

Low Bone Mass in Subjects on a Long-term Raw Vegetarian Diet

Luigi Fontana, MD, PhD; Jennifer L. Shew, BS; John O. Holloszy, MD; Dennis T. Villareal, MD

Background: Little is known regarding the health effects of a raw food (RF) vegetarian diet.

Methods: We performed a cross-sectional study on 18 volunteers (mean \pm SD age, 54.2 \pm 11.5 years; male/female ratio, 11:7) on a RF vegetarian diet for a mean of 3.6 years and a comparison age- and sex-matched group eating typical American diets. We measured body composition, bone mineral content and density, bone turnover markers (C-telopeptide of type I collagen and bone-specific alkaline phosphatase), C-reactive protein, 25-hydroxyvitamin D, insulin-like growth factor 1, and leptin in serum.

Results: The RF vegetarians had a mean \pm SD body mass index (calculated as weight in kilograms divided by the square of height in meters) of 20.5 \pm 2.3, compared with 25.4 \pm 3.3 in the control subjects. The mean bone min-

eral content and density of the lumbar spine ($P = .003$ and $P < .001$, respectively) and hip ($P = .01$ and $P < .001$, respectively) were lower in the RF group than in the control group. Serum C-telopeptide of type I collagen and bone-specific alkaline phosphatase levels were similar between the groups, while the mean 25-hydroxyvitamin D concentration was higher in the RF group than in the control group ($P < .001$). The mean serum C-reactive protein ($P = .03$), insulinlike growth factor 1 ($P = .002$), and leptin ($P = .005$) were lower in the RF group.

Conclusion: A RF vegetarian diet is associated with low bone mass at clinically important skeletal regions but is without evidence of increased bone turnover or impaired vitamin D status.

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RAW FOOD (RF) VEGETARIANS believe in eating only plant-derived foods that have not been cooked, processed, or otherwise altered from their natural state. Because of their low calorie and low protein intake, RF vegetarians have a low body mass index (BMI) and a low total body fat content.¹ It is well documented that a low BMI and weight loss are strongly associated with low bone mass and increased fracture risk,² while obesity protects against osteoporosis.³ However, the underlying mechanisms are not entirely clear. Bone protective effects of obesity involve increased weight bearing⁴ and increased aromatization of androgen to estrogen in adipose tissue.⁵

The availability of individuals eating a RF vegetarian diet made it possible for us to investigate bone mass and bone metabolism in people on a low calorie and low protein diet. In this article, we report data on bone mass, markers of bone turnover, and circulating factors that affect bone metabolism such as 25-hydroxyvitamin D and C-reactive protein (CRP) in individuals

who have been eating a RF diet for 1½ to 10 years.

METHODS

STUDY PARTICIPANTS

Eighteen individuals, 7 women and 11 men, who strictly adhere to a RF vegetarian diet were recruited through advertisements at the St Louis Vegetarian Society and in RF online magazines. Ten were from the St Louis area, and the others came to Washington University Medical Center from other cities in the United States. None of the participants were concerned about their bone health status. Their mean age was 54.2 \pm 11.5 years (age range, 33-85 years). They had been eating a RF diet for a mean of 3.6 years (range, 1½ to 10 years). None of the subjects had a history or clinical evidence of chronic disease (including cardiovascular, lung, gastrointestinal, and autoimmune disease; type 2 diabetes mellitus; and cancer) based on medical history, complete physical examination, routine biochemical studies, hematologic evaluation, and urinalysis. They were all nonsmokers. Eighteen individuals eating a typical American diet who were matched with the RF group in terms of age, sex, and socioeco-

Author Affiliations: Section of Applied Physiology, Division of Geriatrics and Nutritional Science, Department of Internal Medicine, Washington University School of Medicine, St Louis, Mo (Drs Fontana, Holloszy, and Villareal and Ms Shew); and the Division of Food Science, Human Nutrition, and Health, Istituto Superiore di Sanità, Rome, Italy (Dr Fontana).

