factor that determines mesenchymal stem cell lineage specification. ShRNA mediated knockdown of JMD3 in MSCs inhibited TNF- α mediated activation and inhibition of osteogenic and adipogenic differentiation, respectively. **Conclusion:** Our study uncovers the novel mechanisms of TNF-α mediated MSC lineage commitment and differentiation and thus highlight JMJD3 as mediator of TNF-α actions in MSCs.

Bone and Mineral Metabolism
BONE AND MINERAL METABOLISM MISCELLANEOUS

Low Phosphate Diet Exacerbates Hypercalciuria in the Jimbee Mouse Model of SGLT2 Loss-of Function

Kathryn M. Thrailkill, MD[1], Robert Clay Bunn, PhD[1], Philip Ray, MS[1], John Leslie Fowlkes, MD[2].
[1]University of Kentucky - UK Healthcare, Lexington, KY, USA,
[2]University of Kentucky, Lexington, KY, USA.

Selective sodium-dependent glucose co-transporter 2 inhibitors (SGLT2is) are a class of anti-hyperglycemic drugs that lower blood glucose in an insulin-independent manner by inhibiting renal glucose reabsorption and promoting glucosuria. In persons with chronic kidney disease, a potential therapeutic target group for such SGLT2i treatment, dietary phosphate restriction is a mainstay of treatment for metabolic bone disease. We investigated the impact of a low phosphate (LP) diet on the physiology of *Jimbee* mice which, via deletion in exon 10 of the sglt2 gene, provide a model of SGLT2 loss-of-function, albeit with otherwise normal renal function. Male (M) and female (F), 12-week (wk) old, C57BL/6J (genetic control) and *Jimbee* mice were randomized 1:1 to a kcal/g equivalent 0.1% phosphate (LP) or 0.4% phosphate (normal P = NP) diet and monitored for 12 wks (n=9–12 per group x 8 groups). At study end (~24 wks of age), male *Jimbee* vs. C57BL/6J mice had lower body mass (BM: p<0.0001), more-so on LP diet (C57BL/6J vs. *Jimbee*; (M) NP: 31.4 ± 2.1 vs. 28.6 ± 2.0. LP: 30.8 ± 2.0 vs. 26.0 ± 1.6 g). Female mice exhibited no differences in BM. By MRI, male mice demonstrated proportionate decrements in body composition of *Jimbees*, as the % fat vs. lean mass and % total body water were comparable between genotypes. HbA1c and random blood glucose were no different between groups, while glucosuria was increased in M and F *Jimbee* mice (p<0.0001) on either diet [C57BL/6J vs. *Jimbee*; (M) NP: 0.2 ± 0.2 vs. 10.2 ± 4.5. LP: 0.2 ± 0.2 vs. 7.8 ± 2.0 mg/g (body weight)/day. (F) NP: 0.5 ± 0.5 vs. 8.2 ± 2.7. LP: 0.4 ± 0.3 vs. 7.0 ± 2.9 mg/g/day]. Serum calcium and phosphorus were no different between any groups. However, *Jimbee* mice also exhibited hypercalciuria and hyperphosphaturia (p<0.001 for both). Hypercalciuria was amplified by LP diet in both strains, with a significant diet x strain interaction in males (p=0.01) [C57BL/6J vs. *Jimbee*; (M) NP: 4.7 ± 2.3 vs. 15.5 ± 8.2. LP: 27.8 ± 31.5 vs. 73.4 ± 25.8 µg/g/day of urine calcium (Ca^{2+}). (F) NP: 4.9 ± 2.8 vs. 22.7 ± 16.9. LP: 45.8 ± 29.5 vs. 62.6 ± 39.8 µg/g/day]. In contrast, hyperphosphaturia was attenuated by LP diet [C57BL/6J vs. *Jimbee*; (M) NP: 8.7 ± 8.5 vs. 14.7 ± 10.4. LP: 0.9 ± 0.5 vs. 3.2 ± 2.9 µg/g/day of urine phosphate (PO_4). (F) NP: 4.4 ± 6.1 vs. 16.3 ± 9.7. LP: 1.2 ± 0.8 vs. 2.9 ± 1.0 µg/g/day]. Plasma PTH levels were significantly lower (p<0.001) in male Jimbee mice on either diet (C57BL/6J vs. *Jimbee*; NP: 81.1 ± 31.0 vs. 41.3 ± 10.7. LP: 38.2 ± 1.9 vs. 24.1 ± 6.2 pg/mL) and negatively correlated with daily urine Ca^{2+} (r = -0.62; p=0.006). Consistent with PTH, renal 1-α hydroxylase gene expression was decreased by ~60% in Jimbee males, specifically on LP diet (p=0.02). Together, these data suggest that, in mice, dietary phosphate restriction might exacerbate SGLT2i-related hypercalciuria during prolonged treatment, independent of PTH, becoming potentially detrimental to bone mineralization and growth over time.

Bone and Mineral Metabolism
BONE AND MINERAL METABOLISM MISCELLANEOUS

Modeling COVID 19: The Value of Practice

Robert S. Fredericks, MD
Endocrine Associates, Reno, NV, USA.

The necessity of developing models that effectively organize data for the purpose of translating basic science to clinical care is being increasingly recognized. Reliance upon digital computational methods restricts the value of natural experience reportable by patients, often considered subjective. In the course of modeling phosphate metabolism in the context of clinical practice it has become evident that use of categories based on normality, as definition of health, is inconsistent with the experience of patients. Given the opportunity, patients can provide detailed observations upon their experience of heat as the principle component of metabolism. It seems logical that heat should also be the foundational principal component of models developed for the translation of data to clinical care. This strategy has been applied to modeling the role of ACE_2 in the expression of variable phenotypes of COVID 19. Attempts to engage massive data and super-computing to the modeling of COVID 19 supported the assumption that ACE_2 is a critical component causing disease. The finding is attributed to an influence, not on heat, but instead suggested bradykinin that has long been a proposed explanation for ACE inhibition on chronic cough. Our modeling would posit that the ACE system engages aldosterone and subsequent influence on heat and acid/base balance as the mediators of variance in the expression of individual phenotypes. This clarification has been useful for addressing complexity in the presentation of metabolic disorders including thyroid disease, Diabetes, bone health, sleep disorders, vascular disease and Chronic Fatigue Syndrome. It appears that the risk of developing ARDS shares a predisposition to chronic kidney disease mediated by excessive FGF_{23} effects, while the asymptomatic spreaders are more Klotho dependent. The vitamin D system is also complex and involved in the modulation of heat and phosphate. These and other components can be extended to understanding bone and the hematopoietic marrow niche governing immune responses and includes a role for modulation of the microbiome influences by ACE_2.