Diabetes and Osteoporosis

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objectives

- Impact of Diabetes Mellitus on Osteoporosis and vise versa
- Prevalence of OP in Diabetics
- Diabetes mellitus and risk of bone fracture
- Diabetes mellitus and bone microarchitecture
- Mechanisms of increased bone fragility in diabetes mellitus
- Impact of diabetes treatments on bone metabolism
- Impact of low bone mass treatments on diabetes mellitus
- Evaluation of bone health in T1DM and T2DM

Clinical cases

- 58 year-old postmenopausal woman with a normal weight, menopause at age 44
- **Type 1 diabetes** diagnosed at age 2
- Complications of diabetes (nerve, kidney and eye damage)
- Blood glucose not optimal: HbA_{1c} generally around 8-8.5% with frequent hypoglycemic episodes
- Meds for cholesterol and hypertension, insulin, vitamin D and calcium supplements
- No fracture but fall in the last year
- Low bone mineral density (BMD) test

- 58 year-old postmenopausal woman with obesity
- **Type 2 diabetes** diagnosed at age 40
- Complications of diabetes (nerve, kidney and eye damage)
- Blood glucose not optimal: HbA_{1c} generally around 7.5-8%
- Meds for cholesterol and hypertension, diabetes pills (metformin, empagliflozin, semaglutide, gliclazide), vitamin D and calcium supplements
- No fracture but fall in the last year
- Normal BMD test

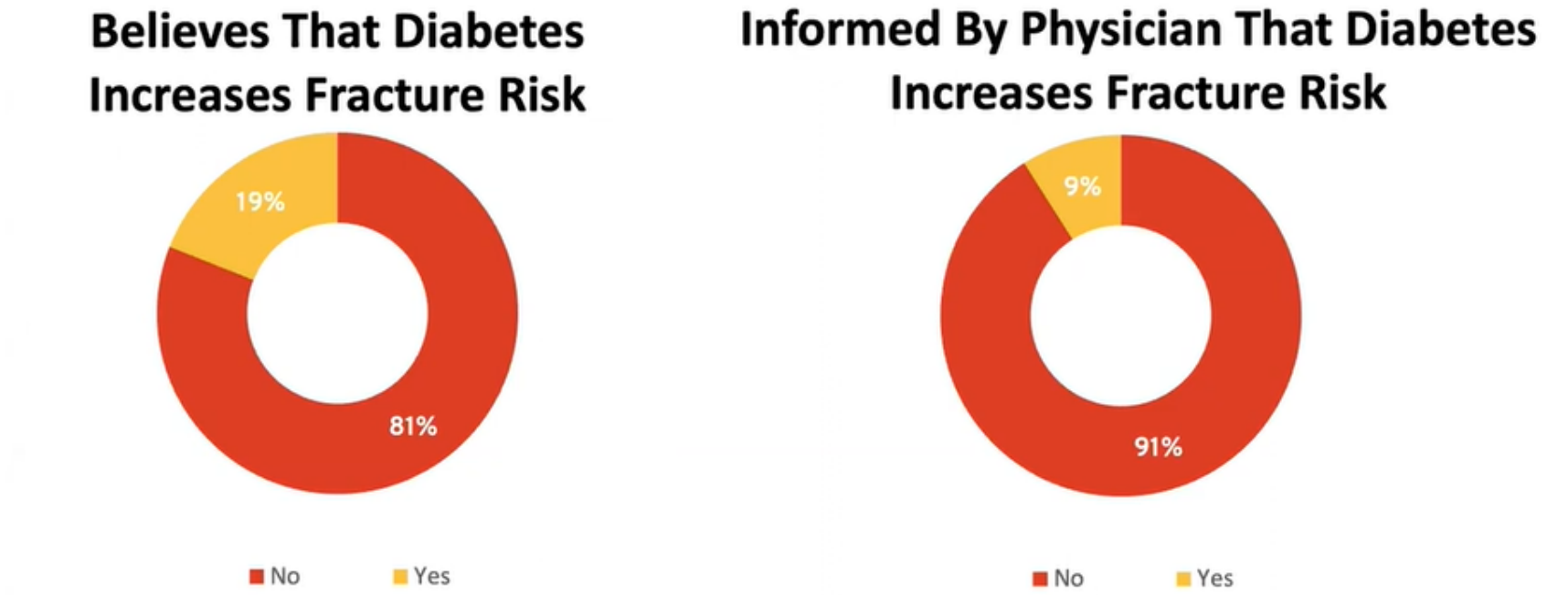
Introduction

Osteoporosis (OP) and diabetes mellitus (DM): two major healthcare issues in the world

- **OP :**
  - older people
  - individuals with predisposing health condition
  - a serious public health concern attributable to its high morbidity, mortality, and healthcare costs
- **DM:**
  - a global health concern:
    - 10.2% in 2030
    - 10.9% in 2045
  - poses a major hazard to human health
  - associated with an increased risk of fracture, particularly the hip fracture,
  - despite normal or high bone mineral density (BMD) in T2DM

Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the international diabetesfederation diabetes atlas, 9(th) edition. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Diabetes Res Clin Pract. 2019;157:107843.