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nomic status served as a control group. Five of 7 women in the RF group were postmenopausal, and 6 of 7 women in the control group were postmenopausal. None of the participants in this study were taking drugs that affect bone metabolism (eg, bisphosphonates, hormone therapy, and corticosteroids) or other medications that could affect the variables that were measured. All of the study participants had stable weight (ie, <2-kg weight change in the preceding 6 months). Informed consent was obtained from all subjects. This study was approved by the Human Studies Committee of Washington University School of Medicine.

ANTHROPOMETRIC, BODY COMPOSITION, AND BONE DENSITY MEASUREMENTS

Height was measured without shoes to the nearest 0.1 cm. Body weight was obtained on a balance scale in the morning after a 12-hour fast. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Bone mineral content (BMC) and bone mineral density (BMD) of the total body, lumbar spine (L2-L4), and proximal femur were measured by dual-energy x-ray absorptiometry using a QDR-1000/W instrument (Hologic Inc, Waltham, Mass), as described by Salamone et al.⁶ Assessments of test-retest reliability of BMC and BMD measurements yielded intraclass correlation coefficients that were greater than 0.98 for all sites of interest. Regarding precision, the coefficients of variation for BMC and BMD were all less than 1.5%. Dual-energy x-ray absorptiometry was also used to estimate body composition using version 5.71 of the enhanced whole-body analysis software (Hologic Inc). The mean \pm SD precision of measuring total mass, fat mass, bone mineral mass, and nonbone fat-free mass was $0.9\% \pm 0.4\%$, $1.6\% \pm 1.0\%$, $1.8\% \pm 0.3\%$, and $1.8\% \pm 0.9\%$, respectively.

BLOOD ANALYSES

A venous blood sample was taken after subjects had fasted for at least 12 hours. Commercial enzyme-linked immunosorbent assay kits were used to measure serum C-telopeptide of type I collagen (Nordic Bioscience Diagnostics, Herlev, Denmark), bone-specific alkaline phosphatase (Quidel Corporation, San Diego, Calif), 25-hydroxyvitamin D (Immuno-diagnostic Systems Limited, Boldon, England), and high-sensitivity CRP (ALPCO Diagnostics, Windham, NH) concentrations. Commercially available radioimmunoassay kits were used to measure insulinlike growth factor 1 (IGF-1) (Diagnostic Products Group, Los Angeles, Calif) and leptin (Linco Research, St Louis); the tests were performed by the Radioimmunoassay Core Laboratory, Washington University Diabetes Research and Training Center. Coefficients of variation for these measurements were less than 8.9%.

DIETARY ASSESSMENT

The study participants were instructed by a research dietician to record for 7 consecutive days in food diaries, at the time of consumption, all foods and beverages consumed, preparation methods, and approximate portion sizes. To assist with portion size determinations, sets of measuring spoons and cups were provided to all participants, and all food diaries had a ruler imprinted on the back cover. The food record was analyzed using the Nutrition Data System for Research software version 4.03/31 from the Nutrition Coordinating Center at the University of Minnesota, Minneapolis. The database compiles information regarding 117 nutrients. The nutrients of interest are calories, total fat, total carbohydrate, total protein, animal pro-

