Effect of phylloquinone supplementation on glucose homeostasis in humans[1–3]

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ABSTRACT

Background: Under-γ-carboxylated osteocalcin (ucOC) increases insulin secretion and decreases glucose concentrations in mice.

Objective: We determined whether changes in ucOC concentrations in humans were associated with changes in insulin and glucose concentrations.

Design: Twenty-one community-dwelling postmenopausal women received 1 mg phylloquinone daily for 12 mo (experimental group), and 21 subjects were treated with a placebo during the same period (control group). Total serum osteocalcin, ucOC, glucose, and insulin concentrations were measured before and 6 and 12 mo after treatment. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated and correlated with ucOC concentrations.

Results: Before administration of the placebo or phylloquinone, total osteocalcin, ucOC, glucose, and insulin concentrations and HOMA-IR (1.24 ± 0.15 for the control group compared with 1.93 ± 0.37 for the experimental group) did not differ. After treatment, total osteocalcin concentrations were similar at 6 and 12 mo. At 6 mo, serum ucOC concentrations in the experimental group were 0.96 ± 0.08 ng/mL compared with 2.94 ± 0.27 ng/mL in the control group ($P < 0.001$). At 12 mo, serum ucOC concentrations were 0.92 ± 0.09 ng/mL and 3.13 ± 0.26 ng/mL ($P < 0.001$) in experimental and control groups, respectively. Despite a decrease of ≈200% in ucOC concentrations, HOMA-IR was similar in the 2 groups at 6 and 12 mo (at 6 mo, HOMA-IR was 2.24 ± 0.54 and 1.52 ± 0.23 in the experimental and control groups, respectively; at 12 mo, HOMA-IR was 2.13 ± 0.38 and 1.47 ± 0.22 in the experimental and control groups, respectively; P = NS).

Conclusions: In postmenopausal women, phylloquinone administration is not associated with changes in insulin secretion and action despite reductions in ucOC concentrations. Changes in ucOC concentrations do not alter glucose metabolism in women. This trial was registered at clinicaltrials.gov as NCT00062595. *Am J Clin Nutr* 2010;92:1528–32.

INTRODUCTION

Recent experiments have shown that mice that lack the osteoblast protein, osteocalcin, have decreased β-cell proliferation, glucose intolerance, and insulin resistance (1–3). In contrast, mice that lack the *Esp* (or *Ptprv*) gene, which is expressed in osteoblasts and Sertoli cells and encodes a protein tyrosine phosphatase termed mouse osteotesticular protein-protein tyrosine phosphatase (OST-PTP) (4–6), were shown to have an increase in β-cell proliferation, insulin secretion, and insulin sensitivity (3). Furthermore, removing one *osteocalcin* allele from *Esp*-deficient mice corrected their metabolic phenotype (3). In cultured β cells, uncarboxylated osteocalcin produced in bacteria by using recombinant methods increased cyclinD1 and insulin expression, and osteocalcin increased adiponectin expression in cultured adipocytes (3). The intravenous administration of uncarboxylated osteocalcin in mice improved glucose tolerance (2, 3, 7). These experiments showed that the release of the bone-specific protein osteocalcin in mice enabled bone to participate in glucose homeostasis. This was accomplished by directly increasing insulin expression in β cells and the release of adiponectin from fat cells, thereby increasing insulin sensitivity. On the basis of these results, a bone-pancreas-fat axis that regulates energy metabolism in mice has been proposed.

The administration of vitamin K or warfarin alters osteocalcin carboxylation via changes in vitamin K–dependent carboxylase activity (8–13). Binkley et al (14) showed that phylloquinone (vitamin K1) supplementation reduced concentrations of serum under-γ-carboxylated osteocalcin (ucOC) in healthy young and elderly adults, and Bach et al (15) showed that low-dose warfarin substantially increases ucOC serum concentrations without affecting prothrombin time or other clotting parameters. Taken together, these reports show that it is possible to substantially and safely manipulate serum ucOC concentrations in humans. However, it is not definitively known if change in circulating ucOC concentrations alter carbohydrate metabolism in humans. Several recent cross-sectional studies examined the association between serum osteocalcin concentrations, glucose and insulin concentrations, and insulin sensitivity with variable conclusions, and some, but not all, studies showed an association between osteocalcin concentrations and glucose metabolism (16–21). A single study examined the effects of phylloquinone administration over 3 y on carbohydrate metabolism and showed an im-

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provement in homeostasis model assessment of insulin resistance (HOMA-IR) in male but not female subjects; however, osteocalcin concentrations were not measured (22).