Bone Disease:
An under-recognized Complication of Diabetes



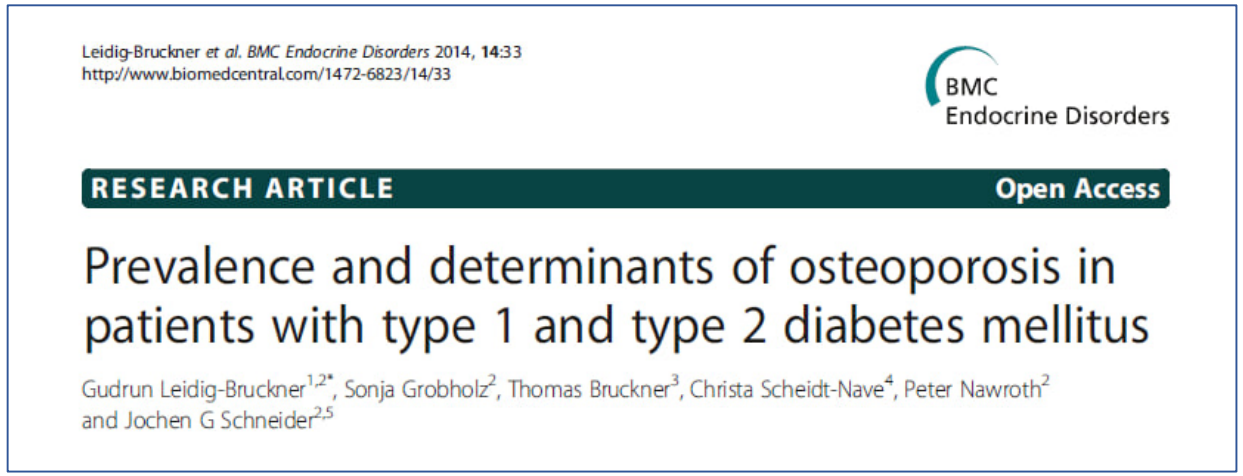
Drummond K et al, presented at the 2021 American Society for Bone and Mineral Research Annual Meeting.

A survey across Canada included people with T1DM and T2DM whether DM increase the risk of Fx.

A survey across Canada included people with T1DM and T2DM whether if they informed by their physician that DM increase risk of Fx.

The prevalence of OP in Diabetic patients

Epidemiologic significanse



Leidig-Bruckner *et al. BMC Endocrine Disorders* 2014, **14**:33
http://www.biomedcentral.com/1472-6823/14/33

BMC Endocrine Disorders

RESEARCH ARTICLE Open Access

Prevalence and determinants of osteoporosis in patients with type 1 and type 2 diabetes mellitus

Gudrun Leidig-Bruckner[1,2*], Sonja Grobholz[2], Thomas Bruckner[3], Christa Scheidt-Nave[4], Peter Nawroth[2] and Jochen G Schneider[2,5]

Background: Increased **risk of osteoporosis** and its **clinical significance** in patients with diabetes is **controversial**.

They analyzed osteoporosis prevalence and determinants of bone mineral density (BMD) in patients with type 1 and 2 diabetes.

- Osteoporosis prevalence (BMD T-score < −2.5 SD) at FN and LS was equivalent in the **type 1** and **type 2** diabetes groups,

- but **compared with controls** type 2 patients had lower prevalence of OP**:**
  - **FN:** 13.0% vs 21.2%, **LS:** 6.1% vs 14.9% men;
  - **FN:** 21.9% vs 32.1%, **LS:** 9.4% vs 26.9% women.

- Osteoporosis prevalence was **higher at FN-BMD** than at LS-BMD.

- BMD was **positively correlated with BMI** and **negatively correlated with age**, but not correlated with diabetes-specific parameters (therapy, HbBA1c, micro- and macrovascular complications) in all subgroups.