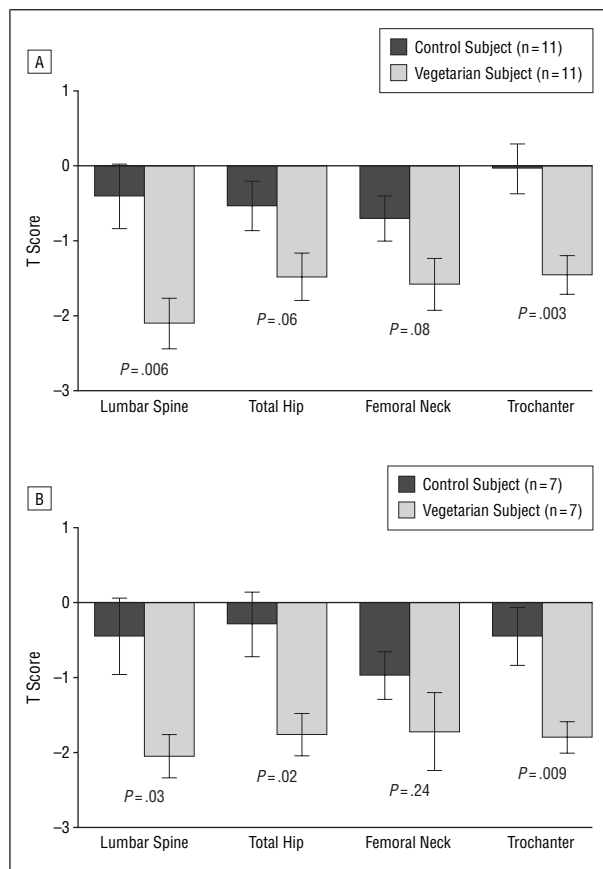


Figure 2. Comparison of T scores in control subjects and individuals on a raw food (RF) vegetarian diet in men (A) and in women (B). The P values represent the significance of differences between the control group and the vegetarian group. Data are given as mean \pm SE.

tein, vegetable protein, calcium, saturated fatty acids, mono-unsaturated fatty acids, polyunsaturated fatty acids, sucrose, starch, soluble fiber, insoluble fiber, folate, vitamin B₁₂, all of the fatty acids (4:0 to 22:6), all of the amino acids, phytic acid, and trans-fatty acids.⁷

STATISTICAL ANALYSIS

The unpaired *t* test was used for normally distributed variables with approximately equal SDs. For variables not normally distributed or with unequal SDs, the Wilcoxon signed rank test was used. Statistical significance was set at $P \leq .05$. Data were analyzed by using SPSS for Windows software version 12.0 (SPSS Inc, Chicago, Ill). Values are expressed as mean \pm SD, except in the **Figure**, in which data are given as mean \pm SE.

RESULTS

BODY WEIGHT AND BODY COMPOSITION

Body mass index was significantly lower in the RF group than in the control group (20.5 ± 2.3 vs 25.4 ± 3.3) (**Table 1**). The BMI values for the individuals in the control group were similar to the mean range for middle-aged people in the United States.⁸ Total body fat and trunk fat were also lower in the RF group (**Table 2**).

Table 1. Anthropometric Characteristics of Raw Food (RF) and Control Subjects*

Characteristic	RF Subjects (n = 18)	Control Subjects (n = 18)	P Value
Age, y			
Men	52.7 ± 10.7	52.3 ± 9.9	.94
Women	56.5 ± 13.1	53.2 ± 4.1	.54
Height, m			
Men	1.8 ± 0.1	1.8 ± 0.1	.96
Women	1.6 ± 0.1	1.61 ± 0.01	.52
Weight, kg			
Men	65.0 ± 7.3	82.5 ± 9.9	<.001
Women	53.9 ± 6.7	66.5 ± 12.6	.04
BMI†			
Men	20.7 ± 2.4	25.5 ± 2.6	<.001
Women	20.1 ± 2.0	25.4 ± 4.4	.01

*Data are given as mean ± SD.

†Body mass index (BMI) is calculated as weight in kilograms divided by the square of height in meters.

Table 2. Body Composition Characteristics of Raw Food (RF) and Control Subjects*

Characteristic	RF Subjects (n = 18)	Control Subjects (n = 18)	P Value
Total body fat, %			
Men	13.9 ± 6.5	20.8 ± 6.4	.004
Women	24.1 ± 5.6	33.5 ± 5.9	.009
Trunk fat, %			
Men	10.8 ± 3.3	22.4 ± 8.8	.001
Women	16.8 ± 6.8	30.7 ± 8.9	.007
Fat-free mass, %			
Men	86.2 ± 3.0	78.1 ± 6.7	.002
Women	75.9 ± 5.5	66.4 ± 5.9	.009
Fat-free mass, kg			
Men	52.3 ± 4.8	58.0 ± 10.0	.11
Women	38.8 ± 4.9	40.9 ± 5.7	.48

*Data are given as mean ± SD.

