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

Maki Yokomoto-Umakoshi, MD, PhD, Hironobu Umakoshi, MD, Takashi Miyazawa, MD, PhD, Masatoshi Ogata, MD, Ryuichi Sakamoto, MD, PhD, Yoshihiro Ogawa, MD, PhD.
Kyushu University, Fukuoka, Japan.

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

Koichiro Yamamoto, MD, Manami Fujita, MD, Hiroyuki Honda, MD, PhD, Yoshihisa Hanayama, MD, PhD, Kazuki Tokumasu, MD, Yasuhiro Nakano, MD, Kou Hasegawa, MD, PhD, Mikako Obika, MD, PhD, Fumio Otsuka, MD, PhD.
Okayama University Grad School, Okayama, Japan.

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

D activation have remained unknown. To clarify the clinical usefulness of markers for vitamin D activation, 87 patients in whom serum 25D and 1,25D level was measured were retrospectively reviewed in the present study. Data for 79 patients (33 males and 46 females) were analyzed after exclusion of 8 patients taking vitamin D. The median serum 1,25D/25D ratio was significantly lower in males than in females: 4.1 (IQR: 2.3–5.8) x 10−3 versus 6.8 (3.0–9.8) x 10−3. However, individual levels of 25D and 1,25D were not different in males and females. The major categories of main disorders were endocrine (30.6 %), inflammatory (18.5 %), and bone-related (16.7 %) disorders. The ratios of serum 1,25D/25D had significant negative correlations with femoral dual energy X-ray absorptiometry % young adult mean (DEXA %YAM) (R=-0.35) and lumbar DEXA %YAM (R=-0.32). Significant correlations were found between 1,25D/25D ratio and serum levels of inorganic phosphate (R=-0.34), intact parathyroid hormone (R=0.64) and alkaline phosphatase (R=0.46) in all patients. Of interest, the 1,25D/25D ratio had gender-specific characteristics: the ratio had a significant correlation with age in males (R=0.49), while it had a significant correlation with body mass index (BMI) in females (R=0.34). Collectively, the results revealed that the ratio of serum 1,25D/25D as a marker for activation of vitamin D had relevance to clinical parameters, especially bone turnover, with gender-specific features. It is suggested that the existence of a gender-specific difference of aging males and obese females regarding the activation of vitamin D that is functionally linked to bone metabolism.

Bone and Mineral Metabolism

VITAMIN D, DIABETES AND ENERGY METABOLISM

Circulating Lipocalin-2 Predicts Changes in Lumbar Spine Bone Mineral Density After Parathyroidectomy in Primary Hyperparathyroidism

Seunghyun Lee, MD[1], Namki Hong, MD[1], Kyoung Jin Kim, MD[1], Jong Ju Jeong, MD[2], Yumie Rhee, MD, PhD[1].
[1]Department of Internal Medicine, Severance Hospital, Endocrine Research Institute, Yonsei University College of Medicine, Seoul, Korea, Republic of, [2]Department of Surgery, Thyroid Cancer Clinic, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, Republic of.

Lipocalin-2(LCN2), known as neutrophil gelatinase-associated lipocalin is known to a regulator of bone homeostasis. Upregulation of LCN2 in mice reduces osteoblast differentiation and stimulates the NF-kB pathway, promoting osteoclastogenesis. High serum LCN2 level was associated with elevated risk of fracture-related hospitalization in elderly women. Bone mineral density(BMD) of primary hyperparathyroidism(PHPT) patients tends to recover after parathyroidectomy, but with different extent. Whether circulating LCN2 can predict the extent of BMD recovery after parathyroidectomy in PHPT remains unclear. Clinical data and preoperative serum samples obtained from 35 PHPT patients (women n=30) who underwent parathyroidectomy at Severance hospital, Seoul, Korea between 2016 and 2019 were analyzed. Among 35 patients, 25 patients underwent BMD before surgery and two years after surgery. LCN2 was measured using enzyme-linked immunosorbent assay kit (DLCN20, R&D Systems, USA). Primary outcome was two-year lumbar spine BMD change (%). Mean age of study subjects was 57±13 years. Calcium and parathyroid hormone (PTH) levels restored to normal range after parathyroidectomy in all subjects (calcium [mean 8.7±0.4mg/dL]; PTH [median 33.3], 25.9 to 47.4 pg/mL). Baseline BMD of lumbar spine(LS), femoral neck(FN), and total hip(TH) were 0.776±0.177 g/cm^2, 0.578±0.138 g/cm^2, and 0.695±0.150 g/cm^2, respectively. At 1 year after parathyroidectomy, BMD increased up to 5.5%, 6.1%, and 4.5% at LS, FN, and TH, respectively. At 2 years after parathyroidectomy, BMD increased up to 8.6%, 7.6%, and 7.2% at LS, FN, and TH, respectively. Log-transformed LCN2 at baseline showed positive correlation with LS BMD changes (%) after 2 years (β Coefficient = 3.46, 95% CI = 0.83 to 6.10, p-value = 0.012). In multiple linear regression model, one log-unit increment in LCN2 was associated with 4.7 percent point increase in LSBMD at two years after parathyroidectomy (adjusted β=4.72, 95% CI = 1.62 to 7.82, p-value = 0.005) after adjustment of PTH, creatinine level, and body mass index. This result remained robust for 3 year change in LSBMD (in subgroup, n=14; adjusted β=4.70, 95% CI = 0.9 to 8.5, p-value = 0.021). In conclusion, preoperative high circulating LCN2 level was associated with more LSBMD gain after parathyroidectomy in patients with PHPT.

Bone and Mineral Metabolism

VITAMIN D, DIABETES AND ENERGY METABOLISM

Dress-Style Effect on Vitamin D3 Metabolic Profile

Samih A. Odhaib, MD[1], Nassar TY Alibrahim, MD[1], Ibrahim A. Zaboon, MD[1], Abbas A. Mansour, MD, FRCP, FACE[2].
[1]Faiha Specialized Diabetes, Endocrine and Metabolism Center, Basrah Health Directorate, University of Basrah, Basrah, Iraq., Basrah City, Iraq, [2]Faiha Specialized Diabetes, Endocrine and Metabolism Center, Basrah Health Directorate, University of Basrah, Basrah, Iraq., Basrah, Iraq.

Background and Objectives: Conservative clothing like niqab and hijab dress-style may affect the vitamin D metabolic parameters even in the predominantly sunny areas of the world, with adequate sunlight exposure throughout the year. Our objective is to evaluate the effect of wearing the niqab or hijab style on different vitamin D3 metabolic parameters in a sample of premenopausal women from Basrah. **Methods:** This was a cross-sectional observational study on premenopausal women who wore a niqab (n=64), with a comparable age-matched group of women who wore the hijab dress-style (n=60). Biochemical evaluation of the vitamin D3 metabolic profile involved 25-OH-vitamin D, corrected serum calcium, parathyroid hormone, phosphorus, and alkaline phosphatase estimation. Statistical comparison of these parameters was made using the independent sample t-test and Mann-Whitney-U test.
Results: The two groups of women were age- and weight-matched, with a median age was 39 years, and median body mass index (BMI) of 31.8 kg/m^2. Overall, age, marital status, and BMI of women in both groups had no significant relationship to the vitamin D3 metabolic parameters (low