Prevalence and determinants of osteoporosis in patients with type 1 and type 2 diabetes mellitus.
Leidig-Bruckner G, Grobholz S, Bruckner T, Scheidt-Nave C, Nawroth P, Schneider JG. BMC Endocr Disord. 2014 Apr 11;14:33.

Liu *et al. BMC Endocrine Disorders* (2023) 23:1
https://doi.org/10.1186/s12902-022-01260-8

BMC Endocrine Disorders

RESEARCH Open Access

Prevalence of osteoporosis in patients with diabetes mellitus: a systematic review and meta-analysis of observational studies

Xueying Liu, Fuhua Chen, Lei Liu and Qiu Zhang*

Background: Osteoporosis (OP) and diabetes mellitus (DM) are **two major healthcare issues in the world.**

Numerous population based-studies have reported **an increased prevalence of OP among individuals with DM,** though, estimates vary significantly.

The objective of this study is **to estimate the prevalence of OP in patients with DM**.

- **Methods:**
  - To identify relevant literature, PubMed, Embase, Medline, CBM and Cochrane Library were searched for studies published from inception **till July 2022**.
  - The search was conducted, and studies were included without countries and language restrictions.

- **Results:** A high OP prevalence of 27.67% (95% confidence interval (CI) 21.37-33.98%) was found in a pooled analysis of 21 studies involving 11,603 T2DM patients.

Conclusions: Worldwide, a high prevalence of OP was found in patients with T2DM.
Therefore, strong measures to prevent and treat osteoporosis in diabetic patients are required.

Prevalence of osteoporosis in patients with diabetes mellitus: a systematic review and meta-analysis of observational studies. BMC Endocr Disord ; Liu X, Chen F, Liu L, Zhang Q.. 2023 Jan 3;23(1):1.

Diabetes Mellitus
and
risk of bone fracture

Systematic Review of Type 1 and Type 2 Diabetes Mellitus and Risk of Fracture

American Journal of Epidemiology
Vol. 166, No. 5
DOI: 10.1093/aje/kwm106
Advance Access publication June 16, 2007

Meta-Analysis

Systematic Review of Type 1 and Type 2 Diabetes Mellitus and Risk of Fracture

Mohsen Janghorbani[1,2], Rob M. Van Dam[2], Walter C. Willett[2,3], and Frank B. Hu[2,3]

[1] Department of Epidemiology and Biostatistics, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran.
[2] Department of Nutrition, Harvard School of Public Health, Boston, MA.
[3] Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.

Received for publication August 20, 2006; accepted for publication March 7, 2007.

- **Research**: the association between diabetes mellitus and fracture.
- **a systematic review** of published data
- **Search in MEDLINE** through June 2006 and examined the reference lists of pertinent articles (limited to studies in humans).
- **Summary relative risks and 95% confidence intervals** were calculated with a random-effects model.
- **The 16 eligible studies** (two case-control studies and 14 cohort studies)
- Included 836,941 participants and 139,531 incident cases of fracture.
- Results were **consistent between studies of men and women** and **between studies conducted in the United States and Europe**.

Systematic Review of Type 1 and Type 2 Diabetes Mellitus and Risk of Fracture
M. Janghorbani, R. M. Van Dam, W. C. Willett and F. B. Hu
American Journal of Epidemiology 2007 Vol. 166 Issue 5 Pages 495-505