BMC AND BMD

The mean BMC (**Table 3**) and BMD (**Table 4**) in the RF group were significantly lower than in the control group at all sites. In men and women, the RF group had significantly lower BMC and BMD values than the control group at the total body, lumbar spine, total hip, and trochanter sites. The mean T scores in the RF group were significantly lower than in the control group at most sites (Figure). None of the participants had clinical or dual-energy x-ray absorptiometry evidence of bone fractures.

MARKERS OF BONE TURNOVER

The serum C-telopeptide of type I collagen and bone-specific alkaline phosphatase concentrations in the RF group were not significantly different from those in the control group (**Table 5**). The serum 25-hydroxyvitamin D concentrations were significantly higher in the

Table 3. Bone Mineral Content of Raw Food (RF) and Control Subjects*

Bone Mineral Content, g	RF Subjects (n = 18)	Control Subjects (n = 18)	P Value
Total body			
All	2156 ± 422	2609 ± 581	.01
Men	2350 ± 397	2897 ± 541	.01
Women	1850 ± 252	2155 ± 279	.054
Lumbar spine			
All	43.4 ± 8.3	54.6 ± 12.4	.003
Men	46.8 ± 8.1	60.1 ± 12.4	.008
Women	37.9 ± 5.4	45.9 ± 6.1	.03
Total hip			
All	32.3 ± 7.8	39.8 ± 9.3	.01
Men	36.9 ± 6.2	45.1 ± 7.4	.01
Women	25.1 ± 3.1	31.5 ± 4.5	.01
Femoral neck			
All	3.8 ± 0.8	4.5 ± 1.0	.04
Men	4.2 ± 0.8	4.9 ± 0.9	.06
Women	3.2 ± 0.6	3.8 ± 0.5	.10
Trochanter			
All	6.9 ± 1.7	9.3 ± 3.0	.007
Men	7.9 ± 1.5	10.8 ± 2.8	.007
Women	5.3 ± 0.7	6.8 ± 1.3	.03

*Data are given as mean ± SD.

Table 4. Bone Mineral Density of Raw Food (RF) and Control Subjects*

Bone Mineral Density, g/cm ²	RF Subjects (n = 18)	Control Subjects (n = 18)	P Value
Total body			
All	1.04 ± 0.10	1.17 ± 0.13	.003
Men	1.07 ± 0.11	1.21 ± 0.14	.02
Women	0.99 ± 0.06	1.10 ± 0.10	.03
Lumbar spine			
All	0.87 ± 0.11	1.05 ± 0.14	<.001
Men	0.88 ± 0.12	1.07 ± 0.15	.006
Women	0.85 ± 0.08	1.03 ± 0.14	.02
Total hip			
All	0.77 ± 0.13	0.96 ± 0.14	<.001
Men	0.80 ± 0.15	0.99 ± 0.14	.009
Women	0.73 ± 0.09	0.91 ± 0.13	.01
Femoral neck			
All	0.68 ± 0.14	0.80 ± 0.12	.01
Men	0.71 ± 0.16	0.83 ± 0.13	.08
Women	0.63 ± 0.10	0.75 ± 0.08	.055
Trochanter			
All	0.56 ± 0.09	0.73 ± 0.13	<.001
Men	0.59 ± 0.10	0.77 ± 0.13	.003
Women	0.52 ± 0.05	0.66 ± 0.09	.007

*Data are given as mean ± SD.

RF group than in the control group (42 ± 20 vs 19 ± 12 ng/mL, *P* < .001).

LEPTIN, IGF-1, AND CRP

Serum concentrations of leptin (2.8 ± 1.7 vs 8.7 ± 7.8 ng/mL, *P* = .005) and IGF-1 (124 ± 35 vs 171 ± 51 ng/mL, *P* = .002) were lower in the RF group than in the control

group. The serum CRP concentrations of the individuals in the RF group were also lower than in the control group (0.6 ± 0.8 vs 1.8 ± 2.4 mg/L, $P = .03$).