To assess whether changes in ucOC are associated with changes in serum glucose or insulin concentrations in humans, we examined total osteocalcin, ucOC, glucose, and insulin concentrations in women who had been treated with phylloquinone for 1 y. We observed that 6 and 12 mo of phylloquinone administration produced a decrease of ≈200% in ucOC concentrations. However, despite the dramatic change in ucOC concentrations, glucose and insulin concentrations remained unchanged.

SUBJECTS AND METHODS

Subjects

In a recent study, healthy, ambulatory, community-dwelling postmenopausal women (≥5 y postmenopausal) were recruited as previously described (23). None of the women met existing criteria for pharmacologic osteoporosis therapy, and none of the women were taking vitamin K–antagonist medication, such as warfarin or skeletally active agents such as bisphosphonates, glucocorticoids, estrogen, or calcitonin. Study participants had a self-reported low dietary vitamin K intake. Participants received 315 mg calcium with vitamin D_3/200 IU (Citracal + D; Mission Pharmacal, San Antonio, TX) twice daily for 2 mo before the baseline visit and subsequently for the 1-y study duration. Serum samples were obtained from participants who had been randomly assigned to one of 2 treatment groups in a double-dummy, double-blind fashion as follows: *1*) subjects in the treatment group received 1 mg phylloquinone (vitamin K1; Roche Vitamins, Parsippany, NJ) daily, and *2*) subjects in the placebo group received a placebo phylloquinone (Roche Vitamins) daily.

Fasting serum specimens were obtained at the time of randomization and subsequently at 1, 3, 6, and 12 mo between 0800 and 1100. Blood specimens were allowed to clot for 30 min and centrifuged, and serum aliquots were quick frozen with liquid nitrogen. Serum aliquots were stored at −80°C until thawed for analyses. This study was reviewed and approved by the University of Wisconsin Health Sciences Human Subjects Committee. All participants provided written informed consent to participate in the study.

From this cohort, serum samples from 21 women who received phylloquinone for 1 y and serum samples from 21 women who received the placebo for 1 y were selected. Pairs of subjects (one subject who received phylloquinone and the other subject who receiving the placebo) were selected on the basis of similar ucOC concentration at the baseline visit. The mean (±SD) difference in the ucOC concentration between the 21 phylloquinone and 21 control women was 0.05 (0.068) ng/mL.

Biochemical measurements

As previously reported y (23), chemistry panels were performed at a regional laboratory (Meriter Medical Laboratories, Madison, WI) in a routine clinical manner with a Roche Integra autoanalyzer. Glucose concentrations were measured at the Mayo Clinic (Rochester, MN) with a Horiba ABX Pentra 400 autoanalyzer (HORIBA ABX Diagnostics, Irvine, CA). Commercially available kits were used to measure bone-specific alkaline phosphatase (BSALP) by using an immunoassay (Metra BAP; Quidel, San Diego, CA) and *n*-telopeptide by using competitive-inhibition ELISA (Osteomark, Seattle, WA). Osteocalcin concentrations were measured by using an immunoradiometric assay (Osteo-riact; CIS bio international, Gif-Sur-Yvette Cedex, France), and ucOC concentrations were determined by using hydroxyapatite binding as previously reported (14). Serum insulin was measured in the Mayo Clinic Center for Translational Science Activities Laboratory with the DxI automated immunoassay system (Beckman Instruments, Chaska, MN). Intra- and interassay percentage CVs, respectively, for these analytes were 3.3% and 7.7% for osteocalcin, 7.5% and 5.1% for BSALP, and 4.5% and 7.9% for *n*-telopeptide. Interassay CVs for determination of insulin concentrations were 6.2% at 5.3 μU/mL, 6.5% at 46.1 μU/mL, and 7.7% at 120.4 μU/mL. To assess insulin resistance and β-cell function, HOMA-IR was calculated as described by Matthews et al (24).

Statistical analyses

Statistical analyses were performed with the JMP program (version 8; SAS, Cary, NC). A nonpaired *t* test was used to compare responses between placebo and treatment groups at various times. A bivariate curve fitting was carried out as described.