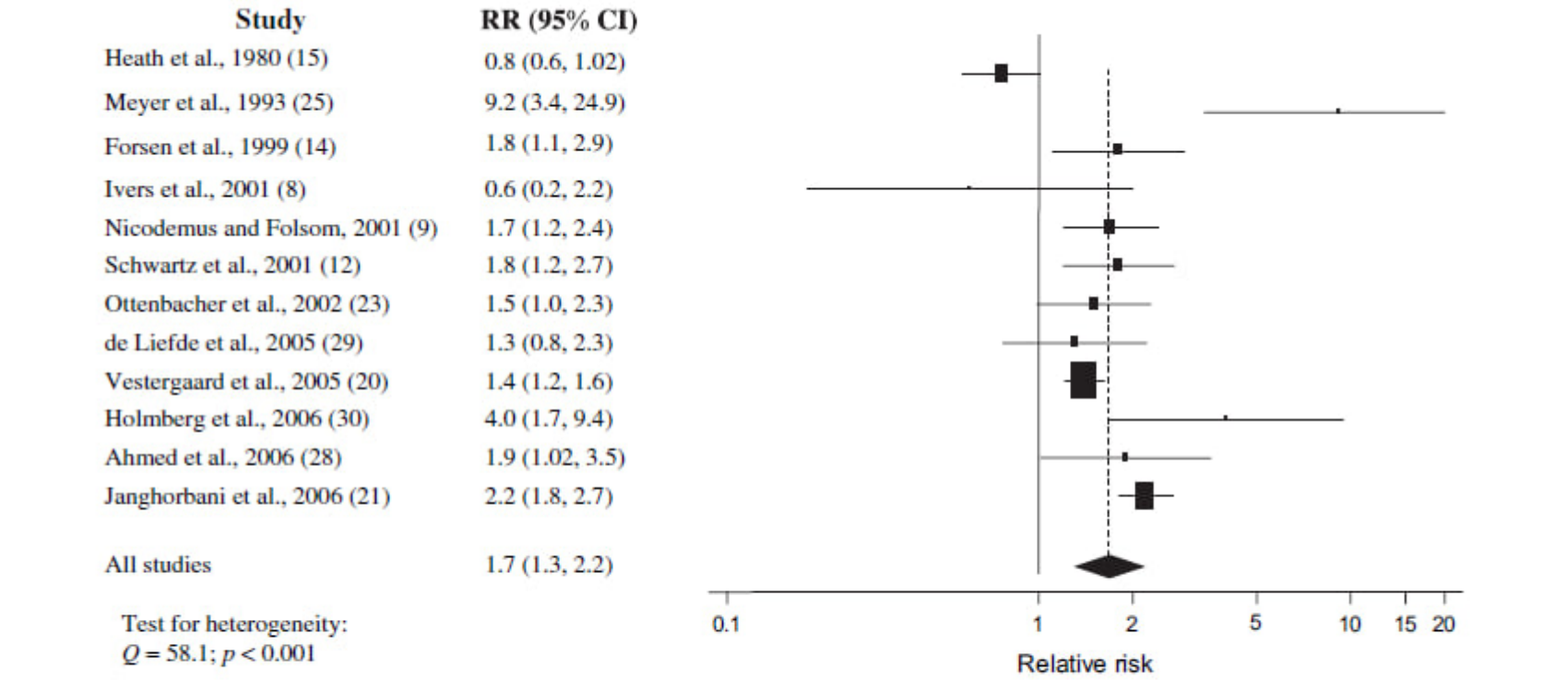


FIGURE 1. Association between type 2 diabetes mellitus and risk of hip fracture in case-control and cohort studies. Each square shows the study-specific relative risk (RR) estimate (the size of the square reflects the study-specific statistical weight, that is, the inverse of the variance), and the horizontal line shows the related 95 confidence interval (CI). The diamond shows the summary RR estimate, and its width represents the corresponding 95% CI. All statistical tests were two-sided. Statistical heterogeneity between studies was assessed with Cochran's *Q* test.

Association between type 2 diabetes mellitus and risk of hip fracture in case-control and cohort studies

Type 2 diabetes was associated with an increased risk of hip fracture in both **men** (summary relative risk (RR) = **2.8,** 95% confidence interval (CI): 1.2, 6.6) and **women** (summary RR = **2.1,** 95% CI: 1.6, 2.7).

