Bone and Mineral Metabolism

BONE DISEASE FROM BENCH TO BEDSIDE

Effect of Hyperglycemia on Bone Mineral Density and Fracture in Pre-Liver Transplant Recipients

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SUN-342

Abstract: The liver plays an important role in bone and mineral metabolism of patients with end-stage liver disease. These patients are known to have an increased risk of osteoporosis and fractures before liver transplant (LT) with reported fracture incidence of 10-56%. The cause is multifactorial, which includes their underlying liver disease, chronic illness, vitamin D deficiency, and hyponatremia. The impact of hyperglycemia and diabetes mellitus on bone health in liver transplant recipients is not known. **Hypothesis:** Hyperglycemia increases risk of fracture and osteoporosis in pre- LT patients undergoing LT. **Methods:** To answer this question, we did a retrospective chart review of consecutive first time, single organ LT recipients at our institution from 2011-2014, who had BMD performed prior to transplantation. We identified 393 patients but included only 209 patients who carried a diagnosis of hyperglycemia or diabetes (type 2 DM, type 1 DM, steroid induced DM and hyperglycemia). BMD was defined based on WHO criteria as Normal, osteopenia and osteoporosis. Hemoglobin A1C was divided into 4 quartiles (A1C ≤5.6%, 5.7-6.4%, 6.5-7.9%, and ≥8%); fasting blood glucose was defined as any venous glucose checked before 9am and labeled as a fasting lab in the chart. Fasting blood glucose was divided into those with BG<100, 101-125, 126-200, >200 mg/dL. We chose labs closest to the transplant date. Pre LT fracture was compared with hemoglobin A1C and BMD as well as fasting glucose. STATA statistical program was used to calculate Fisher T-test. **Results:** Baseline characteristics of our cohort were as follows. Median BMI was 27.9 (16.2, 45.6). Majority had hepatitis C (33%), NASH 12%, and alcoholic liver disease 23%. Average MELD score was 15 (6-40). Average wait time to transplant was 90 days. 29% of patients had normal BMD, 46% osteopenia and 25% osteoporosis. From the total 209 patients reviewed, 17 had a fracture prior to transplant of which 14/17 had vertebral fractures. The only variable that correlated with risk of fracture was hemoglobin A1C. Higher level of Hemoglobin A1C correlated with the presence of fracture p= 0.04. BMD did not correlate with fracture p= 0.28. There was no association between BMD and Fasting glucose level p=0.55. There was no correlation between fasting glucose and risk of fracture p=0.44. **Discussion:** This study suggests that a correlation between the presence of pre LT fracture and HgA1C exists. Other factors such as BMD and fasting BG did not correlate with fracture. Those with higher hemoglobin A1C prior to liver transplant might be at risk for fracture compared to those without diabetes or hyperglycemia (A1C <5.7). Benefit of diabetes control for bone health in this population is not known, however we speculate that those with lower A1C, thus better glucose control, have a lower risk of fracture thus aggressive glucose control should be part of the pre transplant care.

Adipose Tissue, Appetite, and Obesity

NEURAL MECHANISMS OF OBESITY

Hypothalamic ESR1 Gene Knockdown Elicits Intermittent Decrement in Postprandial Energy Expenditure Associated with Obesity Onset in Female Rhesus Monkeys

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SAT-597

Declining serum estradiol (E_2) levels during the menopausal transition are associated with increased central adiposity and heightened risk for metabolic disease. Estrogenic effects on adiposity and metabolism in female rodents are primarily mediated by estrogen receptor alpha (ESR1) activation in ventromedial (VMN) and arcuate (ARC) nuclei within the mediobasal hypothalamus (MBH). The role of hypothalamic ESR1 in the menopausal transition, and in regulating body weight, body composition and energy homeostasis in female primates, however, remains unclear. To investigate the involvement of ESR1 in regulating female primate body weight, we employed RNAi technology to assess ESR1 gene knockdown throughout the MBH of adult, full-grown, ovary intact female rhesus macaques. Using MRI-guided stereotaxic targeting, adeno-associated viral vector 8 (AAV8) expressing shRNA-ESR1 (ERαKD) (n=6), or a scrambled control sequence (n=4), were infused bilaterally into the MBH to knockdown ESR1 expression. Results: ERαKD females exhibited a ~22% (+2.0 ± 0.1 kg) increase in body weight to attain 10.4±0.9 kg after ~12-24 months (mo) ($p<0.05$), compared to ~12% increase in controls (+ 1.1±0.1 kg) attaining 9.1±1.0 kg body mass. The divergence in body weights between female groups, however, began at 6 mo. Daily calorie consumption at ~26 mo was comparable between groups. Assessments at ~28 months enabled customized metabolism cage analysis of energy expenditure (EE) corrected for fat-free mass and respiratory exchange ratio (RER). Postprandial EE (hours (h) 1-5 after once daily feeding) was inconsistently diminished in ERαKD compared to control females (1st day: ERαKD 0.087±0.001 vs. Control 0.104±0.002 kcal/min/kg, $p<0.0002$; 2nd day: ERαKD 0.092±0.0004 vs. Control 0.095±0.002 kcal/min/kg, NS). Overnight fasted RER (hours -1 to -2 prior to feeding) tended ($p<0.06$) to remain higher in ERαKD (1st day, 0.757±0.010, 2nd day, 0.732±0.031) compared to

