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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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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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