I. **Juliet Compston: Are there distinct animal models for type 1 and type 2 diabetes?**
   a. **Lorenz Hofbauer:** Sure. There are specific mouse and rat models for T1 and T2DM.
   b. **Lorenz Hofbauer:** T1DM rodent models typically involve beta cell destruction by streptozotocin in most strains or induction of autoimmune diabetes in NOD mice. The latter is more reflective of human T1DM. As for T2DM, rodent models with insulin resistance are used, including those with altered leptin signaling. A work horse in this regard are ZDF rats, which display leptin receptor mutations and develop insulin resistance and the metabolic syndrome when fed a high calorie diet.
   c. **Juliet Compston:** How do the changes in bone differ between the type 1 and type 2 models
   d. **Lorenz Hofbauer:** In these rodent models, bone mass and strength are decreased in diabetes at large. This differs from the human situation, where T1DM is associated with low BMD, whereas T2DM is associated with normal or even slightly higher BMD, but still higher fragility. Impaired bone quality has been suggested as a mechanism in human T2DM, possibly as a result of cortical porosity (see study by Janina Patsch, et al. JBMR).

II. **ASBMR Headquarters: What is current practice for fracture prevention in diabetic patients?**
   a. **Ann Schwartz:** Diabetic patients tend to be under-treated for fracture prevention. See Fraser et al 2014 study in Canada.
   b. **Lorenz Hofbauer:** Patients with diabetes mellitus should be evaluated for bone health, their risk of falls, and the presence of diabetic complications. Based on this comprehensive assessment, an individual therapeutic approach is required.
   c. **Ann Schwartz:** There are no specific guidelines for diabetic patients currently. Attention to nutrition and exercise as with other patients. Consider pharmacological therapy for those with high fracture risk per FRAX or BMD T-score.
   d. **Juliet Compston:** How well does FRAX perform in diabetics?
   e. **Ann Schwartz:** FRAX tends to under estimate risk in diabetics. It does predict fracture, but under estimates. One proposed solution is to check the RA box when doing estimate for a diabetic patient.

III. **ASBMR headquarters: Insulin is anabolic for bone, but type 2 diabetics are hyperinsulinemic and have higher rates of fracture. What's the explanation?**
   a. **Ann Schwartz:** While insulin is anabolic, DM could have effects on bone thru other pathways. Deficit in bone vasculature, kidney disease, peripheral neuropathy.
   b. **Ann Schwartz:** There is also new evidence that osteoblasts become insulin resistant.
   c. **Lorenz Hofbauer:** Insulin resistance by peripheral tissues, including bone cells leads to a lack of biological effects despite these high insulin levels. If this goes on for a while, the pancreas gets exhausted and produces less insulin, rendering patients insulin-dependent.

IV. **Juliet Compston: What are the changes in bone matrix composition in diabetics and are these also seen in animal models?**
   a. **Ann Schwartz:** Diabetics have higher levels of advanced glycation end products AGEs in bone collagen. Difficult to study in humans. Animal models show reduced toughness of bone with higher AGE levels.

b. **Lorenz Hofbauer:** There is a lot of research in this field. Just as hemoglobin is glycosylated, various ECM proteins, including type I collagen can get glycosylated. Some of these glycation products can be measured. For instance pentosidine has been shown as a marker for ECM glycosylation in human T2DM.
c. **Ann Schwartz:** Study by Farr et al (JBMR) with microindentation showed reduced bone toughness in diabetic women. But study didn't have measures of AGEs. Nice comment on the Farr study in JBMR by Jepsen. Also discussed at ASBMR Topical Meeting on Diabetes and Bone by Deepak Vashishth. See link to those talks.

V. **ASBMR headquarters: Should patients with diabetes have their AGE's measured for clinical decision making about treatment?**
a. **Ann Schwartz:** I don't think it would be helpful for risk assessment. FRAX can be fixed to provide adequate risk assessment. However, in future knowing AGE level might influence type of treatment. Do some therapies work better in context of low turnover and high AGE levels?
b. **Lorenz Hofbauer:** I fully agree. The measurement is not trivial and requires standardization. Right now, I would advise against measuring AGEs for clinical decision making. But it could be evaluated in future studies.