RESULTS

The 2 groups of subjects (placebo-treated or phylloquinone-treated groups) were of equal height, weight, and BMI (**Table 1**). The phylloquinone-treated group was slightly older than the placebo-treated group. Serum albumin, creatinine, BSALP, and *N*-telopeptide concentrations and bone mineral density *T* scores were similar in the 2 groups (Table 1).

At the commencement of the study, total serum osteocalcin concentrations were similar, as were concentrations of ucOC (**Table 2**). Serum glucose and insulin concentrations were also similar. The corresponding HOMA-IR for the placebo-treated and phylloquinone-treated groups were similar (1.24 ± 0.15 for the control group compared with 1.93 ± 0.37 for the experimental group; P = NS; Table 2). There was no statistically significant association between ucOC concentrations and HOMA-IR at the commencement of the study (**Figure 1**).

Six months of treatment with phylloquinone did not significantly change total osteocalcin serum concentrations (20.94 ± 1.35 ng/mL in the placebo-treated group compared with 20.91 ± 1.79 ng/mL in the phylloquinone-treated group; P = NS; Table 2) but did significantly reduced ucOC concentrations (2.94 ± 0.27 ng/mL in the placebo-treated group compared with 0.96 ± 0.08 ng/mL in the phylloquinone-treated group; $P < 0.001$; Table 2). Despite the significant reduction in serum ucOC concentrations, serum glucose and insulin concentrations were similar in the placebo-treated and phylloquinone-treated groups. HOMA-IR was similar in the 2 groups (1.52 ± 0.23 in the placebo-treated group compared with 2.24 ± 0.54 in the phylloquinone-treated group; P = NS; Table 2). As shown in a **Figure 2**, there was no significant association between HOMA-IR and serum ucOC concentrations.

A 12 mo, total osteocalcin concentrations were similar in the placebo-treated and phylloquinone-treated groups, whereas ucOC concentrations were lower in the phylloquinone-treated group [total osteocalcin concentrations: 19.95 ± 1.16 ng/mL in

TABLE 1
Characteristics of postmenopausal placebo-treated or phylloquinone-treated subjects at baseline

	Placebo treatment	Phylloquinone treatment	P^1
n	21	21	
Age (y)	60.0 ± 1.4[2]	63.96 ± 1.29	0.04
Height (cm)	162.5 ± 0.97	163.04 ± 1.32	NS
Weight (kg)	70.2 ± 3.5	71.45 ± 2.8	NS
BMI (kg/m^2)	26.48 ± 1.26	27.01 ± 1.29	NS
Serum albumin (g/dL)	4.30 ± 0.067	4.28 ± 0.057	NS
Creatinine (mg/dL)	0.73 ± 0.022	0.75 ± 0.034	NS
Bone-specific alkaline phosphatase (μg/mL)	27.53 ± 1.28	26.02 ± 1.58	NS
N-telopeptide (nmol/L)	21.79 ± 1.48	18.69 ± 1.52	NS
Bone mineral density (lowest *T* score)	−0.68 ± 0.22	−0.38 ± 0.24	NS

[1] Nonpaired *t* test.
[2] Mean ± SEM (all such values).

the placebo-treated group compared with 19.90 ± 1.54 ng/mL in the phylloquinone-treated group; P = NS; ucOC concentrations: 3.13 ± 0.26 ng/mL in the placebo-treated group compared with 0.92 ± 0.09 ng/mL in the phylloquinone-treated group; $P < 0.001$; Table 2]. Serum glucose and insulin concentrations were also similar in the placebo-treated and phylloquinone-treated groups. Likewise, HOMA-IR was similar in the placebo-treated and phylloquinone-treated groups (1.47 ± 0.22 in the placebo-treated group compared with 2.13 ± 0.38 in the phylloquinone-treated group; P = 0.14; Table 2). There was no significant association between HOMA-IR and serum ucOC concentrations (**Figure 3**).