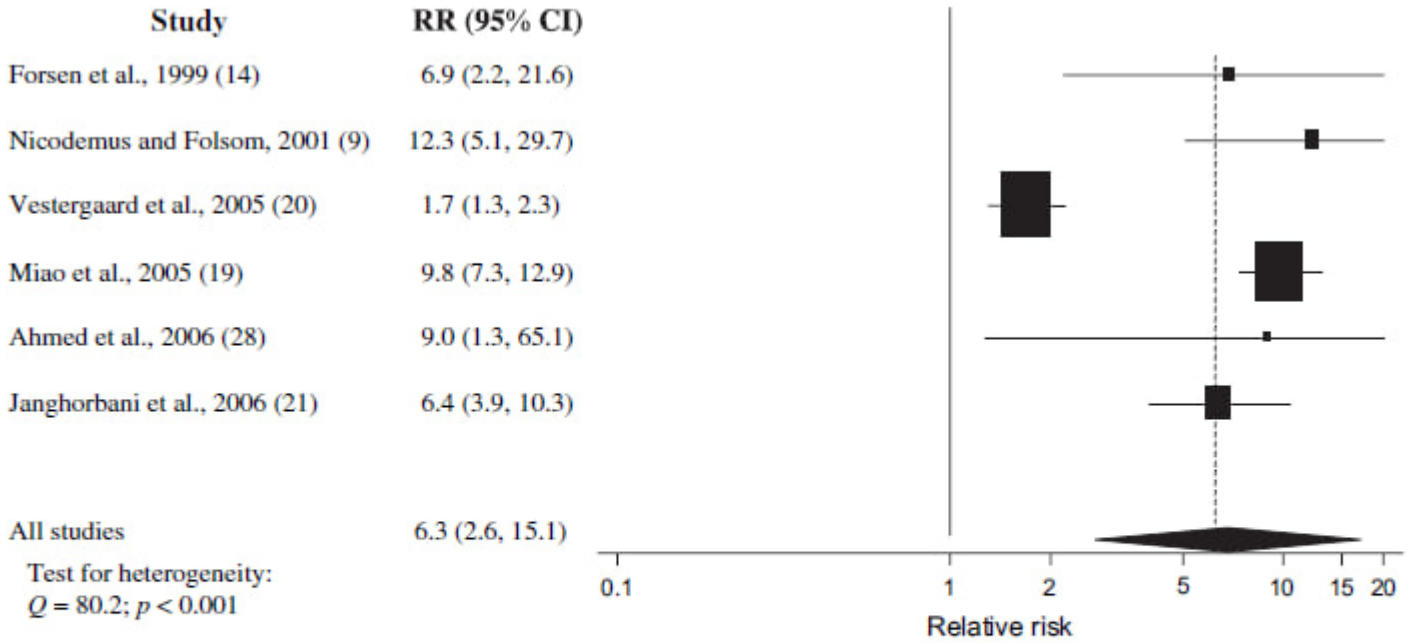


FIGURE 2. Association between type 1 diabetes mellitus and risk of hip fracture in case-control and cohort studies. Each square shows the study-specific relative risk (RR) estimate (the size of the square reflects the study-specific statistical weight, that is, the inverse of the variance), and the horizontal line shows the related 95 confidence interval (CI). The diamond shows the summary RR estimate, and its width represents the corresponding 95% CI. All statistical tests were two-sided. Statistical heterogeneity between studies was assessed with Cochran's *Q* test.

Am J Epidemiol 2007;166:495–505

Association between type 1 diabetes mellitus and risk of hip fracture in case-control and cohort studies

The association between type 1 diabetes and hip fracture incidence:
(summary RR = **6.3,** 95% CI: 2.6, 15.1)

- Individuals with type 1 and type 2 diabetes mellitus **share a common complication** of greater fracture risk relative to controls without DM.

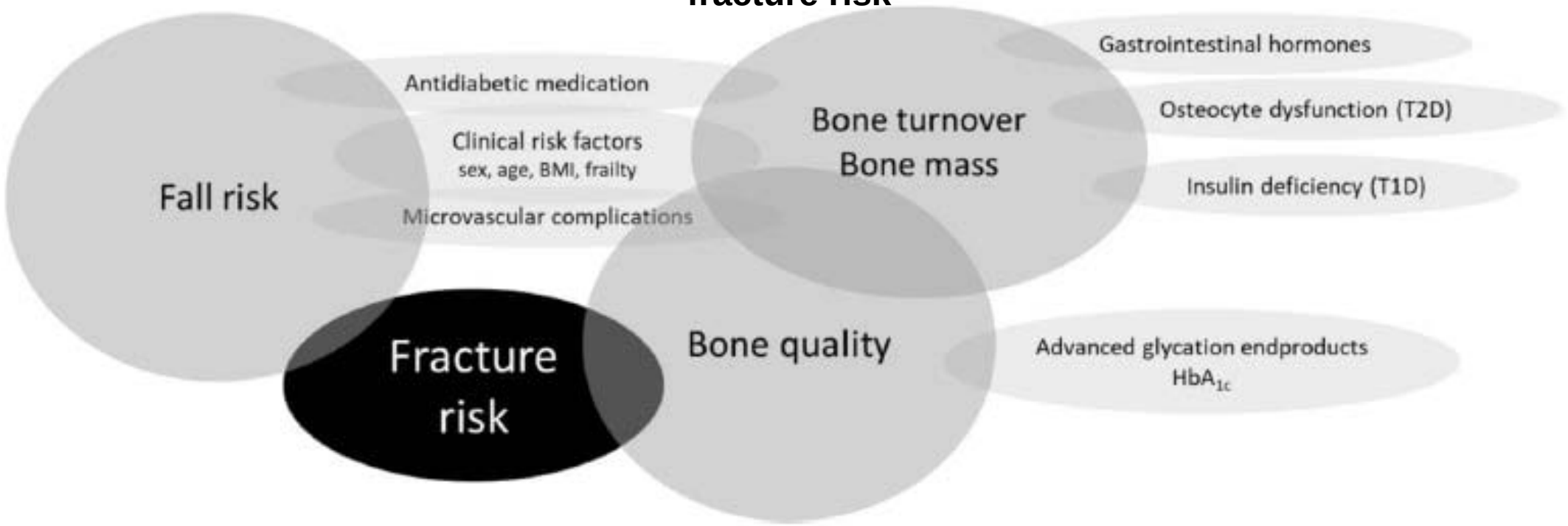
- In meta analyses, **the risk of hip fracture was** greater in individuals with T1DM (RR = 6.9 , 6.3) and in individuals with T2DM (RR = 1.4 , 1.7) both compared to controls without DM.