VI. **Juliet Compston: Should thiazolidendiones be avoided in diabetics with low BMD? What is known about the effects on bone of other drugs used in diabetics?**
a. **Ann Schwartz:** TZDs double fracture risk in women. Well established from analyses of adverse event reports from randomized trials. So, yes, would avoid TZDs in those with low BMD.
b. **Ann Schwartz:** In theory incretion-based medications might have bone effects since gut hormones also affect bone. Limited studies so far. Monami et al meta analysis showed lower fracture risk with DPP4 inhibitors. Su et al showed no overall effect with GLP1Ra but effects of liraglutide and exenatide differed.
c. **Lorenz Hofbauer:** Thiazolidendiones should be avoided in patients at risk for fractures.

VII. **Ann-Kristin Picke: Do you think that it is possible to create a realistic in vitro model to mimic the effects of type 2 diabetes mellitus on bone cells?**
a. **Lorenz Hofbauer:** Short answer: no.
b. **Ann-Kristin Picke:** Thanks!
c. **Lorenz Hofbauer:** As with many models, in vitro studies can provide insights into the cellular and molecular mechanisms, i.e. insulin signaling, PTH action in hyperglycemia, etc. But it only partially reflects the complex in vivo situation. Glucose levels for in vitro studies are typically 100-500 mM, that's close to raspberry jam...
d. **Ann-Kristin Picke:** Nice! What do you think about adding inflammation molecules or signaling molecules from adipocytes? Would you think this could be a step closer to an improved in vitro model?
e. **Lorenz Hofbauer:** Adipokines, such as leptin, adiponectin, and resistin and others have been shown to exert various effects on bone cells. Their action is not fully characterized. Adding these to an in vitro model makes the system even more complex. An alternative is to study cells derived from animals with loss or overexpression of these factors

f. **Ann-Kristin Picke:** I see, it is difficult! Thank you for answering my questions!

VIII. **Juliet Compston: What evidence is there that bone protective medications used in postmenopausal osteoporosis are effective in diabetics with osteoporosis?**

a. **Ann Schwartz:** Some limited evidence from post hoc analyses of trials of these drugs. One limitation is low numbers of T2D and very low numbers of T1D in these trials. Alendronate has similar efficacy in preventing bone loss comparing DM and nonDM women. Raloxifene has similar efficacy in preventing non-vertebral fracture in DM and nonDM.

b. **Lorenz Hofbauer:** The choice of osteoporosis therapy also depends on comorbidities of the diabetic patients. This is individualized medicine at its best. Oral vs. parenteral route of administration? GI problems? Renal function? Typically, you don't have all the options in a patient with advanced diabetes as compared to an otherwise healthy postmenopausal women with osteoporosis

IX. **Juliet Compston: Is cortical bone structure affected in diabetes?**

a. **Ann Schwartz:** Growing evidence of increased cortical porosity in T2D based on high resolution pQCT. Patsch et al JBMR. Yu EW et al 2015 - just published. Also presented at ASBMR (Samelson) - higher cortical porosity in DM in Framingham cohort. Intriguing because can have two people with same BMD but different cortical porosity. May account for observed greater bone fragility at a given BMD in T2D.

b. **Lorenz Hofbauer:** ...and this is not mirrored by standard DXA assessment.

X. **ASBMR headquarters:** How do you see the research landscape/direction in the effects of diabetes on bone changing over the next 5 years?

a. **Ann Schwartz:** Identification of key biomechanical deficit in diabetic bone will be an important step forward. Could be cortical porosity, AGE levels, other. With that information, it will be possible to better focus studies attempting to understand underlying pathophysiology. Instead of asking "how does DM affect bone" we can ask "how does DM lead to greater cortical porosity."

b. **Lorenz Hofbauer:** Prospective phase 3 studies in patients with T2DM

c. Ann Schwartz: I anticipate advances in clinical research on T1D and skeletal health. Very important for this population with high fracture risk. And research in T1D likely to help us understand T2D.

d. **Lorenz Hofbauer:** and better biomarkers that reflect glycosylation of the bone ECM

XI. **ASBMR headquarters: Are there significant obstacles you see that are restricting progress in closing the knowledge gap in this research area?**

a. **Ann Schwartz:** Lack of communication between diabetes and osteoporosis researchers is an important problem. Hard to say exactly what more collaboration would produce but I think it would provide better thinking about research ideas

b. **Lorenz Hofbauer:** Being open-minded and work in an interdisciplinary team helps. The ASBMR Diabetes and Bone Symposium was a good starting point. Let's keep the momentum.

