese (84, 85), and both are linked to poor diets (86, 87) and to insulin resistance and inflammation (88, 89). Bar-induced reduction of mitochondrial stress and improved gut integrity would be expected to have multiple beneficial consequences similar to the metabolic improvements observed in this study. The restoration of an internal metabolic environment that manifests a leaner metabolic profile would also allow the metabolic flexibility required for weight loss and clearance of ectopic adiposity (90, 91).

Mitochondrial stress

The metabolic efficiency of mitochondria in converting fuel (carbohydrates, lipids, and amino acids) to ATP decreases in the obese relative to the lean (92). The generation of oxidants is a consequence of the accumulation of NADH over NAD⁺, which occurs due to chronic hyperglycemia resulting from overnutrition (93–95). Oxidants directly interfere with insulin-signaling efficiency (96–98), and oxidant-initiated oxidative damage triggers inflammation because cells that sustained such injury are cleared by immune cells (98). Fatty acid accumulation resulting from decreased mitochondrial efficiency also inhibits insulin-signaling efficiency (99, 100).

There are several ingredients in the nutrient bar that may positively impact mitochondrial stress. High-viscosity dietary fiber HPMC has been shown to slow glucose absorption (101) and to preserve respiratory quotients in rats consuming a high-fat diet (102). Furthermore, 2 nutrient bars (the daily dose) also contain 400 mg docosahexaenoic acid (DHA), a known peroxisome proliferator-activated receptor (PPAR)- α agonist. Activation of the PPAR pathway leads to increased fatty acid oxidation and preferentially reduces small proatherogenic LDL subfractions (103). The bar also contains high concentrations of polyphenolic compounds from fruit and dark chocolate. Polyphenolic consumption in healthy overweight individuals has been shown to increase resting energy expenditure, which would relieve mitochondrial reductive stress described above (104). Polyphenols also increase cellular antioxidant defense by activating Nrf2 phase-2 detoxification pathways that antagonize inflammation (105).

Gut wall integrity

Gut wall integrity and the intestinal microbiome are impaired by high-fat and high-sugar diets commonly consumed by the obese (106–108). Evidence points to the importance of fiber, its metabolites, and other dietary components (106, 109–111) in maintaining a healthy gut barrier (112, 113) and intestinal microbiome (114) to prevent diet-induced chronic inflammation and insulin resistance (84, 106, 115). The consequence of poor nutrition is a condition termed “leaky gut,” in which fragments of gram-negative bacteria (LPS aka endotoxin) pass through the gut into systemic circulation, leading to chronic inflammation (106, 116, 117). The nutrient bar may help to strengthen the gut barrier epithelium through

provision of nutrients that support the gut’s bioenergetic capacity and thus its resiliency to intestinal permeability (118). These nutrients include soluble fiber and its fermentation products (26, 51) such as short-chain fatty acids (41, 42), glutamine (43–45), and zinc (119–121). Such bar-induced strengthening of the gut epithelium, and consequent reduction in plasma endotoxin, should be possible within the first 2 wk of bar consumption (122), compatible with the observed early (2 wk) rise in HDL-2b and adiponectin. Decreasing endotoxin entry by strengthening the gut wall would result in a reduction in inflammation (106, 123) and the consequent endocrine (*i.e.*, insulin and leptin) (124, 125) and mitochondrial stress responses to inflammation that make it difficult to lose excess fat and maintain a healthy body weight.

Summary

It is suggested that the less inflamed OW/OB subgroup is less metabolically impaired and thus better poised to move toward a leaner metabolic profile in response to improved function resulting from nutrients supplied by the bar. The higher-inflammation subgroup must first reduce inflammation. It is posited that reductions in hsCRP (Fig. 2), most of which occurred in the higher-inflammation subgroup, may reflect what is potentially the first step toward a leaner metabolic profile, which may require a longer period to develop in more chronically inflamed individuals than the 8-wk period of the trials analyzed in this report.

Practical implications for weight management programs

Conventional weight management strategies can be successful [*e.g.*, (126–128)], but results are often disappointing (24, 25). Poor weight loss and maintenance of weight loss are, in part, due to the incompletely understood observation that some people lose weight more easily than others, independent of compliance (23, 25, 129, 130). Results presented here suggest that OW/OB individuals who respond poorly to a weight loss program may be those that have higher baseline chronic inflammation. Such individuals may require a longer, or different, approach than those that are less inflamed.

Poor compliance is also a major cause of low success rates in weight loss management programs (24, 131, 132). This is not surprising because these programs typically require dietary and activity modifications that are difficult for many to initiate and sustain. It is suggested that weight management programs will be more successful if interventions, such as that employed here, are used as a first step to help participants transition to healthier eating and lifestyle habits. In this study, participants were not instructed to make any lifestyle changes other than to eat 2 nutrient bars each day. This study design imposed relatively minor restrictions on participants, and compliance was very high (95%). The modest but statistically significant loss in weight (1.1 ± 0.5 kg; $P = 0.0051$) and waist circumference (3.1 ± 1.4 cm; $P = 0.019$) that occurred in the less inflamed OW/OB subgroup may have been the result of bar-induced improvement in metabolic health that enabled

the metabolic flexibility required to initiate weight loss. Early success in weight management programs may encourage participants toward higher compliance throughout the program, and early identification of participants whose metabolism is resistant to change should also be beneficial.

Potential for use of natural food-based nutrient mixtures as alternatives or companions to drugs used to treat obesity-associated metabolic dysregulation

Obesity-associated metabolic dysregulation is often treated with drugs: dyslipidemia with statins and fibrates (133, 134), insulin resistance with thiazolidinediones and metformin (135, 136), and chronic inflammation with non-steroidal anti-inflammatory drugs (137). All of these drugs have demonstrated clinical benefits. However, because most drugs act by pharmacologically blocking or accelerating cellular pathways, pleiotropic, often poorly understood and sometimes negative side effects can result (134, 138, 139). On the other hand, food-based nutrient mixtures, such as the nutrient bar used here, that contain nutrients at normal dietary concentrations are not expected to have significant negative side effects. The full potential of such food-based nutrient mixtures as alternatives or companions to drugs for treatment of metabolic dysregulation associated with obesity has not been given adequate attention.

Limitations

The clinical trial design used in this and previous (51) nutrient bar trials did not include a placebo control group; instead, participants acted as their own controls. Difficulties in applying the same placebo standards used for drug trials to nutritional interventions have been widely discussed [*e.g.*, (140)]. In addition, dietary intake during the trial was not monitored. Thus, it is not known whether participants altered their food choices or consumed fewer calories during the trials. If such changes occurred, they could have contributed to the positive effects observed.

CONCLUSIONS

The broad-spectrum metabolic and anthropometric improvements observed after 2 months of twice-daily consumption of a low-calorie food-based nutrient bar aimed at filling gaps in poor diets suggest that it is not necessary to impose severe changes in diet and lifestyle patterns to begin to effect positive changes in the OW/OB, and also in the lean. Two-month consumption of the nutrient bar did not make the OW/OB lean or completely correct unhealthy metabolism, but it did begin a process of favorable metabolic change. The fact that almost all statistically significant favorable changes occurred in the subgroup of the OW/OB with less chronic inflammation suggests an explanation for why some OW/OB have difficulty losing weight. This study highlights the power of food-based, targeted, dietary interventions as alternatives or

adjuncts to the use of drugs to treat obesity and associated metabolic dysregulation. FJ

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