Diabetes and Bone: Clinical Outcomes

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Objectives
• What is the risk of fracture in T1D and T2D?
• Can BMD and FRAX predict fractures in T2D?
• Diabetes-specific risk factors
• Glucose-lowering medications and fracture risk

Type 1 Diabetes: Higher Hip Fracture Risk

Type 1 DM: Higher Hip Fracture Risk (UK)

Weber et al. Diabetes Care 2015

Type 1 Diabetes: Higher Hip Fracture Risk

Meta-analysis of 7 studies
Pooled RR for hip fracture
5.8 (3.7, 9.1)
Fan et al. Osteoporos Int 2016

Modest reduction in BMD
Hip BMD Z-score-0.37
Vestergaard Osteoporos Int 2007

Type 2 Diabetes: Higher Hip Fracture Risk

Fan et al. Osteoporos Int 2016
Type 2 Diabetes

• Average or higher BMD
• Overweight

Type 2 Diabetes

• Average or higher BMD
• Overweight
• Higher risk of fractures
• Hip fracture (meta-analysis of 12 studies): 1.34 (1.19, 1.51)

• More frequent post-fracture complications

Fan et al. Osteo Intl 2016

Predicting fracture risk in T2D

• T2D have increased fracture risk but higher BMD
• Can we use BMD and/or FRAX to predict fracture risk?
FN BMD T-score and Hip Fracture (2 US Cohorts)

T-score underestimates risk in DM

Schwartz et al. 2011
T-score underestimates risk in DM

Rough adjustment:
Reduce T-score by 0.5 in T2DM

Canadian study: FRAX underestimates fracture risk in T2D
Canadian study: FRAX underestimates fracture risk in T2D

FRAX underestimates risk in DM

Elements of FRAX Score
- BMD (Femoral neck t-score)
- Age
- Gender
- Race
- BMI
- Fracture history
- Parental history of hip fracture
- Current smoker
- Recent corticosteroid use
- Rheumatoid arthritis
- 3+ alcohol drinks/day

All elements of FRAX predict fracture in T2D - Leslie et al 2014

Under estimation of fracture risk in T2D must be due to other aspects of fracture risk, not captured by these elements.

Fracture Prediction in T2D
- BMD and FRAX predict fractures in T2D
- But underestimate risk
- T2D might be added to FRAX in future
Diabetes-specific risk factors for fracture

- Longer duration of diabetes
- Poor glycemic control
- Hypoglycemic episodes
- Glucose-lowering medications

Duration of diabetes and fracture risk

![Graph showing the relationship between duration of diabetes and fracture risk.]

Poor glycemic control increases hip fracture risk

<table>
<thead>
<tr>
<th>A1C</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥10</td>
<td>1.73 (1.47, 2.03)</td>
</tr>
<tr>
<td>9 – 10</td>
<td>1.51 (1.26, 1.86)</td>
</tr>
<tr>
<td>8 – 9</td>
<td>1.28 (1.09, 1.31)</td>
</tr>
<tr>
<td>7 – 8</td>
<td>1.15 (0.99, 1.34)</td>
</tr>
<tr>
<td>6 – 7</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>≤5</td>
<td>1.15 (0.94, 1.43)</td>
</tr>
</tbody>
</table>

1514 hip fracture cases. Li et al. JAMA 2015
ACCORD: Median A1C

ACCORD BONE: Intensive Control did not affect fractures

Poor glycemic control increases hip fracture risk
Severe hypoglycemia and hip fracture in T2D

Glucose-Lowering Agents & Skeleton

<table>
<thead>
<tr>
<th>Diabetes Medication</th>
<th>Bone turnover markers</th>
<th>BMD</th>
<th>Fracture risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>↑ (a)</td>
<td>↑ (a)</td>
<td></td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>↑ (a)</td>
<td>↑ (a)</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>↓ (a)</td>
<td>↓ (a)</td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>↑ (a); ↑ (b); ↑ (b)</td>
<td>↓ (b)</td>
<td>↑ (b)</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>↓ (b)</td>
<td>↑ (b)</td>
<td>↑ (b)</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>↑ (a); ↑ (b)</td>
<td>↑ (b)</td>
<td>↑ (b)</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>↑ (a); ↑ (b)</td>
<td>↑ (b)</td>
<td>↑ (b)</td>
</tr>
</tbody>
</table>

a = prospective cohort or nested case-control studies
b = randomized controlled trials (AD’s for fractures)

Insulin therapy and increased fracture risk

HR=1.38 [1.06 to 1.80]
ADOPT Trial
RSG: Increased fracture risk in women

ADOPT Trial
RSG: No increased fracture risk in men

Thiazolidinediones (TZDs)
- Meta-analysis of 22 RCTs
- Fractures as adverse events (AEs)
  - Increased fracture risk in women (1.94; 1.60-2.35) but not men (1.02; 0.83-1.27)
  - Both rosiglitazone and pioglitazone - Zhu et al Bone 2014
- Recent RCT found increased risk in men
Pioglitazone vs. Placebo after stroke: Increased fracture in men

Fractures ascertained at quarterly visits and adjudicated

HR 1.83 [1.36 to 2.48]

Men without diabetes

TZDs

• Substantial evidence for increased fracture risk in women; possible increased risk in men
• Avoid in those at high fracture risk

Sodium-glucose cotransporter 2 (SGLT2) inhibitors

• SGLT2 inhibitors prevent reabsorption of glucose from the kidneys, leading to increased urinary glucose excretion and reduced blood glucose. May alter calcium and phosphate homeostasis and thus BMD.
• Weight loss (~3%)
• More frequent falls for initial period of use?
Dapagliflozin and Fracture

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Dapagliflozin 5 mg</th>
<th>Dapagliflozin 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>84</td>
<td>83</td>
<td>85</td>
</tr>
<tr>
<td>Fracture</td>
<td>0</td>
<td>5 (6.0%)</td>
<td>8 (9.4%)</td>
</tr>
</tbody>
</table>

RCT in patients with moderate renal impairment. Fractures as AE’s. 104 weeks.
Kohan et al Kid Int 2014

Canagliflozin and Fracture: Meta-analysis
Adjuticated fracture AEs

Canagliflozin and Fracture (AEs) Integrated CANVAS trials

<table>
<thead>
<tr>
<th>Fracture Rate (per 1,000 patient years)</th>
<th>Placebo</th>
<th>CANA</th>
<th>IRR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>4347</td>
<td>5795</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All fracture</td>
<td>11.9</td>
<td>15.4</td>
<td>1.29</td>
<td>0.02</td>
</tr>
<tr>
<td>Low trauma fracture</td>
<td>9.2</td>
<td>11.6</td>
<td>1.26</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Fractures adjudicated.
Canagliflozin and bone resorption

Canagliflozin and BMD

Empagliflozin (SGLT2i)

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg</td>
</tr>
<tr>
<td>N</td>
<td>2333</td>
</tr>
<tr>
<td>Fracture (AE)</td>
<td>(3.9%)</td>
</tr>
</tbody>
</table>

Median observation 3.1 years

No increase in fracture risk
Sodium-glucose cotransporter 2 (SGLT2) inhibitors

- Some evidence for increased fracture but results are mixed
- Avoid in those at high fracture risk

Summary: Diabetes and Fracture

- Hip fracture risk is 5 times higher in T1D, 30% higher in T2D
- T2D, T-score and FRAX score predict fracture but underestimate risk
- DM duration, poor glycemic control, hypoglycemia, insulin therapy increase fracture risk
- Avoid TZDs and SGLT2i in T2D at higher fracture risk.