- **Thus, the increase in relative hip fracture risk was higher in T1DM than in T2DM.**

Systematic Review of Type 1 and Type 2 Diabetes Mellitus and Risk of Fracture
M. Janghorbani, R. M. Van Dam, W. C. Willett and F. B. Hu
American Journal of Epidemiology 2007 Vol. 166 Issue 5 Pages 495-505

Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes—a meta-analysis
P. Vestergaard
Osteoporosis International 2007 Vol. 18 Issue 4 Pages 427-444

In diabetes, bone disease is caused by underlying mechanisms that **impair bone quality** and **increase fracture risk**



Summary of the different factors that contribute to the increased fracture risk in patients with diabetes
BMI, body mass index; T1D, type 1 diabetes; T2D, type 2 diabetes; HbA1c, glycosylated hemoglobin

Diabetes and bone
K. Hygum, J. Starup-Linde and B. L. Langdahl
Osteoporosis and Sarcopenia 2019 Vol. 5 Issue 2 Pages 29-37

Diabetes mellitus and bone microarchitecture

- Type 1 diabetics have low bone mineral density **and a six- to sevenfold higher risk for fractures**, while
- type 2 diabetics have normal to high bone mineral density and up to **threefold higher fracture risk.**

- Thus, the situation seems more complex in T2DM as **BMD is elevated**, and **the bone quality alterations are multifactorial.**

- Despite the similarity of chronic hyperglycemia, T1DM and T2DM have distinct pathophysiological mechanisms, which may differently affect bone metabolism.

- In both cases, the underlying mechanisms of poor bone strength are not well understood.

Update on the impact of type 2 diabetes mellitus on bone metabolism and material properties.
Picke, A., Campbell, G., Napoli, N., Hofbauer, L. C., & Rauner, M. (2019).
Endocrine Connections, 8(3), R55-R70.

Glycemic control and bone mineral density in children and adolescents with type 1 diabetes

Gitte B. Fuusager[1,2,3] | Henrik T. Christesen[1,2] | Nikolaj Milandt[4] | Anders J. Schou[1,5]

- Poor glycemic status **can adversely affect BMD during childhood and adolescence,** even though dual-energy X-ray absorptiometry (DXA) may not identify osteoporotic range for BMD.

Glycemic control and bone mineral density in children and adolescents with type 1 diabetes. Fuusager GB, Christesen HT, Milandt N, Schou AJ *Pediatr Diabetes* 2019; **20**: 629-63.

