Type 2 Diabetes: Glucose dysregulation, bone material properties and bone fracture.
ASBMR 2023 Annual Meeting: Meet the Professor
Friday, September 9, 1:45 pm - 2:45 pm
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Significance

Individuals with type 2 diabetes mellitus (T2D) are at increased risk of bone fracture despite normal to high bone mineral density (BMD) compared to those without diabetes. This paradox suggests deficits in diabetic "bone quality," a term that broadly encompasses components of bone strength not captured by dual energy x-ray absorptiometry (DXA) alone. In this talk, we will explore the potentially-deleterious metabolic and biochemical changes associated with glycemic derangement that can degrade bone tissue properties and lead to skeletal fragility. An improved understanding of changes observed in the material properties of diabetic bone will help to guide screening, intervention and treatment to prevent fracture in this at-risk population.

Learning Objectives

1. Identify the factors that embrittle bone via altered remodeling and reduced toughness that increase susceptibility to fracture.
2. Understand how hyperglycemia can drive systemic, circulating AGE formation with resultant accumulation in bone tissue.
3. Discuss the implications that altered bone material properties in T2D may have on clinical decision-making to reduce fracture risk.

Outline, Points of Interest

I. Introduction

a. **The clinical problem**:

- Men and women with type 2 diabetes (T2D) have normal-to-elevated BMD assessed by DXA, but their fracture risk is higher at the hip, spine, and peripheral sites when compared to individuals with normal glucose tolerance
- To date, most experts would agree that the relationship between T2D and bone fragility is complex and multifactorial.
- Proposed mechanisms underlying fracture and T2D include medications such as thiazolidinediones, increased fall risk due to hypoglycemia, peripheral neuropathy, retinopathy, and the implications of other end-organ damage observed in T2D (i.e., chronic kidney disease, fatty liver, microvascular insults at the level of the bone).
- As T2D progresses in duration/severity, risk factors that influence bone fragility also change:
    - Early: obesity and insulin resistance have positive and negative influences on bone metabolism and strength
    - Late: increased impact of oxidative stressors, microvascular disease and other factors which have a cumulative, adverse effect on fracture resistance (see below)

b. Bone quality and fracture risk in type 2 diabetes

- The increased risk of fracture persists in epidemiologic studies controlling for extraskeletal variables noted above, suggesting that T2D degrades other determinants of bone strength, often-termed "bone quality."
- Aspects of bone quality hypothesized to contribute to skeletal fragility in type 2 diabetes include the following: bone geometry, bone microarchitecture, **bone material properties**

II. Bone material properties and T2D: Microscale bone tissue composition varies with glycemic control

- Progressive glycemic derangement as T2D evolves may directly influence microscale bone tissue composition (mineral content, age and distribution pattern).
- The mineral that forms in bone is hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$].
- During cell-mediated biologic apatite formation in bone, the collagen matrix is the template for initial mineral formation and crystal growth
- The formation of hydroxyapatite crystals in bone tissues is regulated by physico-chemical and biologic factors. There are several steps in the formation of physiologically mineralized tissues:
    1. The osteoblast secretes the collagen matrix.
    2. The matrix is post-translationally modified so that mineral deposition can be favored at specific sites along the collagen fibers.
    3. Mineral crystals nucleate, i.e., form the first stable apatite crystal, at specific sites where the barriers to crystal deposition are diminished either by elevating Ca_xPO_4 concentrations, removing mineralization inhibitors, or exposing matrix molecules or structures that facilitate mineral deposition.
    4. After a nucleus is formed, crystal growth (maturation) occurs through the addition of ions to the small crystals (nuclei). Bone crystals generally grow larger and more perfect with greater tissue age.
- Cells control the mineralization process, both by regulating local calcium and phosphate concentrations and pH as well as by the production and post-translational modification of collagen and noncollagenous proteins which guide and direct mineral deposition.
- In clinical studies, when the composition of bone from postmenopausal women with varying degrees of glycemic control (normal, impaired, frank T2D) was assessed, the T2D group had increased mineral content and lower bone turnover markers, factors which could embrittle bone.
- Similarly, there were changes in the distributions of mineral properties (more heterogeneous) that suggest non-conventional mineral maturation in T2D compared to normoglycemic individuals.
- A more mineralized, less heterogeneous tissue may affect tissue-level mechanical properties that degrade macroscale skeletal integrity in T2D.

III. Bone material properties and T2D: Advanced glycation endproducts (AGEs)

a. AGEs accumulate within T2D bone, deleteriously affect bone remodeling and increase fragility in T2D:

- AGEs include hundreds of chemical species formed through a nonenzymatic reaction between sugar- derived carbonyl groups and amine residues on amino acids.
- AGEs accumulate with age in the extracellular matrix, especially in long-lived extra-cellular proteins like collagen, a key component of bone tissue.
- AGEs may have both direct and indirect effects on bone fragility (Fig. 1). For example:
    - Pentosidine, a crosslinking AGE, may directly degrade mechanical properties by crosslinking adjacent molecules, thereby embrittling the tissue

- Carboxymethyl-lysine (CML), a non-crosslinking AGE comprising a side chain, may indirectly modulate bone material properties by altering the behavior of osteoblasts and osteoclasts via interaction with RAGE (Receptor for AGEs)

