ORIGINAL ARTICLE

The effect of a low-carbohydrate diet on bone turnover

J. D. Carter · F. B. Vasey · J. Valeriano

Abstract *Introduction:* Low-carbohydrate diets have become popular as weight loss techniques. These diets are high in protein, saturated fats, and omega-6 fatty acids. They also lead to a ketogenic state. These factors could lead to increased bone turnover. This study was designed to see whether a low-carbohydrate diet would lead to increased bone turnover in humans. *Methods:* Thirty patients (15 study subjects and 15 controls) were recruited for this 3-month study. The 15 patients on the diet were instructed to consume less than 20 g of carbohydrates per day for the 1st month and then less than 40 g per day for months 2 and 3. Control subjects had no restrictions on their diet. The primary end point was urinary N-telopeptide (UNTx) at 3 months. Secondary end points included UNTx at 1 month, bone-specific alkaline phosphatase (BSAP) at 1 month, bone turnover ratio (BSAP/UNTx) at 1 month, and weight loss. *Results:* The mean UNTx in the study subjects increased by 1.6 [95% confidence interval (CI) ±22.8] compared with an increase of 1.9 (95% CI ±17.6) in the controls at 3 months (p=0.86). The mean UNTx decreased by 2.2 (95% CI ±27.2) and 3.1 (95% CI ±17.6) at 1 month in the dieters and controls, respectively (p=0.36). The mean BSAP decreased by 0.53 (95% CI ±2.96) in the dieters and increased by 0.34 (95% CI ±2.92) in the controls at 1 month (p=0.27). The bone turnover ratio increased by 0.08 (95% CI ±0.81) in the dieters and by 0.05 (95% CI ± 0.27) in the controls at 1 month (p=0.78). The dieters lost 6.39 kg versus 1.05 kg for the controls at 3 months (p=0.0008). *Conclusions:* Although the patients on the low-carbohydrate diet did lose significantly more weight than the controls did, the diet did not increase bone turnover markers compared with controls at any time point. Further, there was no significant change in the bone turnover ratio compared with controls.

Keywords Bone-specific alkaline phosphatase (BSAP) · Bone turnover · Ketoacidosis · Low-carbohydrate diet · Urinary N-telopeptide (UNTx)

Diets that are very low in carbohydrates have become popular as weight loss techniques. Such diets are also very high in protein and fat. Further, the protein is most often derived from animal rather than vegetable sources. The result is a diet that is high in saturated fats and omega-6 fatty acids.

It has been suggested that the ketoacidosis generated by low-carbohydrate/high-protein diets results in hypercalciuria [1]. This occurs because of the renal response that consists of net acid secretion to compensate for the dietary acid challenge. In turn, the skeleton supplies serum buffer by active resorption of bone, thereby leading to hypercalciuria and an adverse effect on bone quality.

Early data suggest that diets high in animal protein, saturated fats, and omega-6 fatty acids may have deleterious effects on bone quality and bone turnover [2–6]. These data exist primarily in animal studies. Such diets may have adverse effects on calcium absorption and, consequently, bone mineralization. Also, diets that are high in animal proteins and omega-6 fatty acids can lead to bone loss via acidotic stimulation of osteoclastic bone resorption [6–8]. Conversely, evidence suggests that a more balanced diet that includes higher levels of omega-3 fatty acids can blunt inflammatory bone-resorbing cytokines [3, 8] and may have beneficial effects on bone mineral density [9–12].

Far less is known about the effect of a low-carbohydrate, high-protein/fat diet in humans. It has been estimated that when protein intake doubles, urinary calcium increases by 50% [13]. This estimate was borne out in a small study of 16 young healthy women, demonstrating a 52% increase in urinary calcium in those individuals on a high-protein diet

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(2.1 g/kg) compared with those on a medium-protein diet (1.0 g/kg) [14]. This same study revealed a 47% increase in urinary N-telopeptide (UNTx) in the high-protein diet group versus those on a low-protein diet (0.7 g/kg). However, the subjects in this trial were on their respective diets for only 4 days.