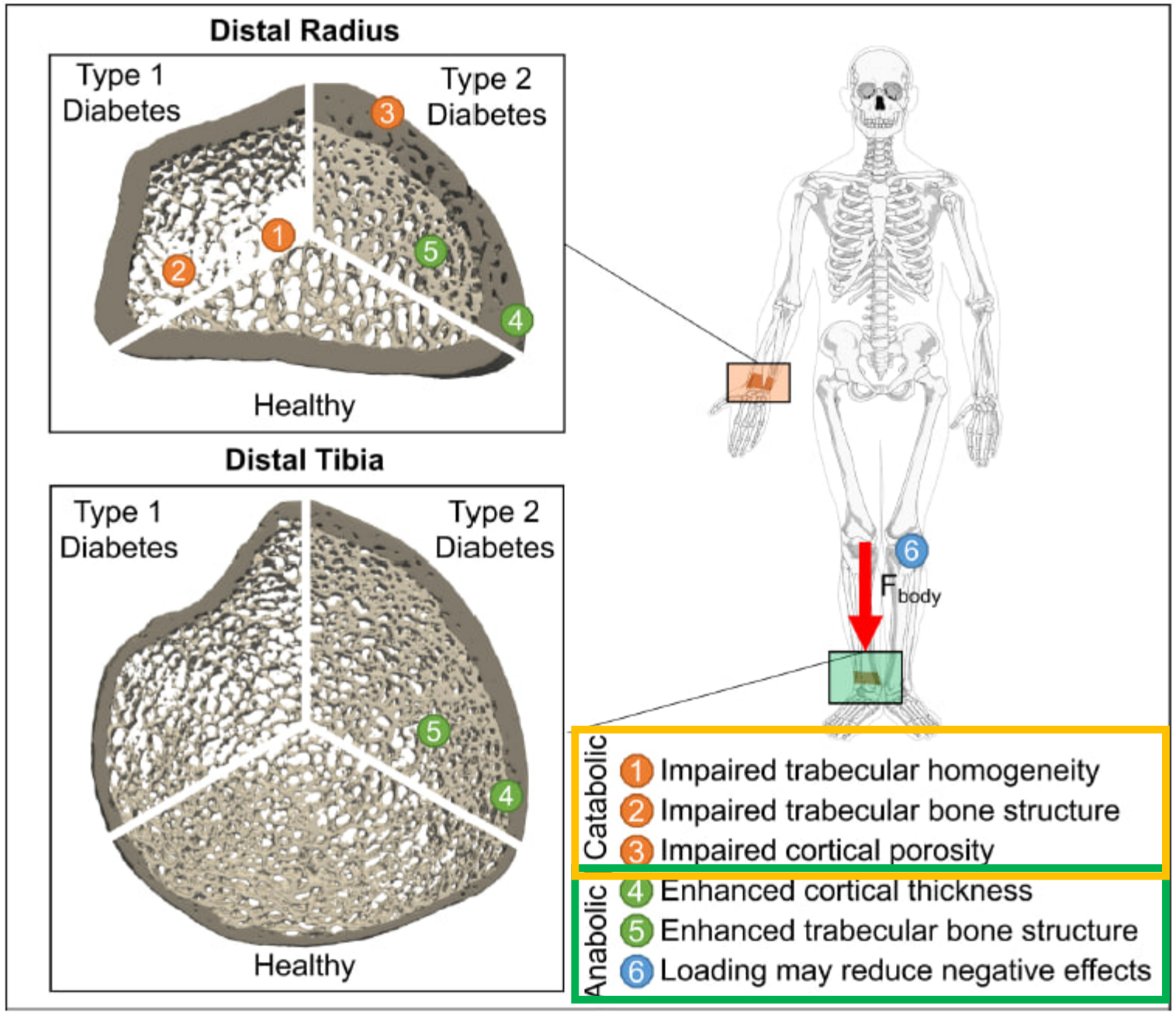
- An inverse correlation between BMD scores with glycated hemoglobin/hemoglobin A1c (HbA1c) and the duration of diabetes has been noticed in many but not all studies, yet the **association with microvascular complications have been more consistent**.

Decreased lumbar spine bone mass and low bone turnover in children and adolescents with insulin dependent
diabetes mellitus followed longitudinally.
Gunczler P, Lanes R, Paz-Martinez V, Martins R, Esaa S, Colmenares V, Weisinger JR.
J Pediatr Endocrinol Metab 1998; 11: 413-419

Quantitative volumetric bone mineral density and microarchitecture in patients with diabetes

- High-resolution peripheral computed tomography (HR-pQCT)
- A clinically applicable, 3-dimensional, volumetric imaging technique;
- For studying bone microarchitecture in vivo.
- As a research tool, may be used to:
  - detect treatment effects through changes in erosion volume in as little as 3 months.
  - It assess quantitative volumetric bone mineral density and microarchitecture in patients with diabetes, including characteristics of:
    - trabecular (e.g. number, thickness and separation) and
    - cortical bone (e.g. thickness and porosity).

Meta-analysis of Diabetes Mellitus-Associated Differences in Bone Structure Assessed by High-Resolution Peripheral Quantitative Computed Tomography
M. Walle, D. E. Whittier, M. Frost, R. Müller and C. J. Collins
Current Osteoporosis Reports 2022 Vol. 20 Issue 6 Pages 398-409



Graphical summary of the meta-analysis

- Computer generated illustration of distal radius and distal tibia bone microarchitecture in type 1 and type 2 diabetes mellitus **compared to healthy controls.**
- Annotations 1–3 show **impaired bone microarchitecture characteristics**, while annotations 4–5 show **enhanced bone microarchitecture characteristics.**
- Increased loading (6) at the weight-bearing tibia may explain differences in bone microarchitecture at the radius and tibia

