a rhTSH (0.1 mg i.m) and a T3 challenge (100 μg orally) with an interval of at least 3 m. Bone markers were measured at baseline and hereafter once daily for 3–4 days. **Outcome Measures:** Bone markers and changes after T3 and rhTSH. The influence of sex, group and time, and relations with incremental changes in TSH, fT4 and T3. **Results:** CTX (bone resorption) was lower in offspring than controls (mean ± SEM), 0.324±0.026 *vs* 0.443±0.036 ng/mL, P= 0.02. P1NP (bone formation) was also lower in offspring than in controls (40.3±2.2 *vs* 59.0± 4.7 ng/mL, P=0.004). No sex differences were found. In offspring, CTX but not P1NP was positively related to TSH and fT4 (R=0.48, P=0.001 and R=0.55, P=0.005). In controls, CTX was negatively related to TSH (R=-0.50, P=0.009), while P1NP was positively related with fT4 (R=0.52, P=0.006). TSH administration increased bone resorption and formation (P<0.0001 and 0.005, respectively). CTX was maximal at 48 h, increasing from 0.415±0.032 to 0.470 ±0.037 ng/mL, P=0.001. P1NP increased from 51.1±4.09 to a maximum of 56.2±3.9 ng/mL at 24 h (P=0.005). T3 also increased bone resorption (P=0.049) and formation (P=0.001). CTX increased from 0.386±0.034 to 0.410± 0.041 ng/mL, P=0.05, and P1NP from 48.9± 4.3 to 55.5±4.2 ng/mL, P=0.007), with maximal values at 48 h. Offspring and controls had similar responses and sex had generally no statistical impact. Significant linear regressions were found between the incremental changes of CTX and TSH at 24 h (R=0.44, P=0.003), but not later. Here, significant linear relation were found for the incremental fT4 and CTX (R=0.60, P=0.001 at 48 h, and R=0.49, P=0.013 at 72 h). For P1NP such relations were not present (R values between from 0.002 to 0.14). T3 changes did not correlate with bone markers at any time point. **Conclusion:** This study demonstrates that bone turnover is diminished in members of long-lived families where bone resorption was positively related to serum TSH and fT4. Nevertheless, the responses to TSH (and fT4) and T3 were similar in offspring and controls. Interestingly, the maximal effect of TSH increment on bone resorption preceded that of fT4, suggesting that TSH may have an independent stimulatory effect on bone resorption. At physiological TSH concentrations such stimulatory effect on bone resorption may be postulated in offspring, along with many other factors, *e.g* PTH, vitamin D, GH, sex hormones and cytokines.

Bone and Mineral Metabolism

VITAMIN D, DIABETES AND ENERGY METABOLISM

Causal Effect of Fibroblast Growth Factor 23 on Osteoporosis and Cardiometabolic Disorders: A Mendelian Randomization Study

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Pathological excess of fibroblast growth factor 23 (FGF23) causes mineral and bone disorders. However, the causality of FGF23 in the development of osteoporosis remains unknown. Whether FGF23 has systemic effects on cardiometabolic disorders beyond regulating mineral metabolism is also controversial. In this study, we evaluated the causal effect of FGF23 on osteoporosis and cardiometabolic disorders using Mendelian randomization (MR) analysis. Summary statistics for single-nucleotide polymorphisms with traits of interest were obtained from the relevant genome-wide association studies. As a result, FGF23 was found to be inversely associated with femoral neck-BMD (odds ratio [OR] 0.682, 95% confidence interval [CI] 0.546–0.853, p = 8e-04) and heel estimated BMD (eBMD) (OR 0.898, 95%CI 0.820–0.985, p = 0.022) in the inverse-variance-weighted analysis, but not lumbar spine-BMD and fractures. The results were supported by the weighted-median analysis, and there was no evidence of pleiotropy in the MR-Egger analysis. FGF23 was directly associated with FN-BMD and eBMD after adjustment for estimated glomerular filtration rate, height, and body mass index in multivariable MR analysis. On the other hand, there was no association between FGF23 and cardiometabolic traits including cardio artery disease, brachial-ankle pulse wave velocity, intima-media thickness of carotid arteries, systolic and diastolic blood pressure, fasting glucose, high and low-density lipoprotein cholesterol, and triglycerides. Therefore, FGF23 has been causally associated with bone loss. In contrast, FGF23 has not been causally associated with cardiometabolic disorders. The data of this study provides important insights into the role of FGF23 in the pathogenesis of osteoporosis and cardiometabolic disorders.

Bone and Mineral Metabolism

VITAMIN D, DIABETES AND ENERGY METABOLISM

Characteristics of Serum Ratios of 1,25-Dihydroxyvitamin D to 25-Hydroxyvitamin D for Assessment of Bone Metabolism

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Vitamin D is obtained in the body by food intake or by production from 7-dehydrocholesterol by exposure of the skin to ultraviolet B radiation. It is first metabolized in the liver to 25-hydroxyvitamin D (25D), which is a major circulating metabolite. In the kidney, 25D is subsequently metabolized to the hormonally active form, 1,25-dihydroxyvitamin D (1,25D), via 1α-hydroxylase encoded by the CYP27B1 gene. 1,25D has a cellular effect through the vitamin D receptor, which leads to calcium absorption in the gut, bone metabolism, and parathyroid function. A recent study showed that a low vitamin D status is common worldwide and is associated with various diseases including kidney, heart, and liver failure, secondary hyperparathyroidism, osteomalacia, inflammatory bowel disease, granuloma-forming disorders (sarcoidosis and tuberculosis), and cancer. Vitamin D deficiency also increases the risks of falls, fractures, bone loss, sarcopenia, leading to worse outcomes of illness severity, morbidity, and mortality. The 1,25D/25D ratio is considered to be a useful tool for diagnosis of ocular sarcoidosis; however, its clinical utility and relevance to pathophysiology of evaluation of the ratio 1,25D/25D which indicates vitamin