We designed this study as a pilot trial to establish proof of principle that a strict low-carbohydrate diet will lead to increased bone turnover in adult humans. This trial consisted of 15 patients who followed such a diet for 3 months, with 15 matched controls. All of the patients were monitored for diet compliance and were followed with bone turnover markers at baseline, 1 month, and 3 months.

Materials and methods

Patients

The study was conducted from September 2004 until August 2005. Patients and controls were recruited from the rheumatology division at the University of South Florida Medical Clinics in Tampa, Florida. All of the study subjects had an underlying diagnosis of osteoarthritis or were employees of the clinic without an underlying rheumatic condition. Because of the potential unknown adverse effects of a very low-carbohydrate diet, study subjects were not encouraged to start a low-carbohydrate diet (such as the Atkins diet); rather, they were enrolled only after the patient had made an independent decision to start such a diet.

All patients had to have a body mass index (BMI) greater than 26 and had to be willing to stay on a low-carbohydrate diet for 3 months. Patients were excluded if they had a diagnosis of osteoporosis or osteopenia. They were also excluded if they were on any type of osteoporosis preventive medication. Postmenopausal and perimenopausal women were excluded because of the effects of these normal physiological states on bone turnover. Because urinary ketones were followed to assess diet compliance at each visit, both type I and type II diabetics were also excluded. Patients with chronic renal insufficiency (creatinine >1.5), pregnant or lactating women, and any patients on corticosteroids or with an inflammatory condition, such as rheumatoid arthritis, were also excluded. Finally, patients could not be enrolled if they were already on a low-carbohydrate diet or had been on one in the previous 6 months. Calcium and vitamin D intake and the use of oral contraceptives in women were not tracked.

The institutional review board at the University of South Florida approved the study. The study was funded by a grant from Procter & Gamble. All patients provided written informed consent.

Protocol

Patients were enrolled in the study after making an independent decision to start a low-carbohydrate diet for weight loss purposes. Patients were informed of the unknown effects of such a diet on bone turnover in humans. They were also informed that animal data exist to suggest that this type of diet may adversely affect bone turnover, potentially increasing one's risk for osteoporosis.

At their baseline visits, all patients had their height, weight, BMI, and waist and hip measurements recorded. Serum bone-specific alkaline phosphatase (BSAP), UNTx, and urinary ketone level were also obtained in all patients. All samples for UNTx were collected with the second morning voided urine approximately 2 h after awakening. The methodology for measuring the UNTx was enhanced chemiluminescence; for the BSAP, immunoenzymatic methodology was employed. Finally, the subjects were asked to describe their current diet from the following choices: no restrictions, calorie counting, low-fat, or another. If their baseline diet restricted carbohydrate intake, then they were not enrolled.

At the baseline visit we gave formal instructions on the type of diet to follow throughout the study. The subjects were instructed to consume less than 20 g of carbohydrates (total) per day for the 1st month and then less than 40 g of carbohydrates (total) per day for months 2 and 3. On the day of enrollment, we counseled each study subject (dieter) about carbohydrate intake and the aforementioned carbohydrate limits for the next 3 months. We also supplied a list of the most common foods consumed and the amount of carbohydrates per serving, and we informed the subjects that their diet compliance would be monitored at each visit.

At their 1-month follow-up visit, each study subject received the same work-up as at the baseline visit. We asked them how well they were following the low-carbohydrate diet guidelines, including whether they had been more compliant in the 3 days prior to their visit. The 3-month evaluation was the same as the 1-month evaluation with the exception being that a BSAP level was not obtained at that visit.

Controls had to be gender-, age-, and BMI-matched in order to be enrolled. The control subjects were not allowed to be on any type of restricted diet (low-calorie, low-carbohydrate, vegetarian, etc.). We enrolled them only if they agreed to stay on an unrestricted diet for the 3-month study period. With regard to age and BMI, the controls were considered a match if they were within 15% of the study subject. All of the controls were followed in an identical fashion. We instructed them to inform us if they decided to change their normal, unrestricted diet in any way.

Adverse events

We queried the study subjects at each visit about any potential side effects from the low-carbohydrate diet. These included, but were not limited to, nausea, vomiting, diarrhea, constipation, epigastric or chest pain, dysphagia, or joint pain. Patients were also provided a telephone number to report any potential side effects at any point during the study.

