anorexia induced osteoporosis resulting in pelvic osteomyelitis. Untreated osteoporosis may lead to fracture, resulting in inflammation and predisposing patients to infections. Thus, early recognition and evaluation of osteoporosis in patients at high risk for fracture, such as patients with anorexia, is critical for prevention.

Bone and Mineral Metabolism

BONE AND MINERAL CASE REPORT

Vitamin D Supplements: Over-the-Counter Accessibility... It Is Safe?

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Calcium is the fifth most abundant element in earth and human body. It has multiple functions within our system such bone mineralization, neuromuscular excitability regulation, hemostasis, membrane transport, release of hormones and neurotransmitters, among others. For duodenal absorption of calcium, we need vitamin D, reason for which supplementation of both components is important to maintain adequate calcium homeostasis. However, it is entirely beneficial or can be harmful? As we know everything in excess has its consequences, as we describe below.
72 y/o male is brought to the ED after relative find him lethargic, she reports noticing generalized weakness that has been progressing over weeks, prominent in upper extremities with associated increased in urinary frequency. Patient past medical history is relevant for CAD, hypothyroidism, dyslipidemia, and DMT2. On physical examination patient is found hypoactive, but arousable to verbal stimuli, without distress, focal neurologic deficit, thyromegaly nor lymphadenopathy. Presents with Ca+: 18.8mg/dL (n:8.0–10.5mg/dL), that could explain patient clinical presentation for which workup for hypercalcemia is done finding PTH suppress: 14.57pg/mL (n:15-65pg/mL). Patient now with non-PTH related hypercalcemia is further evaluated and found with negative UPEP and SPEP ruling out multiple myeloma and PTH-rp <2.0pmol/L (negative). While etiology of severe hypercalcemia is being study, patient complications of it are being managed such as AKI stage 3 as he presents with Cr: 3.85mg/dL, BUN: 62.5, CrCl:18ml/min and GFR: 15ml/min. Aggressive IV hydration and bisphosphonate therapy failed to decrease calcium and renal function continues worsens, for which hemodialysis is required for calcium clearance. Patient then found with vitamin D25-OH levels: 210.4ng/mL (n:30-100ng/mL), upon questioning he reports taking multivitamins and supplements equivalent for a daily ingestion of 50,700IU of Vitamin D3 and 334mg of calcium carbonate. Patient calcium levels normalize after dialysis but develops renal failure for which he has to be discharged on permanent hemodialysis.
Although prevalence is unknown, hypercalcemia due to vitamin D intoxication is relatively uncommon in comparison to hyperparathyroidism and malignancy. An exact dose intake that leads to intoxication has not yet being stablished but supplementation besides dosage is also dependent on duration of therapy. This case has a lot to teach us, starting with detrimental effects of hypercalcemia, follow by the consequences of lack of counseling and close follow-up of patient over-the-counter supplementation. As physicians we should inquire more about OTC medications and supplements our patients are taking not only for intoxication concerns, but also for drugs interactions. Counseling must be the cornerstone of our practice to avoid life changing consequences as in this case.

Bone and Mineral Metabolism

BONE AND MINERAL METABOLISM MISCELLANEOUS

Blocking Oxidized Phospholipids Attenuates the Age-Associated, but Not the Ovariectomy- or Unloading-Induced, Bone Loss in Mice

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Oxidized phospholipids (OxPL), such as oxidized phosphatidylcholine, are generated by oxidative stress (OS)-induced lipid peroxidation. E06 IgM is a natural antibody that recognizes the phosphocholine (PC) moiety of OxPLs, but not native PLs. Generation of transgenic mice expressing a single chain (scFv) form of its antigen-binding domain, "E06-scFv" mice, protects against atherosclerosis, hepatic steatosis and high fat diet-induced loss of bone mass. In addition, E06-scFv increases cancellous and cortical bone mass in both male and female adult mice fed chow diet, by increasing bone formation. Age-related bone loss is associated with increased OS and lipid peroxidation, and is characterized by a reduction in osteoblast number and bone formation. Oxidative stress is involved also in the bone loss caused by sex-steroid deficiency and elevated OS markers are found in unloading-induced bone loss, raising the possibility that an increase of OxPLs induced by OS might be contributing to the pathogenesis of these conditions as well. We aged homozygous E06-scFv transgenic female and male mice and their wild-type littermates up to 22 and 24 months respectively. Serial DXA BMD every 3 months showed that overexpression of E06-scFv attenuated the age-associated bone loss in both sexes. In addition, male and female E06-scFv transgenic mice also accumulated less fat mass than WT littermates during aging. Micro-CT analysis revealed that E06-scFv attenuated the age-associated decline in cancellous, but not cortical, bone mass. The histological analysis of the vertebrae indicated that the aged E06-scFv transgenic mice had increased osteoblasts and decreased osteoclasts compared to the WT mice. To investigate whether the beneficial effect of the E06-scFv could be seen after ovariectomy, 4.5 month old E06-scFv homozygous females and WT controls were ovariectomized (OVX). DXA and micro-CT measurements 6 weeks post- surgery indicated that, unlike aging, E06-scFv did not protect against OVX-induced bone loss in either the cancellous

or the cortical compartment. Lastly, we tail-suspended 5.5 month old male mice and sacrificed them 21 days later. E06-scFv transgenic mice had similar cortical bone loss compared to WT mice. In conclusion, the E06-scFV transgene attenuates the age-associated cancellous bone loss in both female and male mice, but has no effect on the OVX- or unloading-induced bone loss. These results fully support our hypothesis that an increase in PC-OxPLs with age, caused at least in part by a decrease in natural anti-PC antibodies, contributes to the age-associated bone loss. This evidence provides proof of concept that blocking PC-OxPLs represents a therapeutic approach to countering the increase of PC-OxPLs with age and their adverse effects on age-related bone loss as well as atherosclerosis and NASH. It also confirms that the mechanisms of cancellous and cortical bone loss are distinct.