DISCUSSION

In this study, we showed that phylloquinone administration in normal postmenopausal women did not alter fasting serum glucose or insulin concentrations despite significant (≈200%) changes in serum ucOC concentrations. These women had similar characteristics including anthropometric parameters, bone mineral density, and markers of bone formation at the commencement and over the course of the study. The data showed that phylloquinone administration and attendant changes in ucOC concentrations do not have a significant effect on carbohydrate metabolism in humans. Reductions in ucOC concentrations would be predicted to worsen glucose homeostasis because infusions of uncarboxylated osteocalcin in mice have been shown to improve glucose homeostasis and increase insulin gene expression in isolated islets (7). It remains to be shown whether significant changes in insulin secretion and action would occur in response to an oral or intravenous glucose challenge after phylloquinone treatment. However, the current data suggest that, in humans, unlike in mice, significant changes in ucOC concentrations do not alter fasting glucose or insulin

TABLE 2
Total serum osteocalcin, under-carboxylated osteocalcin, glucose, and insulin concentrations and glucose:insulin ratios before and 6 and 12 mo after treatment with a placebo or phylloquinone[1]

	Placebo treatment	Phylloquinone treatment	P^2
Total osteocalcin (ng/mL)			
0 mo	23.88 ± 1.22	27.96 ± 1.68	NS
6 mo	20.94 ± 1.35	20.91 ± 1.79	NS
12 mo	19.95 ± 1.16	19.90 ± 1.54	NS
Under-γ-carboxylated osteocalcin (ng/mL)			
0 mo	4.24 ± 0.31	4.26 ± 0.31	NS
6 mo	2.94 ± 0.27	0.96 ± 0.08	<0.001
12 mo	3.13 ± 0.26	0.92 ± 0.09	<0.001
Serum glucose (mg/dL)			
0 mo	79.79 ± 1.42	78.64 ± 2.06	NS
6 mo	81.60 ± 1.52	81.66 ± 1.86	NS
12 mo	78.92 ± 2.2	82.88 ± 1.77	NS
Serum insulin (μIU/mL)			
0 mo	6.22 ± 0.78	9.63 ± 1.75	NS
6 mo	7.37 ± 1.08	10.62 ± 2.36	NS
12 mo	7.29 ± 1.02	10.24 ± 1.78	NS
HOMA-IR			
0 mo	1.24 ± 0.15	1.93 ± 0.37	NS
6 mo	1.52 ± 0.23	2.24 ± 0.54	NS
12 mo	1.47 ± 0.22	2.13 ± 0.38	NS

[1] All values are means ± SEMs. HOMA-IR, homeostasis model assessment of insulin resistance.
[2] Nonpaired *t* test.

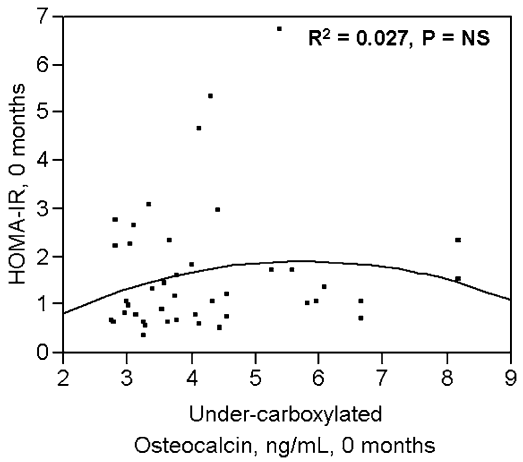

FIGURE 1. Relation between homeostasis model assessment of insulin resistance (HOMA-IR) and under-γ-carboxylated osteocalcin (under-carboxylated osteocalcin) before administration of placebo or phylloquinone (n = 42).

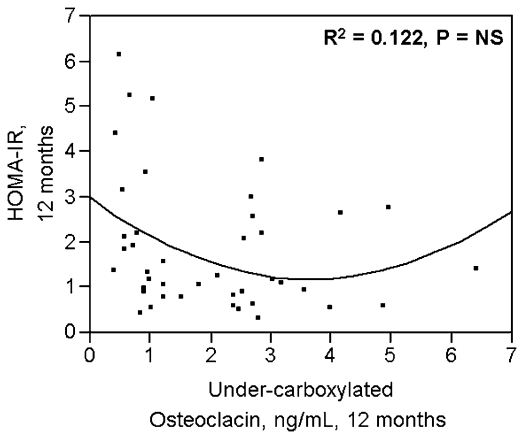

FIGURE 3. Relation between homeostasis model assessment of insulin resistance (HOMA-IR) and under-γ-carboxylated osteocalcin (under-carboxylated osteocalcin) after 12-mo administration of placebo or phylloquinone (n = 42).