Outcome measures

The primary end point was the change in UNTx at 3 months in the study subjects versus the controls. Secondary end points included change in BSAP, UNTx, and bone turnover ratio (BSAP/UNTx) at 1 month. Other end points included urinary ketones, weight, BMI, and waist and hip measurements at 1 month and 3 months.

Statistical analysis

We designed this study with an 80% power to detect a 50% increase in UNTx from baseline in the study subjects compared with the controls at 3 months. All statistical tests were two-sided, with $p<0.05$ considered statistically significant. The target sample was 30 subjects (15 dieters and 15 controls) to allow for withdrawal of two subjects. The change from baseline was calculated for each study subject. The mean changes were then compared using the Mann-Whitney test. Similar techniques were performed to calculate all of the secondary end points.

Results

Patients

Twenty-two women and eight men were enrolled in the study. Two of the study subjects in the diet group were lost to follow-up, so they (and their controls) were excluded from the analysis. The baseline demographics are shown in Table 1. The mean age was approximately 40 years in both groups. There was no statistical difference between the groups regarding height and weight, but there was with BMI and waist and hip measurements. It proved difficult to find controls with significant increased BMI. All of the controls had a lower BMI than the active study subjects,
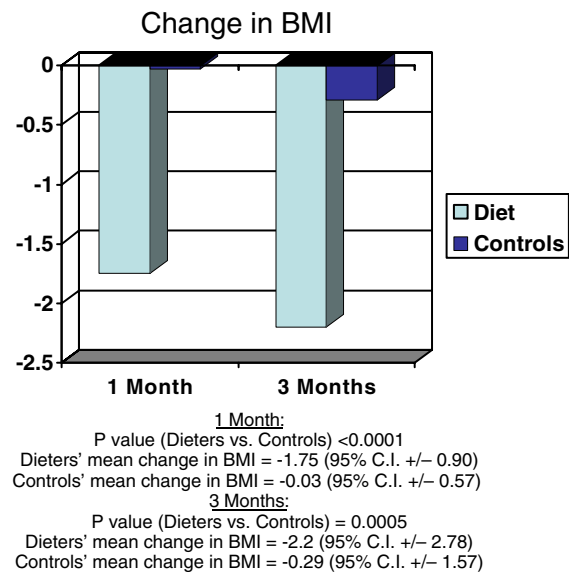

Change in BMI

1 Month:
P value (Dieters vs. Controls) <0.0001
Dieters' mean change in BMI = -1.75 (95% C.I. +/– 0.90)
Controls' mean change in BMI = -0.03 (95% C.I. +/– 0.57)
3 Months:
P value (Dieters vs. Controls) = 0.0005
Dieters' mean change in BMI = -2.2 (95% C.I. +/– 2.78)
Controls' mean change in BMI = -0.29 (95% C.I. +/– 1.57)

Fig. 1 Change in body mass index

most being nearly 15% less, thus accounting for the significant difference in BMI. Waist and hip measurements were not used as a screening tool. The majority of the subjects were Caucasian. Two study subjects in each group were of Hispanic origin, and one person in the diet group and three in the control group were African-American. It is unlikely that the small difference in the number of African-American study subjects created a significant impact on the overall bone turnover indices.

Diet compliance

Diet compliance was very good. The patients who followed the low-carbohydrate diet lost an average of 6.39 kg [95% confidence interval (CI) ±8.4 kg], or approximately 14.1

Table 1 Baseline demographics of the study subjects (*CI* confidence interval)

|	Diet (*n*=13)	Controls (*n*=13)
Gender	9 women, 4 men	9 women, 4 men
Average age	40.08 years (range 24–54; female range 24–43; male range 47–54)	40.46 years (range 27–56; female range 27–42; male range 48–56)
Race	10 Caucasian, 2 Hispanic, 1 African-American	8 Caucasian, 2 Hispanic, 3 African-American
Smoking status	12 nonsmokers, 1 smoker (<1 pack/day)	11 nonsmokers, 2 smokers (<1 pack/day)
Alcohol use	9 nondrinkers, 3 had <3 drinks/week, 1 had 3–7 drinks/week Mean (±95% CI)	8 nondrinkers, 3 had <3 drinks/week, 2 had 3–7 drinks/week Mean (±95% CI)
Height (cm)	168.27±26.4	168.06±21.9
Weight (kg)	95.99±46.9	82.49±27.4
Body mass index	33.51±11.76[a]	29.03±3.88[a]
Waist (cm)	102.9±28.5[b]	92.7±13.9[b]
Hips (cm)	119.1 (±23.7)[c]	109.1 (±15.7)[c]