NUTRIENT INTAKE

Nutrient intakes differed significantly between the groups. The RF vegetarians ate a variety of raw vegetables, fruits, nuts, seeds, sprouted grains, and cereals, dressed with olive oil (1285-2432 kcal/d; approximately 9.1% of calories from protein, 43.2% from fat, and 47.7% from complex carbohydrates). All of them strictly avoided cooked and processed foods containing *trans*-fatty acids, highly glycemic foods, and foods of animal origin. Their mean daily dietary intakes of calcium and vitamin D (calciferol) were low, 579 ± 260 mg/d and 16 ± 36 U/d, respectively. The control group ate usual American diets containing foods of plant and animal origin (1976-3537 kcal/d; approximately 17.9% of calories from protein, 32.1% from fat, and 50.0% from carbohydrates). Their mean daily dietary intakes of calcium and vitamin D were 1093 ± 394 mg/d and 348 ± 192 U/d, respectively.

COMMENT

In this cross-sectional study on 18 individuals eating a RF vegetarian diet, we found significantly lower BMC and BMD at the lumbar spine and hip sites compared with age- and sex-matched individuals eating a typical American diet. Osteoporosis is a complex multifactorial disease, characterized by reduced bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture risk.⁹ It is well documented that diet plays an important role in modulating bone metabolism through changes in body weight and composition, hormonal status, and nutrient availability.¹⁰ In particular, low body weight and low BMI are strongly associated with low bone mass and increased fracture risk.² In our study, body weight, BMI, and total body fat were markedly lower in the RF group than in the control group. We also found that total body, lumbar spine, total hip, and trochanter BMC and BMD were markedly reduced in men and women in the RF group.

Surprisingly, serum C-telopeptide of type I collagen¹¹ and bone-specific alkaline phosphatase,¹² well-accepted markers of bone resorption and formation, respectively, were not significantly different between the 2 groups. This finding provides evidence that these RF vegetarians are in a steady state in regard to their bone turnover and suggests that their low bone mass may be due to a transient increase in bone degradation or decrease in bone synthesis that occurred during the early adaptive weight loss response to the RF diet. Although low bone mass is a risk factor for fracture, bone quality also plays a role.¹³ It is therefore possible that RF vegetarians with a low bone mass may not have an increased incidence of fractures because of good bone quality. Clearly, it will be necessary to follow up a large number of RF vegetarians for a sufficiently long period to deter-

Table 5. Markers of Bone Turnover of Raw Food (RF) and Control Subjects*

Marker	RF Subjects (n = 18)	Control Subjects (n = 18)	P Value
C-telopeptide of type I collagen, ng/mL	0.7 ± 0.3	0.5 ± 0.2	.14
Bone-specific alkaline phosphatase, U/L	21.5 ± 5.9	18.9 ± 8.9	.38

*Data are given as mean \pm SD.

mine whether they have an increased risk of developing fractures.

Evidence that bone quality plays an important role in determining fracture risk is provided by the finding that persons with type 2 diabetes mellitus with a high BMI have increased bone fracture risk, despite a high bone mass.¹⁴ Rodent models also provide support for the hypothesis that diabetic bone has poorer quality that is not explained by bone mass.^{15,16} Changes in collagen chemical and mechanical properties due to glycosylation, as well as oxidative and inflammatory modifications, may play a major role in increasing bone fracture risk. It has been shown that increased interleukin 6 production after menopause is associated with increased bone resorption and bone loss.¹⁷ Interleukin 6 produced by osteoblasts and mononuclear cells is critical in promoting osteoclast differentiation and activation in bone.¹⁸ The recent discovery of the importance of osteoprotegerin and the receptor activator of nuclear factor ligand in modulating osteoclast formation and activity provides further support for the importance of inflammation in determining the rate of bone turnover and quality.¹⁹ Older frail people tend to have high levels of interleukin 6 and tumor necrosis factor α , which are associated with sarcopenia and osteoporosis.^{20,21} Therefore, it is possible that, in people with chronic systemic inflammation, osteoporosis fracture risk may involve aspects of bone quality other than bone mass. In our study, circulating levels of CRP were significantly lower in the RF group than in the control group, suggesting a low level of systemic inflammation. C-reactive protein is an acute-phase response molecule, produced by the liver in response to circulating levels of interleukin 6, which is a good marker of inflammation.²²

