KTaV-3 and KtaR-1 cells were treated with a range of doses of E2 (5-100pM) and/or progesterone (20nM) for varying durations (4-96h), exposed to steroid hormones either constitutively or via modulating levels over time, approximating concentration changes found during the murine estrous cycle. Following RNA isolation, cDNAs were probed with primers for *gnrhr*. Preliminary results in KTaV-3 cells reveal the expression of *gnrhr* is induced only following elevated (50-100pM) E2 treatment for 18-24h. These same E2 exposure conditions were also found to increase expression of the homeobox protein *dlx3,* a transcription factor required for GnRHR expression in pituitary gonadotropes. In Arc-derived KTaR-1 cells, *gnrhr* expression was observed only following decreases in E2 concentration, while *dlx3* remained constitutively elevated in this cell line. While reciprocal GnRH-Kisspeptin connections have not yet been observed *in vivo*, these observations suggest the potential for Kisspeptin neurons to respond to GnRH secretory changes under particular E2 exposure conditions, by modulating receptivity to GnRH at the level of the AVPV and/or Arcuate nuclei. We are continuing to explore the temporal parameters of this induction of GnRHR in KP cells, and if exposure of immortalized KP neurons to GnRH *in vitro* elicits expression and signaling changes in a time- and E2-dependent manner. Results will provide a more complete understanding of positive and negative feedback mechanisms required for normal neuroendocrine regulation of reproduction.

Thyroid

THYROID HORMONE ACTION AND SIGNALING

Thyroid Receptor Alpha Interacts with COUP-TFII in the Regulation of Postnatal Skeletal Muscle Regeneration

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OR01-03

Myopathic changes, including muscular dystrophy and weakness, are commonly described in hypothyroid and hyperthyroid patients. Thyroid hormone signaling, via activation of thyroid nuclear receptors (TRs), plays an essential role in the maintenance of muscle mass, function, and regeneration. TRs are ligand-inducible transcription factors expressed in almost all tissues, including skeletal muscle. In a mouse model of Resistance to Thyroid Hormone carrying a frame-shift mutation in the TRα gene (TRα1PV)[1,2] we observed skeletal muscle loss with aging and impaired skeletal muscle regeneration after injury. We recently described that TRα interacts with the nuclear orphan receptor Chicken Ovalbumin Upstream Promoter-factor II (COUP-TFII, or NR2F2), which is known to regulate myogenesis negatively and has a role in Duchenne-like Muscular Dystrophies[3]. We showed that COUP-TFII expression declines with age in WT mice, while the skeletal muscle of TRα1PV mice shows a sustained significantly higher expression of COUP-TFII. Our findings suggest that the TRα/COUP-TFII interaction might mediate the impaired skeletal muscle phenotype observed in TRα1PV mice. To better characterize this interaction, we isolated SC from 10 months old WT and TRα1PV mice and cultured them in vitro using novel methods established within our lab. Using siRNA probes, we next silenced COUP-TFII and characterized the cells via RNA-seq analysis. In vitro, we assessed myoblast differentiation and proliferation using differentiation assays and EdU incorporation. We observed that satellite cells from TRα1PV mice display impaired myoblast proliferation and in vitro myogenic differentiation compared to WT SCs. However, when COUP-TFII was silenced, the myogenic potential of TRα1PV satellite cells was restored, with a higher proliferation of myoblasts and a higher number of fully differentiated myotubes after 4 days of myogenic induction. RNAseq analysis on satellite cells from TRα1PV mice after COUP-TFII knockdown showed upregulation of genes involved in the myogenic pathway, such as Myod1 and Pax7, and of genes in the thyroid hormone signaling, such as Dio2. Ingenuity Pathway Analysis further showed activation of pathways regarding cell growth, differentiation, matrix remodeling along with muscle function, muscle contractility, and muscle contraction. These in vitro results suggest that by silencing COUP-TFII we promote the myogenic pathway and may further rescue the impaired phenotype of TRα1PV mice. These studies can help increase our knowledge of the mechanisms involved in thyroid hormone signaling in skeletal muscle regeneration, which will ultimately increase the possibility of designing more specific treatments for patients with thyroid hormone-induced myopathies. References: [1]Milanesi, A., et al, Endocrinology 2016; [2]Kaneshige, M. et al, Proc Natl Acad Sci U S 2001; [3]Lee HJ, et al, Sci Rep. 2017.

Bone and Mineral Metabolism

NEW FRONTIERS IN BONE AND MINERAL METABOLISM

Natural Language Processing of Radiology Reports Improves Identification of Patients with Fracture

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OR29-02

Fracture liaison services (FLS) address the treatment gap for those with osteoporosis (OP) who fracture and are not treated. Given the limited human resources in FLS, screening high volumes of radiology reports for fractures with Natural Language Processing (NLP) could identify patients that have not been recognized or treated. This study is an analytical and clinical validation of X-Ray Artificial Intelligence Tool software (XRAIT) at its development site (a tertiary hospital) and external validation in an adjudicated cohort from the Dubbo Osteoporosis Epidemiology Study (DOES).Methods: XRAIT uses NLP to perform a Boolean search of radiology reports for fracture and related terms.