[a]*p*-value: 0.03
[b]*p*-value: 0.02
[c]*p*-value: 0.04

lbs, after 3 months (average weight at baseline: 96 kg versus 89.6 kg at 3 months). The controls lost an average of 1.05 kg (95% CI ±4.0 kg). This represents a *p*-value of 0.0008 versus controls. Figure 1 displays the average change in BMI throughout the study. All of the patients on the low-carbohydrate diet lost weight with the exception of one patient, who gained 0.5 kg. The most significant weight loss was 15.9 kg, which represented a decrease of 5 kg/m^2 on that patient's BMI. Changes in waist and hip measurements were also statistically significant in dieters versus controls at 1 month and 3 months (waist at 1 month and 3 months: *p*-value 0.0002, <0.0001, respectively; hip at 1 month and 3 months: *p*-value 0.01, 0.002, respectively). Dieters lost an average of 4.3 cm in the waistline and 5.4 cm in the hips. There was no significant change in the waist-to-hip ratio with the diet.

Two of the study subjects and one control had "trace" urinary ketones at their baseline visit, with the rest being negative. All of the patients on the low-carbohydrate diet had at least "trace" urinary ketones at their 1-month visit, and nine of the 13 had "small" to "large." None of the control subjects had urinary ketones detected at their 1-month visits. Similar findings were seen at the 3-month evaluation regarding ketonuria. All of the patients rated their diet compliance as average or better throughout the study.

Outcome measures

After 3 months of a strict low-carbohydrate diet, the mean change in UNTx was not significantly different in the study


Urinary N-Telopeptide (UNTx)

[nmol BCE/mmol creatinine]
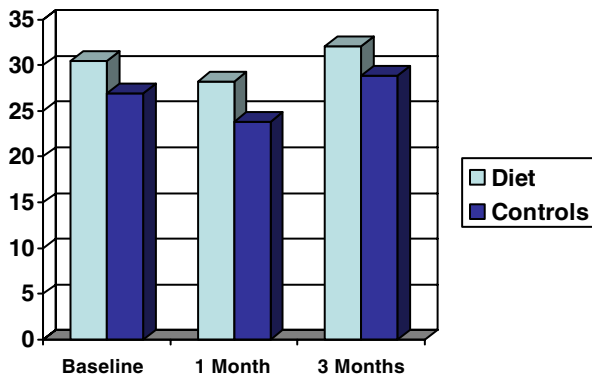
Baseline
P value (Diet vs. Controls): 0.36 (95% CI: Diet +/-16.8; Controls +/-18.3))
1 Month
P value (Diet vs. Controls): 0.36
P value (Diet vs. Baseline): 0.26
Mean change in Diets'UNTx-2.2 (95% CI +/-27.2)
Mean change in Controls'UNTx-3.1 (95% CI +/-17.6)
3 Months
P value (Diet vs. Controls): 0.86
P value (Diet vs. Baseline): 0.98
Mean change in Diets'UNTx+1.6 (95% CI +/-22.8)
Mean change in Controls'UNTx+1.9 (95% CI +/-17.6)

Fig. 2 Urinary N-telopeptide (UNTx; nmol BCE/mmol creatinine)