Bone and Mineral Metabolism

BONE AND MINERAL METABOLISM MISCELLANEOUS

Chronic Stimulation of Arcuate Kiss1 Neurons Decreases Bone Mass in Female Mice

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Loss of peripheral estrogen in postmenopausal women is often associated with decreased physical activity and loss of bone mass, leading to an increased risk of metabolic diseases, osteoporosis, and skeletal fragility. While it is well-established that loss of peripheral estrogen signaling results in bone loss, we previously found that eliminating central estrogen signaling paradoxically results in an unexpected massive increase in bone mass only in female mice. Specifically, deletion of estrogen receptor alpha (ERα) signaling in kisspeptin 1 (Kiss1) expressing neurons of the arcuate nucleus (ARC^{Kiss1}) increases bone mass at the expense of reproduction in female mice. Currently, the mechanisms and the neurocircuits that modulate these unexpected responses are unknown. Here, to begin addressing these questions, we asked if changing the neuronal output of ARC^{Kiss1} neurons using chemogenetic manipulation of ARC^{Kiss1} neurons might also alter bone mass and locomotion in female mice. To do this, we delivered stimulatory (AAV2-hM3Dq-mCherry) designer receptors exclusively activated by designer drugs (DREADDs) to the ARC of wild type and Kiss1-Cre+ ($Kiss1\text{-}Cre^{hM3q\text{-}DREADDs}$) female mice and asked if chronic activation of ARC^{Kiss1} neurons might alter bone mass as analyzed by standard ex-vivo μCT imaging. Clozapine N-oxide (CNO) was delivered for 22 days (0.1 mg/mL). We also leveraged the ANY-Maze system to assess home cage activity over an extensive 96-hour period. Acute activation of ARC^{Kiss1} tended to decrease home cage activity by nearly 40% in $Kiss1\text{-}Cre^{hM3q\text{-}DREADDs}$ mice during the dark period compared to WT females. Interestingly, chronic activation of ARC^{Kiss1} neurons significantly lowered trabecular bone volume by nearly 30%. Current studies are underway to ask if inhibiting ARC^{Kiss1} neurons results in increased bone mass. Our findings collectively suggest that the neuronal activity of ARC^{Kiss1} neurons is sufficient to shift energy allocation away from locomotion and bone-building to maximize reproductive capacity. We speculate that the widely used SERM in breast cancer treatment, Tamoxifen, might exert its bone sparing effect by silencing ARC^{Kiss1} neurons.

Bone and Mineral Metabolism

BONE AND MINERAL METABOLISM MISCELLANEOUS

Comparative Transcriptomic Profiling Revealed Distinctive Patterns in Differentially Expressed Genes Related to Clinicopathologic Features of Parathyroid Carcinoma and Adenoma

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Parathyroid carcinoma is a rare malignancy which remains as a clinical unmet need lacking effective therapeutic intervention. (1) In this study, we compared mutational profile of parathyroid carcinoma, adenoma, and normal parathyroid tissue using RNA-Seq based transcriptomics analysis and whole exome sequencing. A total of 40 parathyroid specimens [parathyroid carcinoma (n=8), adenoma (n=24), and normal tissue incidentally obtained from thyroidectomy for various reasons (n=8)] from 39 individuals (women n=34, 87%; mean age 51 year) were analyzed. Compared to adenoma and normal parathyroid groups, parathyroid carcinoma group had younger age (carcinoma 35 ± 12 vs. other 56 ± 16 year, p=0.001) and higher serum parathyroid hormone (PTH; 231 [145–474] vs. 114 [88–196] vs. 34 [29–41] pg/mL, p=0.001) prior to surgery. CDC73 mutation was found in 7 of 8 carcinoma specimens, which harbored germline mutation in 6 of them. Among top feature gene mutations for classifying adenoma and carcinoma, carcinoma-specific genes showed high specificity, whereas adenoma-related key features were largely overlapped with normal tissues. Transcriptional profiling revealed 546 carcinoma-specific differentially expressed genes (DEGs), 135 adenoma-specific DEGs, and 323 common DEGs. Hierarchical clustering with 546 carcinoma-specific DEGs detected four clusters with distinctive clinicopathologic characteristics (cluster 1 [n=12]: 7 normal tissues and 5 adenomas; cluster 2 and 3 [n=22]: all adenomas except one normal tissue; cluster 4 [n=9]: all parathyroid carcinomas except one adenoma). Carcinoma-specific DEGs include upregulation of GRIN2A, LYPD1, and SOX2 and downregulation of ENTPPL, MYO3B, and PIK3C2G. Gene ontology enrichment revealed that these DEGs were mainly involved in the binding of cell adhesion molecule, actin, and Rho GTPase, and extracellular matrix