concentrations. We are not aware of reports in which altered glucose metabolism has been reported after the administration of phylloquinone. A cross-sectional study showed that phylloquinone intake was associated with higher insulin sensitivity and glycemic status during a 2-h oral-glucose-tolerance test after adjustments for a variety of parameters (17). However, HOMA-IR and fasting insulin and glucose concentrations were not associated with vitamin K intake (17). Osteocalcin concentrations were not measured in the study. A recent cross-sectional study by Shea et al (16) showed no correlation between ucOC concentrations and insulin resistance in older adults, although elevated total serum osteocalcin and carboxylated osteocalcin concentrations were associated with increased insulin sensitivity. Other cross-sectional studies have shown inverse correlations between osteocalcin concentrations and fasting plasma glucose concentrations and HOMA-IR (18–21). Yoshida et al (22) showed that the administration of 500 μg phylloquinone for 36 mo was associated with a decrease in HOMA-IR in men but not in women. Osteocalcin and osteocalcin carboxylation were not measured in the study. Warfarin, which blocks vitamin K–dependent γ-carboxylation (9–13) and, thereby, leads to a significant rise in ucOC concentrations (15), has not been reported to alter blood glucose concentrations. It has been stated that warfarin therapy is linked to altered glucose homeostasis through the blockade of protein γ-carboxylation (25). However, the referenced report (26) deals with a single case in which an interaction between warfarin and acarbose was observed (26, 27).

Although our study did not demonstrate an increase in serum glucose concentrations after a reduction in ucOC concentrations and suggests that ucOC is not involved in glucose homeostasis in humans, there were limitations to our study. First, serum glucose and serum insulin concentrations were only studied in the basal fasting state before and after phylloquinone administration. It is possible that changes in glucose disposition and insulin concentrations might have been present in the ucOC-deficient state after the administration of a glucose load. Second, experiments in mice, in which the amount of osteocalcin produced was diminished, were conducted after the deletion of one of the mouse *osteocalcin* genes (2, 3). In this situation, reduced osteocalcin production was present throughout intrauterine, neonatal, and adult life which may have had additional effects on carbohydrate metabolism. Third, experiments in which bacterially produced, recombinant osteocalcin was intravenously infused into mice and was shown to have a salutary effect on carbohydrate metabolism (and on insulin and adiponectin synthesis in cultured cells) are not analogous to the current experiments because the amount of osteocalcin administered was likely to have been in considerable excess of that observed in physiologic circumstances. Fourth, our study had a duration of 12 mo. It is possible that changes in HOMA-IR may have occurred over a longer period. Finally, serum insulin concentrations were reflective of insulin secretion by the β cell into the portal circulation and hepatic clearance of insulin. It is possible that increases in hepatic insulin clearance may have masked an increase in insulin secretion by the pancreas. However, we are unaware of any effects of ucOC concentrations on hepatic insulin clearance.

Nevertheless, our experiments demonstrate that significant changes in carbohydrate metabolism do not occur within the context of large changes in ucOC concentrations in women. Further studies are required to investigate the influence of altered osteocalcin synthesis on carbohydrate metabolism in humans.

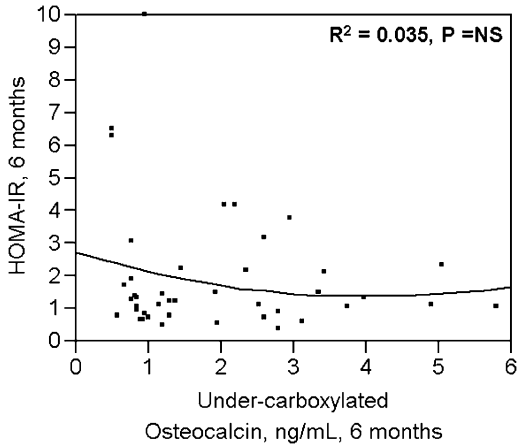

FIGURE 2. Relation between homeostasis model assessment of insulin resistance (HOMA-IR) and under-γ-carboxylated osteocalcin (under-carboxylated osteocalcin) after 6-mo administration of placebo or phylloquinone (n = 42).

The authors' responsibilities were as follows—RK, NB, and AV: designed the study and contributed equally to the overall scientific plan; and RK: wrote the manuscript. None of the authors had a conflict of interest.

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