been treated for hypophosphatasia and have subsequently been recommended for genetic testing. **Conclusions:** Hypophosphatasia is an uncommon condition with a highly variable presentation often resulting in a missed diagnosis. Surveillance of practices by identifying patients with low ALP levels is a reasonable screening approach to identifying potential patients with hypophosphatasia.

Bone and Mineral Metabolism
PARATHYROID AND RARE BONE DISORDERS

Total, Free and Bioavailble 25 OH D and Bone Disease in Primary Hyperparathyroidism

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Background: Low levels of vitamin D 25OHD are frequently described in PHP patients. The aim of this study was to evaluate bone parameters and vitamin D status in PHP patients and controls. **Methods:** Prior to surgery, 64 PHP patients and 63 healthy matched control subjects regarding age, gender and body mass index were enrolled in this study along 18 months. 25OHD and PTH were measured using Roche® Immunoassays. Bone mineral density (BMD) by dual X-ray absorptiometry (DXA) (Hologic QDR 4500) and TBS (InSight™) were determined in all patients and controls. Distribution of total, bioavailable and free (calculated) 25OH and its correlation with TBS and DXA in both groups was evaluated. DBP (vitamin D binding protein) SNPs genetic analysis was performed by ABI 7500 real time PCR System. None of the patients and controls were taking vitamin D supplements before the study. **Results:** PHP patients had lower BMD values than controls in all sites (p<0.01). TBS measurements were also reduced in PHP patients compared to controls, as expected (1233 vs 1280, p=0.04). There was no statistical difference in free, total and bioavailable 25OHD measurements between the PHP and the control group, mean±SD: 3.4±1.7 vs 3.1±1.7 pg/mL (p=0.44), 22.6± 6.1 vs 20.6± ng/dL (p=0.13) 1.53±0.66 vs 1.41±0.61 ng/mL (p=0.28), respectively. Likewise, there was no statistical difference in DBP haplotypes 1s/1s, 1f/1f, 1s/1f, 2/2, 1s/2, 1f/2 analysis between groups. There was no correlation with 25OHD and DXA measurements in both groups. However, total 25OHD presented statistical significant correlation with TBS measurements in the PHP group (r=0.28; p=0.02) and total, free and bioavailable 25OHD measurements with TBS in the control group (r=0.42; r=0.42; r=0.43; p<0.01). **Conclusion:** Vitamin D status correlates with TBS, but not with DXA, highlighting the relation of the vitamin D with the microarchitecture bone parameters in both PHP patients and controls. However, this correlation was more evident among controls than in PHP patients, spotlighting the primary hyperparathyroidism effects in bone.

Bone and Mineral Metabolism
VITAMIN D, DIABETES AND ENERGY METABOLISM

A Comparison of Free and Total 25-hydroxyvitamin D Levels as Functional Indicators of Bone Health in Healthy Children

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Abstract Context: The "free hormone" hypothesis suggests that the free 25-hydroxyvitamin D ($25OHD_{Free}$) level may usefully indicate bone health. **Objective:** To determine which vitamin D measure is optimally correlated with clinical and bone parameters in healthy children. **Design and Participants:** A cross-sectional study including 146 healthy children (71 boys, 9.5±1.9 years) at a tertiary medical center. **Main Outcome Measures:** We used a multiplex liquid chromatography-tandem mass spectrometry-based assay to simultaneously measure vitamin D metabolites. The $25OHD_{Free}$ level was directly measured (m-$25OHD_{Free}$) or calculated using genotype-constant or genotype-specific affinity coefficients of vitamin D-binding proteins (con-$25OHD_{Free}$ or spe-$25OHD_{Free}$). Bone mineral content (BMC) and density (BMD) were assessed via dual-energy X-ray absorptiometry. **Results:** The concentrations of total 25OHD ($25OHD_{Total}$), the three forms of $25OHD_{Free}$, and 24,25-dihydroxyvitamin D_3 correlated with parathyroid hormone levels (all p<0.01). Serum $25OHD_{Total}$ and m-$25OHD_{Free}$ levels reflected age, puberty, season, body mass index (BMI), daylight hours, and vitamin D intake (all p<0.05). The con-$25OHD_{Free}$ level better reflected puberty and daylight hours than did the spe-$25OHD_{Free}$ level (both p<0.01). The association between the $25OHD_{Total}$ level and bone parameters varied according to the BMI (interaction p<0.05). In 109 normal-weight children, the con-$25OHD_{Free}$ level correlated with BMC and BMD (both p<0.05), but the $25OHD_{Total}$ and 24,25-dihydroxyvitamin D_3 levels were associated with BMC (both p<0.05). No association was found in overweight or obese children. **Conclusions:** In healthy children, total and free 25OHD levels comparably reflected lifestyle factors. In normal-weight children, the con-$25OHD_{Free}$ level reflected BMC and BMD, whereas the $25OHD_{Total}$ level was associated with BMC.

Bone and Mineral Metabolism
VITAMIN D, DIABETES AND ENERGY METABOLISM

Association Between Population Vitamin D Status and SARS-CoV-2 Related Serious-Critical Illness and Deaths

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Background: Vitamin-D population status may have possible unappreciated consequences to the COVID-19 pandemic. A significant association between vitamin-D sufficiency and reduction in clinical severity and inpatient

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

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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

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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