Zinc Intake and Biochemical Markers of Bone Turnover in Type 1 Diabetes

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OBJECTIVE — To examine the relationship between Zn nutritive status and biochemical markers of bone turnover in type 1 diabetes.

RESEARCH DESIGN AND METHODS — Serum osteocalcin, urine N-telopeptides, and dietary intake data, obtained by 3-day food records, were assessed for 66 individuals with type 1 diabetes.

RESULTS — Zn intake correlated with osteocalcin in the group overall ($r = 0.48$; $P < 0.001$) but not with N-telopeptides. Examined by sex, both Zn and osteocalcin correlated for men ($r = 0.57$; $P < 0.001$), but the correlation did not reach statistical significance for women ($r = 0.34$; $P = 0.09$). A direct-entry linear regression model with osteocalcin as the dependent variable was performed. Duration, sex, A1C, insulin use per kilogram, total calorie intake, and Zn intake were entered as potential independent variables. The model was statistically significant ($R^2 = 0.32$; $P < 0.01$). Zn intake ($P < 0.001$), however, was the only independent correlate of osteocalcin.

CONCLUSIONS — This study provides evidence of a positive relationship between Zn intake and osteocalcin in type 1 diabetes.

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Zinc is important in bone metabolism (1). Work in cell cultures and animal models have shown stimulation of osteoblasts by Zn (2), while osteoclastic cell formation was inhibited (3). Reduced Zn levels associated with decreased bone mineral content have been observed for type 1 diabetic individuals (4). To our knowledge, there have been no studies in type 1 diabetes that examine Zn nutritive status and biochemical markers of bone turnover.

RESEARCH DESIGN AND METHODS

— Type 1 diabetic participants ($n = 66$; mean ± SD age 42 ± 10 years) were evaluated in the Human Performance Laboratory, University of Delaware, Newark, Delaware. This study had the approval of the institutional review board of the University of Delaware. Individuals with possible secondary causes of osteoporosis (e.g., hyperparathyroidism) were excluded, although seven did have borderline decreased vitamin D levels but normal parathyroid hormone levels. Analysis of the data omitting these subjects produced similar results; thus, they were included in the study cohort.

Women who were in menopause were excluded from participation. Menopausal status was based on self-reported frequency of menstrual cycles.

Participants recorded their dietary intake for 3 days. Nutrient content was determined with the Food Processor Nutrition Analysis and Fitness software package (version 8.0; ESHA Research, Salem, OR).

Blood and urine samples were collected in the morning following an overnight fast. Serum osteocalcin was measured via an immunoradiometric assay. Urine N-telopeptides were determined via a Vitros ECi competitive assay on a morning spot sample.

Univariate analyses included Student's t test, the χ^2 test, and Pearson correlations. Linear regression was used to assess potential independent associations for markers of bone turnover (i.e., dependent variable).

RESULTS

— Biomarkers of bone turnover stratified by sex are presented in Table 1. Participants consumed, on average, slightly more Zn than the daily recommended dietary allowance (RDA) (11 mg/day for men and 8 mg/day for women). It should be noted, however, that approximately one-third of the individuals demonstrated values less than the RDA. Osteocalcin levels were lower for individuals with Zn intake levels below the RDA (15.9 ± 5 [$n = 21$] vs. 19.6 ± 6 ng/ml [$n = 45$]; $P < 0.05$).

Zn intake correlated with osteocalcin in the group overall ($r = 0.48$; $P < 0.001$). When examined by sex, both Zn intake and osteocalcin levels were highly correlated for men ($r = 0.57$; $P < 0.001$), but the correlation did not reach statistical significance for women ($r = 0.34$; $P = 0.09$). No significant correlations were observed for N-telopeptides and Zn.