XII. **ASBMR headquarters: What about type 1 diabetic patients? Do they have worse bone? Respond to bone meds any differently?**

a. **Ann Schwartz:** T1D have lower BMD than non-DM patients but reduction is modest. They have higher hip fracture risk than would be expected from the level of reduction in BMD. Suggests a bone quality problem in addition to the lower BMD. T1D have very high risk of hip fracture - 6 times higher in meta-analysis.
b. **Lorenz Hofbauer:** Typically, the large phase 3 studies have about 10% of patients with T2DM included. Sub-analysis for alendronate and denosumab show that these drugs work equally well in diabetic and non-diabetic women with postmenopausal osteoporosis. There are no studies on what type of osteoporosis drug is ideal for patients with T1DM.
c. **Lorenz Hofbauer:** From a pathophysiological point of view, bone-anabolic therapy may be required for extremely low bone mass and high fragility. But that's my personal opinion.
d. **Henrique Carrico da Silva:** If bone affected by diabetes have AGE, do you believe that anti -reabsorptives have the same action or guarantee of efficacy as in non-diabetics patients?
e. **Ann Schwartz:** There is theoretical concern about effect of anti-resorptives in presence of high levels of AGEs, based on animal models. May allow greater accumulation of AGEs which are cleared out with bone turnover. But, no clinical evidence that I'm aware that anti-resorptives lack efficacy in presence of AGEs.
f. **Lorenz Hofbauer:** That's not clear at present. We should also emphasize the need for improved glycemic control, probably the best way of preventing AGE accumulation in the skeleton. I have rarely seen a diabetic patient with a HBA1c of 6.5% and high bone fragility.
g. **Ann Schwartz:** Good point on glycemic control. There are several studies now showing increased fracture risk with poor glycemic control. Including Li et al 2015 JBMR. We didn't see reduction in fracture risk with intensive glycemic control in ACCORD but that compared median A1C of 6.4% and 7.5%. Probably not a large enough difference in glycemic control to measurably affect fracture risk.

XIII. **Fay Louise: How does adding vit k2 help with diabetes and bone strength? What is not clear to me is that uncarboxylated osteocalcin is one of the factors in calcium dysregulation, but, carboxylated oc increases blood sugar,...? confusing, diabetes and bone metabolism are intimately linked, so i would think that the combination of adding supps vit d3 and vit k2 would help with carboxylation of osteocalcin. anyone know?**

a. **Ann Schwartz:** Agree it's confusing. Some thoughts: Vitamin K2 will reduce the proportion of osteocalcin that is uncarboxylated. Not clear that vit k2 will reduce fracture risk although it's used in Japan. I believe it's not used alone but is prescribed in combination with other osteoporosis therapies. ucOC and total OC are higher in T2D in cross-sectional studies, possibly because bone formation is lower in T2D. Low ucOC increases susceptibility to high fat diet induced diabetes in rodent models. But not established in human studies that ucOC is associated with risk of incident diabetes. For example, anti-resorptive therapy which lowers ucOC and total OC doesn't increase risk of diabetes.

XIV. **Zay Khan: What is the role of Wnt/b-catenin signaling in Diabetes?**

a. **Lorenz Hofbauer:** That is still an area of research. Some components of the signaling pathway, including its ligands, receptors and inhibitors may function differently in a glycosylated status.

XV. **Juliet Compston: Should all diabetic patents have a BMD measurement?**

a. **Ann Schwartz:** I would apply same guidelines as with non-DM patients. For example, postmenopausal women 65 and older should have a BMD in the US. Providers should not assume that diabetic patients don't need a BMD scan.

b. **Lorenz Hofbauer:** The recently published German/Austrian/Swiss guidelines recommend lab exam and DXA in T1DM in all postmenopausal women and men above 60 and in T2DM in all postmenopausal women and men above 70.

c. **Henrique Carrico da Silva:** I know that there are no cutoffs for others techniques , but in T2DM, whatever complimentary, is not interesting to use them? Mainly techniques that access the structure, patterns of trabecular bone?

d. **Lorenz Hofbauer:** CT-based technologies provide greater details on the cortical vs. trabecular compartment. Detection of cortical porosity requires to employ these technologies.