OBSERVATIONS

Vitamin K2 Supplementation Improves Insulin Sensitivity via Osteocalcin Metabolism: A Placebo-Controlled Trial

Undercarboxylated osteocalcin (ucOC) is reported to function as an endocrine hormone, affecting glucose metabolism in mice (1,2). Vitamin K, which converts ucOC to carboxylated osteocalcin (cOC), has been suggested to regulate glucose metabolism by modulating osteocalcin and/or proinflammatory pathway (3–5).

We studied whether modulation of ucOC via vitamin K2 supplementation for 4 weeks affects β-cell function and/or insulin sensitivity in healthy young male subjects. Forty-two healthy young male volunteers received vitamin K2 (menatetrenone; 30 mg; Eisai Co., Japan) or placebo t.i.d. for 4 weeks. Frequently sampled intravenous glucose tolerance test was performed to determine insulin sensitivity index (S_i), acute insulin response to glucose (AIRg), and disposition index (DI) before and after treatment. Adiponectin, interleukin (IL)-6, C-reactive protein (CRP), ucOC, and cOC were measured before and after treatment.

After excluding frequently sampled intravenous glucose tolerance test failures ($n = 4$) and extreme outliers ($n = 5$), 18 subjects in the treatment group and 15 subjects in the control group were finally analyzed. The institutional review board of Seoul National University Hospital approved this study.

The age (29 [24–31] vs. 29 [25.5–31.5] years, median [interquartile range]) and BMI (24.9 [22.9–26.8] vs. 25.3 [21.9–27.0] kg/cm^2) of the control and treatment groups were not significantly different. Vitamin K2 supplementation significantly increased S_i (4.4 [3.2–5.6] vs. 6.6 [4.3–9.6]; $P = 0.01$) and DI (2,266 [1,536–2,785] vs. 3,025 [2,441–4,835]; $P < 0.01$), but these indices were not affected by placebo treatment. The percent increase in DI was significantly higher in the vitamin K2 group compared with the placebo group (50.9 [20.8–87.3] vs. 2.7 [-10.0 to 39.2]%; $P = 0.03$) resulting in higher posttreatment DI (3,025 [2,441–4,835] vs. 1,838 [1,320–2,741]; $P = 0.01$). These differences persisted even after adjusting for baseline S_i, AIRg, DI, ucOC, cOC, IL-6, adiponectin, and CRP ($P = 0.008$ for percent increase in DI and $P = 0.001$ for posttreatment DI). Treatment with vitamin K2 decreased ucOC (0.9 [0.5–1.8] vs. 0.4 [0.4–0.6] ng/mL; $P = 0.02$) and increased cOC (9.6 [7.1–15.1] vs. 16.0 [12.4–16.0] ng/mL; $P = 0.01$). However, no significant changes were observed in AIRg, fasting plasma glucose, weight, IL-6, CRP, or adiponectin (data not shown). S_i fold change was significantly associated with baseline cOC, baseline ucOC, and cOC fold change even after adjusting for age and weight fold change (all $P < 0.05$).

To summarize, we have demonstrated for the first time that vitamin K2 supplementation for 4 weeks increased insulin sensitivity in healthy young men, which seems to be related to increased cOC rather than modulation of inflammation. Small sample size limits firm interpretation on β-cell function. Our results are consistent with previous studies that demonstrated improved glucose intolerance or relieved insulin resistance by treatment with vitamin K1 (3) or vitamin K2 (4), respectively. We conclude that unlike in rodents, cOC rather than ucOC may be the endocrine hormone that increases insulin sensitivity in humans. Although our study could not provide the underlying mechanism, we speculate that cOC or vitamin K could modulate adipokines or inflammatory pathways other than the IL-6 pathways. Alternatively, cOC can directly regulate glucose disposal at skeletal muscle or adipose tissues. Further studies to elucidate the mechanism of action are warranted.

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