A direct-entry linear regression model, with osteocalcin as the dependent variable, was performed. With duration of diabetes, sex, A1C, insulin use per kilogram, total calorie intake, and Zn entered as potential independent variables, the overall model was significant ($R^2 = 0.32$; $P < 0.01$). Zn intake ($P < 0.001$), however, was the only independent correlate of osteocalcin, whereas sex was borderline statistically significant ($P = 0.061$). A potential interaction between sex and Zn intake was investigated and found not to be significant. In sex-specific models, controlling for the other variables, Zn intake ($P < 0.01$) was independently associated with osteocalcin for men ($R^2 = 0.34$ and $P < 0.05$ for the model) but

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Table 1—*Bone biomarkers and Zn intake levels for the study cohort (n = 66)*

	Men	Women	*P*
n	39	27	—
Osteocalcin (ng/ml)	19.9 ± 5.5	16.2 ± 5.8	<0.05
N-telopeptides (nmol/mmol)*	31.2 ± 12.8	25.1 ± 10.3	<0.05
Zn (mg)	15.8 ± 9.0	14.2 ± 7.1	NS
Subjects below the RDA for Zn intake per day	15 (38)	6 (22)	NS

Data are means ± SD or *n* (%) unless otherwise indicated. *Units of measurement for urine N-telopeptides are nmol bone collagen equivalents/mmol creatinine. NS, nonsignificant.

not for women. We also examined the R^2 for the model when Mg, phosphorus (P), or Ca was entered as a potential independent variable replacing Zn. No other micronutrient produced as strong an R^2 for the regression model as that for Zn, and only P was independently associated with osteocalcin ($P < 0.05$). No independent association with Zn was found when N-telopeptides were used as the dependent variable.

CONCLUSIONS — This study indicates that Zn intake is associated with a marker of bone turnover. Although it has been shown that Zn stimulates osteoblasts and the Zinc Effects on Nutrient/nutrient Interactions and Trends in Health and ageing (ZENITH) study (5) showed some, albeit inconsistent, evidence of a relationship between Zn nutritive status and bone turnover, to our knowledge this is the first study in type 1 diabetes that shows an independent association for Zn intake and osteocalcin. Our results, however, suggest that this relationship may be stronger for men than for women.

Zn plays several roles in bone metabolism. Zn stimulates bone protein synthesis and bone formation in tissue cultures (2). The anabolic effect of IGF-I in osteoblasts is enhanced by Zn (6). Zn deficiency, however, impairs DNA synthesis and protein metabolism, negatively impacting bone formation (1). In type 1 diabetic individuals with poor glycemic control, Arreola et al. (4) showed a significant decrease in both bone mineral content and Zn, suggesting that Zn deficiency may be a contributory factor to bone loss. Some have suggested that Zn deficiency leads to an increase in free radical production (7). Oxidative stress has been shown to be an independent risk factor for osteoporosis (8).

Why Zn intake appears to be more strongly associated with osteocalcin for men than for women is not clear. It may be because the women in our study were not in menopause. Herzberg et al. (9) showed that urinary discharge of Zn is increased in postmenopausal women with osteoporosis. Thus, perhaps the role of Zn in bone metabolism plays a larger role for women once they have reached menopause. It should be noted that there was no significant association of age with markers of bone turnover for either sex. No association between Zn intake and N-telopeptides was noted. Only one morning urine sample was collected for N-telopeptides, which may explain the lack of association because of a large intra-individual variability for N-telopeptides.

This study provides evidence of a relationship between Zn and a marker of bone turnover in type 1 diabetes. As for its limitations, the cross-sectional nature of the study indicates associations, and causality remains to be clarified. In addition, for 9 of 25 subjects who were taking a multivitamin, the exact Zn content of their supplement could not be determined. A common multivitamin with an average Zn, Ca, Mg, and P content was assigned to these subjects. This assignment could have attenuated the associations, potentially obscuring that between N-telopeptides and Zn intake. Multivariate analysis omitting these subjects, however, produced similar results.

Although the importance of higher levels of osteocalcin with regard to bone health is not clear, dietary factors are modifiable. Given that an inadequate intake of Zn has been reported as a risk factor for fractures in men (10), Zn may be important in reducing this risk in people with type 1 diabetes.

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