**Bone Specific Alkaline Phosphatase (BSAP)**

[ug/L]
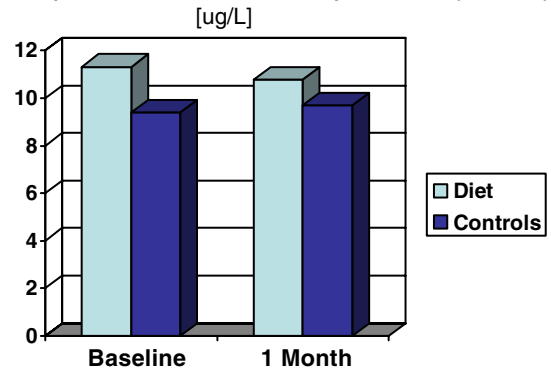
P value at Baseline (Diet [95% CI +/-8.1] vs. Controls [95% CI +/-5.6]): 0.27
P value (Diet vs. Baseline): 0.53
P value (Controls vs. Baseline): 0.92
Mean change in Diets' BSAP -0.53 (95% CI +/-2.96)
Mean change in Controls' BSAP +0.34 (95% CI +/-2.92)

Fig. 3 Bone-specific alkaline phosphatase (BSAP; ug/l)

subjects versus controls (see Fig. 2). The mean UNTx increased by 1.6 nmol BCE/mmol creatinine [n/m] (95% CI ±22.8) in the study subjects compared with an increase of 1.9 n/m (95% CI ± 17.6) in the controls (*p*=0.86). Further, there were no significant differences in the UNTx or BSAP at any time point, including at baseline (Figs. 2 and 3). The mean UNTx decreased by 2.2 n/m (95% CI ±27.2) and 3.1 n/m (95% CI ±17.6) at 1 month in the dieters and controls, respectively (*p*=0.36). The mean BSAP decreased by 0.53 ug/l (95% CI ±2.96) in the dieters and increased by 0.34 ug/l (95% CI ±2.92) in the controls at 1 month (*p*=0.27). Although the bone turnover ratio (BSAP/UNTx) increased slightly in both groups, the diet seemed to have no effect (Fig. 4). The bone turnover ratio increased by 0.08 (95% CI ±0.81) in the dieters and 0.05 (95% CI ± 0.27) in the controls at 1 month (*p*=0.78).

Bone Turnover Ratio (BSAP/UNTx)
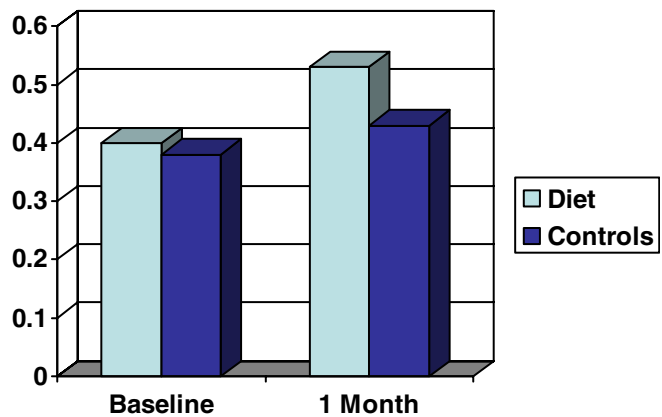
P value at Baseline: 0.76
P value at 1 month: 0.78
Baseline 95% C.I.: Dieters +/- 0.34; Controls +/- 0.30
1 Month 95% C.I.: Dieters +/- 0.69; Controls +/- 0.28

Fig. 4 Bone turnover ratio (BSA/UNTx)

When selecting out only those patients who lost more than 1.5 kg/m^2 on their BMI (nine of 13 patients), there was still no significant change in bone turnover ratio versus controls (p=0.97), change in UNTx at 1 month or 3 months (p=0.3 and 0.7, respectively), or change in BSAP at 1 month (p=0.2; data not shown).

Adverse events

There were no serious adverse events. One patient on the low-carbohydrate diet experienced a probable attack of gout (podagra). This was believed to be secondary to the diet. Another patient on the low-carbohydrate diet experienced abdominal pain 2 weeks after starting the diet. The pain resolved after she increased her diet from 20 g to 40 g of carbohydrates daily. Two other study subjects reported minor gastrointestinal complaints (intermittent nausea, constipation).

