mortality from COVID-19 disease was recently shown while a recent study has claimed lower COVID-19 cases in European countries with a better vitamin D status. **Aims:** To further elucidate the possible role of vitamin D population status in the COVID-19 pandemic, we examined the associations between published representative and standardized population vitamin D data on European population vitamin D status and the Worldometer COVID-19 data. **Methods:** Data from the Worldometer on 26 European countries populated >4 million (M) were analyzed. **Results:** On 19-June-2020, linear regression found no correlation between published representative-standardized population vitamin-D concentrations and the total cases-recovered/M, but negative correlations predicting a reduction of 47-64-80% in serious-critical illnesses/M and of 61-82-102.4% in deaths/M, further enhanced when adapting for life expectancy by 133-177-221% if 25(OH)D concentrations reach 100-125-150 nmol/L. On 15-August-2020 these correlations were sustained indicating a truthful association, yet not proving causality. Weighted ANOVA was performed to evaluate serious-critical/M (R^2=0.22) by the vitamin-D population status (deficient-D <50, insufficient-IN 50–62.5, mildly insufficient-MIN >62.5–75 and sufficient-S >75 nmol/L) and ANCOVA the deaths/M (R^2=0.629) after controlling for life expectancy (R^2=0.47). Serious-critical showed a decreasing trend (p<0.001) from population status D (p<0.001) to IN: 9.2%, p<0.001, MIN: 47.6%, p<0.044 and S: 100% (reference). For deaths/M the respective decreasing trend (p<0.001) was 62.9% from D (p<0.001) to IN (p<0.001), 65.15% to MIN (p<0.001) and 78.8% to S (p=0.041). **Conclusions:** Following the Endocrine Society's expert committee recommendations, without previous testing being necessary, reaching and maintaining a serum 25(OH)D of 100–150 nmol/L (40–60 ng/ml) could be achieved by an initial supplementation with the upper tolerable daily intake doses (IU/day) for up to two months: <1yr 2000, 1-18yrs 4000 and all adults 10,000 (obese x 2–3 times more) and then with the maintenance proposed doses that do not require medical supervision, practically identical with the IOM's upper tolerable limits: 1000 <6m, 1500 6m-1yr, 2500 1-3yrs, 3000 4-8yrs, and 4000 >8yrs, with adults and adolescents requiring 4000–5000 (obese x 2). Vitamin D may not prevent SARS-CoV-2 from spreading but may protect, without any risk of toxicity, from serious-critical illness and death from COVID-19 disease. While awaiting well-designed prospective studies, following the proposed approach, the gain for global public health and not only against SARS-CoV-2 may just prove invaluable.

Bone and Mineral Metabolism

VITAMIN D, DIABETES AND ENERGY METABOLISM

Body Composition And Bone Mineral Differences According to Lamin A (LMNA) Genotype in Familial Partial Lipodystrophy Type 2

Maria Cristina Foss de Freitas, MD PhD, Baris Akinci, MD, Callie Corsa, PhD, Amy E. Rothberg, MD, PhD, Ormond A. MacDougald, PhD, Elif A. Oral, MD.
University of Michigan, Ann Arbor, MI, USA.

Phenotypic heterogeneity is well known in Familial Partial Lipodystrophy Type 2 (FPLD2), a rare form of adipose tissue disorder caused by pathogenic mutations in *LMNA* gene. Animal studies from our group have identified an association between adipose tissue loss and an increase in bone mineral density (BMD) in a mouse model with adipose tissue specific knockout of *LMNA* gene. Aiming to translate this observation to patients with FPLD2, we analyzed body composition data obtained by dual X-ray absorptiometry from 61 patients diagnosed with FPLD2 and 61 individuals with no diagnosis of FPLD (nFPLD) matched for sex, age and body mass index. As expected, we observed lower total fat mass in FPLD2 patients compared to nFPLD (15.8±9.3 kg vs. 28.5±12.4 kg, p=0.001), as well as lower fat mass in regions of arms, legs and trunk. Interestingly, patients with FPLD2 showed lower bone mineral density (BMD) compared to nFPLD 1.0±0.2 g/cm^3 vs 1.2±0.1 g/cm^3, p=0.01) and lower t-score (0.2±1.8 vs.1.5±1.2). We then aimed to determine if the patients with FPLD2 displayed differences with respect to genotype. For these analyses, the FPLD2 group was divided according to the pathogenic variant; 42 with mutations on the hot spot codon of the LMNA gene (R482: 50.2 ± 164.8 years, 76% women) and 19 with non-hot spot codon mutations (nR482: 44.8 ± 12.8 years, 78% women). Patients in the R482 group were older when they were first diagnosed with lipodystrophy (39.6 ± 18.6 years vs. 36.5 ± 12.3 years, p=0.05). Also, nR482 group presented with more progeroid characteristics. Patients in n-R482 group also had lower weight compared to R482 and nFPLD groups (64.4±14.4 vs. 73.3±18.5 and 77.6±16.6 kg, p=0.01), as well as lower total fat mass (15.3±5.1 vs. 15.8±9.3 and 25.7±11.4 kg, p=0.01) and fat mass ratio (5.8±1.9 vs. 5.9±3.1 and 9.0±4.1, p= 0.01). Control group bone mass was significantly higher in arms, legs and trunk compared to the R482 and nR482 groups. Moreover, the R482 group had lower bone mass in the legs compared to nR482 (690.5±227.2 vs.703.5±95.3 g, p=0.01), while showing higher trunk bone mass (676.4±266.7 vs. 674.1±79.3, p=0.04), in addition to greater fat mass in the legs (3.3±1.6 vs. 2.6±0.7 kg, p=0.05) and trunk areas (10.3±6.1 vs. 10.0±4.2 kg, p=0.03). There were no differences in total bone mass, BMD, and t-scores, according to genotype. Our data showed more fat preservation in LMNA R482 than nR482, presumably leading to a later lipodystrophy diagnosis. Furthermore, bone mass in different regions may be affected by LMNA genotype; however, more studies are needed to define the bone phenotype and fracture risk in FPLD2 population fully.

Bone and Mineral Metabolism

VITAMIN D, DIABETES AND ENERGY METABOLISM

Bone Markers Are Diminished in Offspring of Long-Lived Families Compared With Matched Controls, but Respond Equally to T3 and rhTSH

Anna Zutinic, MD[1], Ferdinand Roelfsema, PhD, MD[1], Diana van Heemst, PhD[2].
[1]Leiden University Medical Center, Leiden, Netherlands,
[2]LEIDEN University MEDICAL CENTER, Leiden, Netherlands.

Objective: We explored the effects of T3 and rhTSH administration on bone turnover in subjects of the Leiden Longevity Study. **Design:** Twenty-six subjects (13 offspring and 13 matched controls), mean age 68 y, underwent

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