adaptation of TNBC cells to high circulating Ca^{2+}, but also suggests that mutations of the CaSR at rs1801725 are predictive of the likelihood for metastasis to lungs and bone.

Bone and Mineral Metabolism
PARATHYROID AND RARE BONE DISORDERS

The Effects of Encaleret (CLTX-305) on Mineral Physiology in Autosomal Dominant Hypocalcemia Type 1 (ADH1) Demonstrate Proof-of-Concept: Early Results From an Ongoing Phase 2b, Open-Label, Dose-Ranging Study

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Autosomal dominant hypocalcemia type 1 (ADH1) is a rare form of hypoparathyroidism caused by gain-of-function pathogenic variants in the gene (*CASR*) encoding the calcium-sensing receptor (CaSR). It is characterized by variable degrees of hypocalcemia, hyperphosphatemia, and hypomagnesemia, inappropriately low levels of parathyroid hormone (PTH) and hypercalciuria. Conventional therapy includes oral calcium and activated Vitamin D, targeting blood calcium at or slightly below the low-normal level to minimize hypocalcemic symptoms. This supplementation typically causes or exacerbates hypercalciuria, which may lead to nephrolithiasis, nephrocalcinosis, and renal insufficiency. It has been demonstrated in *in vitro* and *in vivo* models of ADH1, as well as in a Phase 2b clinical study (Roberts et al, JBMR 2019) that calcilytics (negative allosteric modulators of the CaSR), have the ability to shift the concentration-response relationship between extracellular calcium and the mutant CaSR towards normal.

Six adults with ADH1 due to four distinct activating variants of the *CASR* were studied in an ongoing, three period, Phase 2b, open-label, dose-ranging study [NCT04581629] of the calcilytic encaleret (CLTX-305). Calcium, magnesium, and calcitriol supplements were discontinued at the start of Period 1, and subjects received sequential, increasing daily doses of encaleret for 3d (30 mg, 90 mg, 180 mg) followed by 120 or 180 mg twice daily on day 4 and 5, while undergoing frequent blood and urine sampling. The mean baseline PTH was 3.4 ± 4.5 pg/mL (mean ± SD; nl 10–65); on encaleret, there was a rapid, dose-dependent increase in PTH to a mean level of 64.8 ± 49.6 pg/mL over 24 hours by day 5. Albumin-corrected blood calcium (cCa) increased from a baseline of 7.6 ± 0.6 mg/dL (nl 8.4–10.2) to a 24-hour mean on day 5 of 9.0 ± 0.5 mg/dL. Phosphorus decreased from a baseline of 4.5 ± 0.7 mg/dL (nl 2.3–4.7) to a 24-hour day 5 mean of 2.9 ± 0.5 mg/dL. Magnesium increased from a baseline of 1.6 ± 0.4 mg/dL (nl 1.6–2.6) to a 24-hour day 5 mean of 2.0 ± 0.5 mg/dL. Blood calcium, phosphorus and magnesium were mostly maintained within the normal range in ADH1 subjects by days 4 and 5. Twenty-four hour urine calcium was elevated at the screening visit while subjects were on conventional therapy (436 ± 255 mg/day, nl < 250–300) and decreased with increasing doses of encaleret to 63 ± 127 mg/day on day 5. Urinary calcium excretion became normal in 3 subjects and undetectable in 3 subjects while on encaleret. Encaleret was well-tolerated, with no serious adverse events reported.

The consistent mineral responses following encaleret administration in all six ADH1 subjects with four distinct *CASR* genotypes represents preliminary proof-of-concept that encaleret may be an efficacious treatment for ADH1. The longer-term evaluation of encaleret in ADH1 subjects is ongoing.

Bone and Mineral Metabolism
PARATHYROID AND RARE BONE DISORDERS

The Prevalence and Burden of Hypophosphatasia in an Ambulatory Endocrinology Practice

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Introduction: Hypophosphatasia (HPP) is an autosomal disease resulting from loss-of-function mutations in the ALPL gene encoding tissue-nonspecific alkaline phosphatase (TNSALP). The presentation and severity of the disease is highly variable ranging from perinatal-onset HPP with mortality rates as high as 100%, to adult onset with little mortality but with high disease-burden. Overall estimated prevalence of HPP in the general population is 1:100,000 though it may be significantly higher in specific populations. Hypophosphatasia is a heterogeneous disease that can reveal itself at any age, presenting within a wide range of symptoms. Adult HPP typically presents during middle age and is often misdiagnosed or missed in practice. The objective of this study was to determine the prevalence and burden of hypophosphatasia in an ambulatory care endocrinology practice. **Methods:** Potential subjects were identified via a computerized text search of the laboratory fields of patient electronic medical records (EMR). Search terms included serum ALP levels of less than or equal to 40 mg/dL. Records of patients with at least two low ALP levels were reviewed manually to identify potential patients with a history consistent with HPP. **Results:** A total of 315 patients with ALP levels < 40 mg/dL were identified via text search from an estimated 20,000 patient records. Fifty-six patients with a single low level were not considered for further review. The remaining 259 patients were reviewed for histories consistent with hypophosphatasia. These patients were predominantly white (64.9%), with an average age of 55 (+ 15) years, and an average BMI of 28 (+ 7) kg/m^2. Ten of these patients had histories consistent with hypophosphatasia including musculoskeletal pain requiring scheduled use of pain medications, polyarthropathy, chondrocalcinosis, deformity secondary to fractures, low BMD, a history of nontraumatic fracture, delayed or incomplete fracture healing, a history of multiple orthopedic surgeries, fatigue, impaired mobility, impaired gait, impairment of daily activities, a history of renal stones or nephrocalcinosis, and/or high serum B6 levels. None of the identified ten patients were currently being treated or had previously

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