control females (1st day, 0.728±0.007, 2nd day, 0.728±0.060) suggesting constrained switching between lipids and other carbon sources for energy metabolism during fasting in ERαKD females. We found no significant differences in 24 hr, 12 hr light or 12 hr dark EE and RER. Overall, these findings highlight MBH ESR1 roles in regulating body weight, energy expenditure and carbon sources utilized in daily energy metabolism, and suggest a discrete MBH location for development of therapeutic targeting to combat female obesity.

Diabetes Mellitus and Glucose Metabolism

DIABETES TECHNOLOGY

Is the Freestyle Libre Flash Glucose Monitor Accurate in the Critically Ill?

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SAT-639

The FreeStyle Libre flash glucose monitor (FGM) has made the use of continuous glucose monitors more accessible to the typical diabetes patient in an outpatient setting given the significantly lower cost and ease of use of FGM as compared to other systems. However, FGM is not labeled for use in a critically ill population. The critical care department at our institution queried the endocrine department about studying the use of FGM in critically ill patients. The interest of the critical care department was due to the potential of decrease in patient discomfort and decrease in time and effort of nursing and support staff related to the performance of fingerstick capillary glucoses if FGM was an adequate replacement measure.

As of yet, there has been only minimal study of flash glucose monitoring in critically ill patients. One Australian study evaluated 8 patients in an ICU setting and determined that as compared with arterial blood glucose monitoring, flash glucose monitoring provided acceptable numerical and clinical accuracy.[1] A Swedish study evaluated a total of 26 patients undergoing cardiac surgery and compared the use of FGM to use of a microdialysis intravascular system and concluded that the microdialysis system was more accurate, though in this study, only 25% of patients had diabetes. [2]

To further investigate use of FGM in a critically ill population, we plan to undertake a single center, prospective, single arm study enrolling at least 20 and up to 40 patients. Inclusion criteria include a known diagnosis of type 1 or type 2 diabetes, age of 18 or older, and admission to the medical intensive care unit (MICU) with expected MICU stay of at least 48 hours.

Participating subjects will have a sensor applied by a study investigator. After confirmation that the sensor is operational, the investigator will place opaque tape over the monitor to blind the monitor data. Nurses or medical assistants will conduct the standard of care fingerstick glucose monitoring per hospital protocol but will also have been notified of request to also pass FGM reader over the sensor at time of fingerstick glucose data collection.

The primary objectives are to determine numerical accuracy in a critical care setting using the mean absolute relative difference and to determine clinical accuracy in a critical care setting using the surveillance error grid and the clarke error grid analyses. Preliminary data should be available by March, 2020.

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Neuroendocrinology and Pituitary

NEUROENDOCRINOLOGY AND PITUITARY

Retrospective Analysis of Gonadotropin-Mediated Pubertal Induction in Male Patients with Congenital Hypogonadotropic Hypogonadism (CHH)

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MON-273

CHH is a rare disease characterized by a failure to enter (complete forms) or to complete (partial forms) pubertal development. It has a strong genetic background and it needs a treatment to allow the puberty to complete. In male this goal could be achieved either by the classic testosterone replacement therapy or by the exogenous gonadotropins (Gn) administration which allows both the endogenous testosterone production and the testicular development. So far, only few studies have explored this latter therapeutic approach in inducing the CHH pubertal development and no internationally recognized protocols are available. Aim of this retrospective analysis is to (i) investigate clinical and biochemical predictors of testicular response to Gn-induced puberty in CHH; (ii) study the non-reproductive outcomes of this treatment (height, body proportions) and their determinants. A total of 19 CHH male patients, undergoing two years of Gn-mediated (FSH and hCG) puberty induction started between the ages of 14 and 23 years, were retrospectively evaluated. For each patient clinical history, physical examination, hormonal evaluation, and genetic analysis using Targeted Next Generation Sequencing for CHH genes was performed; 8 patients accepted to perform a semen analysis (SA) at the end of their treatment.Mann Whitney test and multiple regression analysis showed testicular volume after 24 months of Gn-mediated pubertal induction, to be significantly associated with: (i) the presence