Serum leptin concentration was markedly lower in the RF group compared with the control group. Leptin is associated with antiosteogenic activity in mice, mediated by hypothalamic pathways and the sympathetic nervous system.^{23,24} However, cross-sectional studies on humans have provided conflicting results, with some supporting an antiosteogenic effect of leptin^{25,26} and others supporting an osteogenic effect of leptin.^{27,28} Leptin is secreted by white adipose tissue, and its circulating levels are correlated with the size of the fat mass.²⁹ Lean people have low body fat and therefore lower circulating leptin levels that are independent of their systemic inflammatory status. The discrepancies between the studies on the role of leptin in bone turnover in humans may be because of confounding effects of differences in the levels

of proinflammatory cytokines in the subjects studied. However, if leptin has an antiosteogenic effect, reducing this effect by lowering serum leptin clearly did not protect against development of osteoporosis in the RF vegetarians.

Serum IGF-1 concentrations were markedly lower in the RF vegetarians than in the control group. Insulin-like growth factor 1, a potent growth factor regulated by energy and protein intake, seems to play an important role in the acquisition and maintenance of bone.³⁰ However, cross-sectional studies of the links between serum IGF-1 and bone metabolism have also shown conflicting results. Serum IGF-1 has been reported to be positively associated with bone mass at different skeletal sites in postmenopausal women, and low concentrations of IGF-1 have been observed in patients with spinal fractures.^{31,32} Others found no association between serum IGF-1 and bone mass³³ or between control subjects and patients with fracture.³⁴ The discrepancies between the studies on humans may be because of confounding effects of differences in the levels of proinflammatory cytokines in the populations studied. An antagonistic relationship between the proinflammatory cytokines and IGF-1 is generally observed during degenerative conditions.^{35,36} However, in the RF vegetarians, the levels of inflammation appear to be extremely low as reflected in CRP concentrations, and low IGF-1 levels are therefore due to the low calorie and low protein intake³⁰ and not due to chronic inflammation.

In our RF group, serum 25-hydroxyvitamin D concentrations were markedly higher than in the control group. Dietary intake of 25-hydroxyvitamin D was extremely low in the RF group, and therefore their high serum values can be explained in part by a greater exposure to sunlight. Indeed, questioning of our RF subjects revealed that they generally made an effort to spend time in the sun, including sunbathing. Moreover, because vitamin D is predominantly stored in adipose tissue³⁷ and obesity is associated with decreased vitamin D bioavailability,³⁸ it is possible that the markedly diminished adipose mass in the RF group, in addition to regular sun exposure, may have contributed to their higher circulating vitamin D levels. The finding of high vitamin D levels in the RF group appears to exclude secondary hyperparathyroidism as a cause of the low bone mass.

Our study has limitations. Our sample size was small, and we recruited a convenience sample of individuals on long-term RF diets primarily through advertisement. All of them were convinced of the beneficial effects of a RF diet and were motivated to confirm this belief by participating in our study. Although we think it is likely that the low bone mass is due to bone loss after institution of a RF diet, because this is a cross-sectional study, we cannot completely exclude the possibility that this could also be due to low peak bone mass.

In conclusion, the results of this cross-sectional study of 18 individuals on a RF diet provide preliminary evidence that a RF diet is associated with low bone mass at clinically important skeletal regions. However, evidence of increased bone turnover or impaired vitamin D status was not found.

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Correspondence: Luigi Fontana, MD, PhD, Section of Applied Physiology, Division of Geriatrics and Nutritional Science, Department of Internal Medicine, Washington University School of Medicine, Campus Box 8113, 4566 Scott Ave, St Louis, MO 63110 (lfontana@im.wustl.edu).

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