Discussion

This study was powered to detect a substantial increase in bone resorption from a low-carbohydrate diet, but a more modest effect cannot be ruled out. Not only was there no significant effect on bone resorption (UNTx), but there was also no apparent effect on bone formation (BSAP) or alterations in overall bone turnover (BSAP/UNTx) in patients who followed a strict low-carbohydrate diet. The study subjects also were very good at diet compliance as evidenced by their subjective evaluation and objective measures such as weight loss and urinary ketones. This was a "real-world" study in that the dieters followed guidelines very similar to the Atkins diet, and the controls followed a normal American diet without restrictions.

Animal data exist suggesting that low-carbohydrate diets can lead to poor bone quality [1, 2, 4, 6, 9–11]. The pathophysiologic mechanism is thought to result from poor gastrointestinal calcium absorption [8, 15], ketoacidosis that leads to increased osteoclast activity [1, 2, 7, 8], and poor bone mineralization from abnormal bone formation [6, 9–11]. Diets high in omega-6 fatty acids and low in omega-3 fatty acids could have deleterious effects on bone quality [12]. While the amount of omega-3 and omega-6 fatty acids consumed by our study subjects was not formally tracked, by following a strict low-carbohydrate diet one would be forced to consume a diet high in animal and dairy products. Such diets are high in omega-6 and low in omega-3 fatty acids. Thus, a strict low-carbohydrate diet, with resultant ketoacidosis, would seem to provide an imbalance leading to increased bone turnover in humans. However, our data suggest that a low-carbohydrate diet actually has no effect on bone turnover in humans.

A potential limitation of this study is its short duration. It is possible that significant changes in bone turnover could have developed if these patients were followed for a longer time course. However, significant changes in bone biochemical markers were routinely displayed at 1 month in many previous osteoporosis therapeutic trials [16]. One such trial demonstrated a significant change in UNTx at as soon as 12 h [17]. While these trials analyzed changes in biochemical markers in the setting of decreased turnover, rapid changes in these same biochemical markers have also been demonstrated in the setting of increased bone turnover [18–20]. Two such studies demonstrated significant changes as quickly as 5 and 7 days, respectively, in the setting of ovariectomy [18, 19]. Clearly, a low-carbohydrate diet would not be expected to have as profound an effect on bone turnover as ovariectomy or, perhaps, pharmaceutical intervention. However, the rapid changes that have been observed in bone turnover markers in these other settings suggest that 3 months should have been an adequate observation period. Further, the aforementioned study that compared a high-protein diet versus a low-protein diet in healthy young women revealed a 47% increase in UNTx after only 4 days [14]. Although these data seem to contradict ours, it is possible that there is an initial increase in bone resorption immediately after starting a low-carbohydrate/high-protein diet, to which the body soon accommodates. This point deserves further study.

The fact that there was a significant difference in the baseline BMI of the study subjects versus the controls is another limitation. While all of the controls had to have a BMI of ±15% of their matched study subject, the baseline characteristics were different in this regard. Despite this difference, there were no significant differences in the baseline UNTx, BSAP, bone turnover ratio, or urinary ketones. Given the lack of even any trends in the changes of the biochemical markers, we feel that the difference in baseline BMI does not negate the null effect of a low-carbohydrate diet on bone turnover in these overweight and obese patients.

A final potential limitation of this study is that weight loss itself has been associated with increased bone resorption [21, 22]. There was significant weight loss in those subjects on the low-carbohydrate diet compared with the control subjects. However, not only was there no significant difference in any of the markers of bone turnover in this study, but the UNTx was slightly higher in the control subjects compared with the dieters at 3 months.

This study supports the growing body of evidence suggesting that low-carbohydrate diets are effective weight loss tools [23–25]. The study subjects demonstrated significant weight loss compared to baseline and their controls. Diet adherence was also very good in this study in that 13 of 15 patients (87%) completed 3 months of this diet. However, this study and the others referenced [18–20] were of 3 and 6 months' duration. Diet adherence and compliance would be expected to decrease with increased duration.

Previous data argue that a strict low-carbohydrate diet used for weight loss would have deleterious effects on bone turnover. This trial prospectively analyzed such a diet over a 3-month span in regard to its effect on bone turnover. Although the relatively short observation period does challenge the generalizability of these findings, we suggest

that a low-carbohydrate diet used for weight loss does not increase bone turnover in humans.

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