It can be trained for site-specific reporting styles and use rules to refine identification (e.g. age>50y; bone involved; etc). At the development site, XRAIT was used to search the emergency patient presentations of people over 50 years of age and compared to referrals to FLS (usual care) during the same 3-month period. XRAIT analyzed all plain radiographs and CT scans (n = 5089) while n = 224 were referred to FLS for usual care. External validation: XRAIT was used to analyze digitally readable radiology reports in an untrained cohort from DOES (n = 327) to calculate sensitivity and specificity.Results: XRAIT identified a 5-fold higher number of potential significant fractures (349/5089) compared to manual case finding (70/224). 339/349 were confirmed fractures (97.1%). Only 29% of those eligible were started or recommended anti-resorptive therapy, including those seen by the fracture liaison service. XRAIT unadjusted for the local radiology reporting styles in DOES had a sensitivity of 69.6% and specificity of 95%. Conclusion: XRAIT identifies clinically significant fractures efficiently with minimal additional human resources. Its high specificity in an untrained cohort suggests it could be used at other sites. Automated methods of patient identification may assist fracture liaison services to identify fractures that still remain largely untreated.

Adrenal

ADRENAL - CORTISOL EXCESS AND DEFICIENCIES

The Effect of Exogenous Cushing's Syndrome on All-Cause and Cause-Specific Mortality: A Systematic Review

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MON-157

Chronic oral glucocorticoid (GC) exposure from therapeutic anti-inflammatory or immunosuppressive use is the most common cause of Cushing's syndrome (CS). Previous studies of glucocorticoid therapy and mortality have produced inconsistent results and systematic reviews have only focused on endogenous CS. This is the first study that aimed to investigate all-cause and cause-specific mortality in association with exogenous CS from chronic oral GC therapy. The protocol was designed according to the principles of the PRISMA statement and registered in PROSPERO reference CRD42017067530. A literature review was performed in PubMed/MEDLINE (1966 to 31 Mar 2019), EMBASE (1974 to 31 Mar 2019), web of science (1900 to 31 Mar 2019), CINAHL (1981 to 31 Mar 2019) and reference lists within selected articles. Of 104,064 studies, 127 met the inclusion criteria, encompassing 51,380 patients. The Risk Of Bias In Non-randomized Studies of Interventions (ROBIN-I) tool was chosen and modified for evaluation of quality. The weighted percentage mortality by 5 groups of diseases including vasculitis, connective tissue diseases, inflammatory diseases, haematologic diseases and respiratory tract diseases, was 18.1, 12.7, 16.1, 28.2 and 5.7, respectively. The leading causes of death were cardiovascular disease (25.6%), malignancy (15.6 %), infection (13.4) and respiratory failure (10.8%). Although these studies showed high mortality in patients exposed to GC, estimates were not adjusted for known confounders and available data do not allow disentangling the relative contribution of CS vs. the underlying disease or non-GC immunosuppressive therapies. More extensive, high quality, prospective studies are needed to evaluate these associations and to identify modifiable risk factors.

Bone and Mineral Metabolism

BONE AND MINERAL CASE REPORTS II

A Case of Uremic Tumoral Calcinosis with Secondary Hyperparathyroidism

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MON-368

Background: Uremic tumoral calcinosis is an uncommon clinical entity that can be seen in patients with end-stage renal disease, characterized by development of calcific deposits in the soft tissue. This condition can cause significant pain and impairment of mobility for patients. While it appears that elevation in calcium-phosphate product and hyperparathyroidism may each play a role in the development of these deposits, these conditions are neither necessary nor sufficient for this process to occur. As a result, the optimal treatment of this condition is not well-established.
Case: A 50-year-old man with history of ESRD since 2015 secondary to autosomal dominant polycystic kidney disease on peritoneal dialysis, HTN, and secondary hyperparathyroidism presented to the emergency room with progressive right lateral hip pain, reaching the point where the patient could no longer ambulate. Exam demonstrated a thin man whose right hip was tender to palpation with limited range of motion, as well as a palpable, deep right upper leg mass. Laboratory findings were significant for a creatinine of 14.83mg/dL (n <1.5mg/dL), calcium of 9.1 mg/dL (n 8.5-10.5mg/dL), phosphate of 7.9mg/dL (n 2.5-4.5mg/dL), intact PTH of 1129pg/mL (n 15-65pg/mL), and 25-OH Vit D of 20.4ng/mL (n>30ng/mL). X-ray of the right femur demonstrated a 9cm calcified soft tissue lesion, which was not present on imaging 7 months earlier. Subsequent CT of the pelvis showed a cystic, multilobulated calcified mass in the right gluteus, measuring 6.1 x 3.5 x 7.5cm, consistent with tumoral calcinosis. Attempts to normalize his serum phosphorous level using treatment with phosphate binders or changes to his dialysate had failed previously, and the patient declined transitioning to hemodialysis. Nuclear medicine parathyroid scan demonstrated four-gland hyperplasia, and the decision was made to perform 3.5 gland parathyroidectomy. Two days post-operatively calcium had dropped to 7.7 mg/dL, phosphate to 6.8mg/dL, and intact PTH to 29pg/mL.
Conclusions: Uremic tumoral calcinosis is a very rare but potentially debilitating consequence of end-stage renal disease that can be significantly detrimental to quality of life in patients with ESRD. Elevated calcium-phosphate product is frequently implicated in its development, and evidence exists that lowering these levels can lead to complete resolution of these lesions. However, in patients