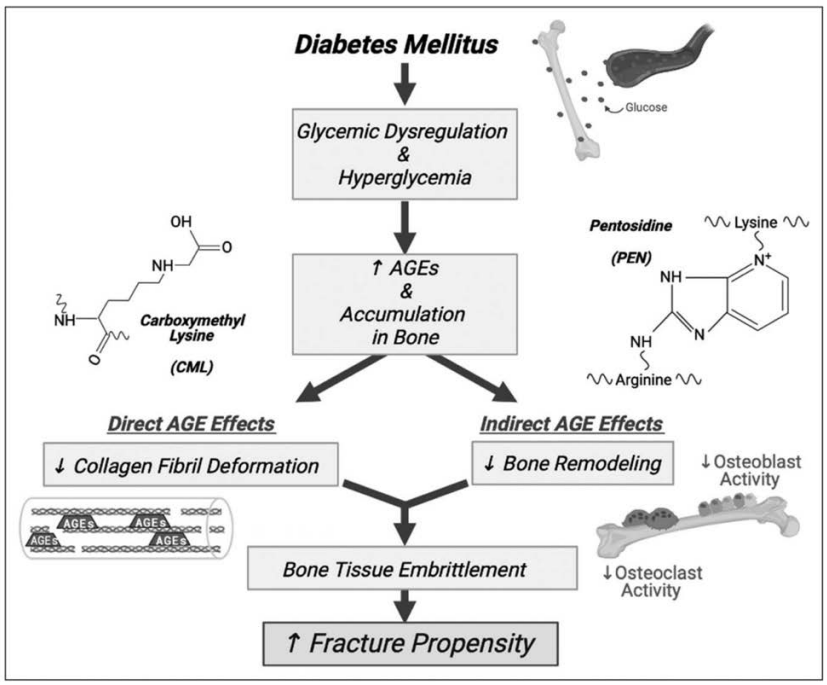

Figure 1: AGEs compromise bone integrity in T2D. AGEs have direct and indirect effects on tissue quality that lead to bone tissue embrittlement and increased fragility.
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    - Because AGEs inhibit bone resorption by osteoclasts and slow bone remodeling, AGEs exacerbate additional accumulation in tissue due to decreased turnover of previously-deposited AGEs
- The majority of current analyses of human bone show greater AGEs in cancellous and cortical bone when compared to nondiabetic controls, although some show no differences.
- In vitro studies of AGEs in bone have been leveraged to generate the most conclusive evidence to date that AGEs embrittle bone tissue.
    - In vitro glycation increased AGEs and reduced toughness and deformation required for failure in both cancellous and cortical bone
    - AGE accumulation inhibits deformation of collagen fibers
- The findings of clinical studies linking serum/urine AGEs, or surrogate measures of bone AGEs, and bone fragility are mixed.
    - Population-based data show that fracture risk in DM appears to be correlated with circulating AGEs, as measured by serum/urinary PEN and CML. (e.g., Health ABC) (Schwartz *et al.* 2011, Dhaliwal *et al.* 2022)
    - The weak correlations between peripheral and bone AGEs may reflect that AGEs in bone are one of many sources that are detected in serum/urine and/or serum AGE levels are tied to bone turnover.

<u>Clinical Pearls</u>

- Current clinical practice involving the use of DXA for osteoporosis screening, diagnosis and treatment may not adequately capture those with T2D at risk for fracture.

- To date, there are very few diagnostic tools (lab, imaging) used in the clinical setting that adequately characterize bone quality, especially the sub-category of bone material properties.
- While some algorithms have been proposed to evaluate fracture risk in T2D with subsequent therapeutic initiation (i.e. FRAX adjustment), they are not founded on an abundance of data. As such, clinical expertise and a patient-specific approach is needed until larger, prospective trials can be conducted.
- Greater understanding of the changes in bone quality that occur with progressive diabetes will 1) guide clinical decisions on which existing therapeutics will best address the underlying pathology of bone fragility in T2DM, and 2) motivate the development of new drugs and interventions based on determinants of bone fragility observed in T2DM.

Clinical Cases

Case 1: Patient is a 62y white female with a history of 6-years insulin-requiring T2D. No noted end-organ damage (micro- or macrovascular). Additional history is notable for controlled rheumatoid arthritis (no prednisone use). No fractures.

DXA: L-spine T-score -1.8
Femoral neck T-score -1.6
Total hip T-score -1.1
1/3 radius T-score -1.9

Pertinent labs: Ca 9.5 mg/dL [8.5-10.2], 25OHD 32 ng/mL [20-60], PTH 35 pg/mL [15-65], GFR 55 mL/min [>60], ALP 60 U/L [40-120], CTX 300 pg/mL, 24h urine calcium 125 mg Ca/24h [100-300]

Case 2: Patient is a 68y black female with a history of 7-years insulin-requiring T2D complicated by stage 3B moderate CKD (GFR = 30-44 mL/min). Additional history is notable for T9 vertebral compression fracture incidentally found on CT scan (no trauma, not present one year prior).

DXA: L-spine T-score -1.1
Femoral neck T-score -0.9
Total hip T-score -0.5
1/3 radius T-score -1.3

Pertinent labs: Ca 9.2 mg/dL [8.5-10.2], 25OHD 26 ng/mL [20-60], PTH 72 pg/mL [15-65], GFR 40 mL/min [>60], ALP 40 U/L [40-120], CTX 150 pg/mL, 24h urine calcium 200 mg Ca/24h [100-300]

Questions for discussion

- Should BMD assessment/screening be obtained in all patients with T2D given that this disease state is a risk factor for fracture? What are the implications for information dissemination (PCPs) and health care costs?
- Is there additional work up that you get in patients with T2D presenting with low BMD? With T2D and fracture?
- If the bone fragility observed in T2D is thought, in part, to be due to low turnover and alterations in bone material properties, how should these factors guide your therapeutic selection (anti-resorptive vs. anabolic agents)?
- Should the treatment threshold be different for patients with T2D presenting without fracture (i.e. T-score < -2)?

- How should patients be monitored if conservative management is selected? On pharmacotherapy?
- What are the future directions for research?

References and recommended reading

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