Meta-analysis of Diabetes Mellitus-Associated Differences in Bone Structure Assessed by High-Resolution Peripheral Quantitative Computed Tomography

M. Walle, D. E. Whittier, M. Frost, R. Müller and C. J. Collins

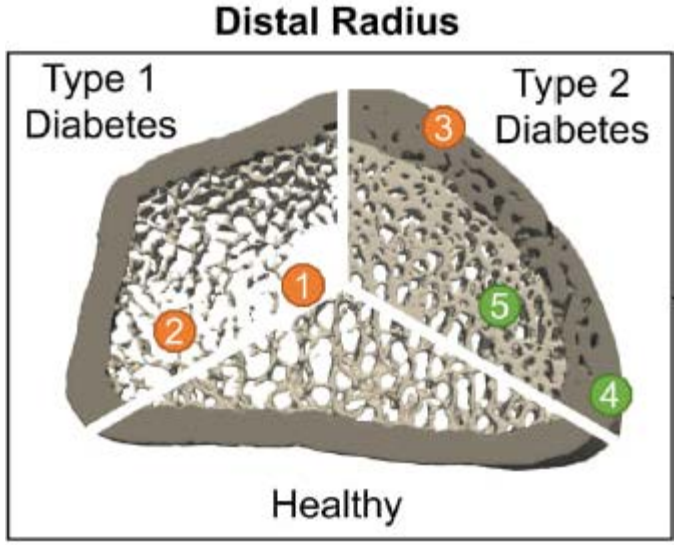
Current Osteoporosis Reports 2022 Vol. 20 Issue 6 Pages 398-409

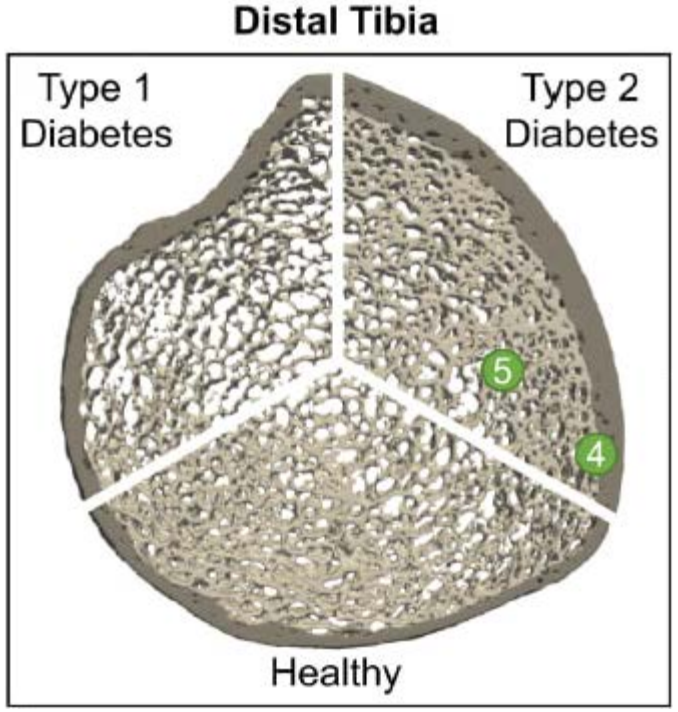
Conclusion

- T1DM:
  - Primarily causes adverse **trabecular** characteristics
- T2DM:
  - Primarily causes adverse **cortical** characteristics

- These adverse effects were more severe **at the radius** than the tibia, possibly resulting from differences in site-specific conditions such as physiological loading.
- Diabetes patients exhibit different, if not contradictory, alterations in cortical and trabecular microarchitecture that **are not detectable using current clinical standard evaluation methods such as dual-energy Xray absorptiometry.**

- This study highlights the significance of HR-pQCT imaging in the assessment of skeletal complications to T1DM and T2DM.





Meta-analysis of Diabetes Mellitus-Associated Differences in Bone Structure Assessed by High-Resolution Peripheral Quantitative Computed Tomography
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TBS

- Results of the trabecular bone score (TBS) in T1DM have been inconsistent.
- Diabetics with microvascular disease have been seen to have **lower total, cortical and trabecular volumetric BMD** on high-resolution peripheral quantitative computed tomography (HRpQCT) of the radius.

Bone Geometry, Volumetric Density, Microarchitecture, and Estimated Bone Strength Assessed by HRpQCT in Adult Patients With Type 1 Diabetes Mellitus.

Shanbhogue VV, Hansen S, Frost M, Jørgensen NR, Hermann AP, Henriksen JE, Brixen K.

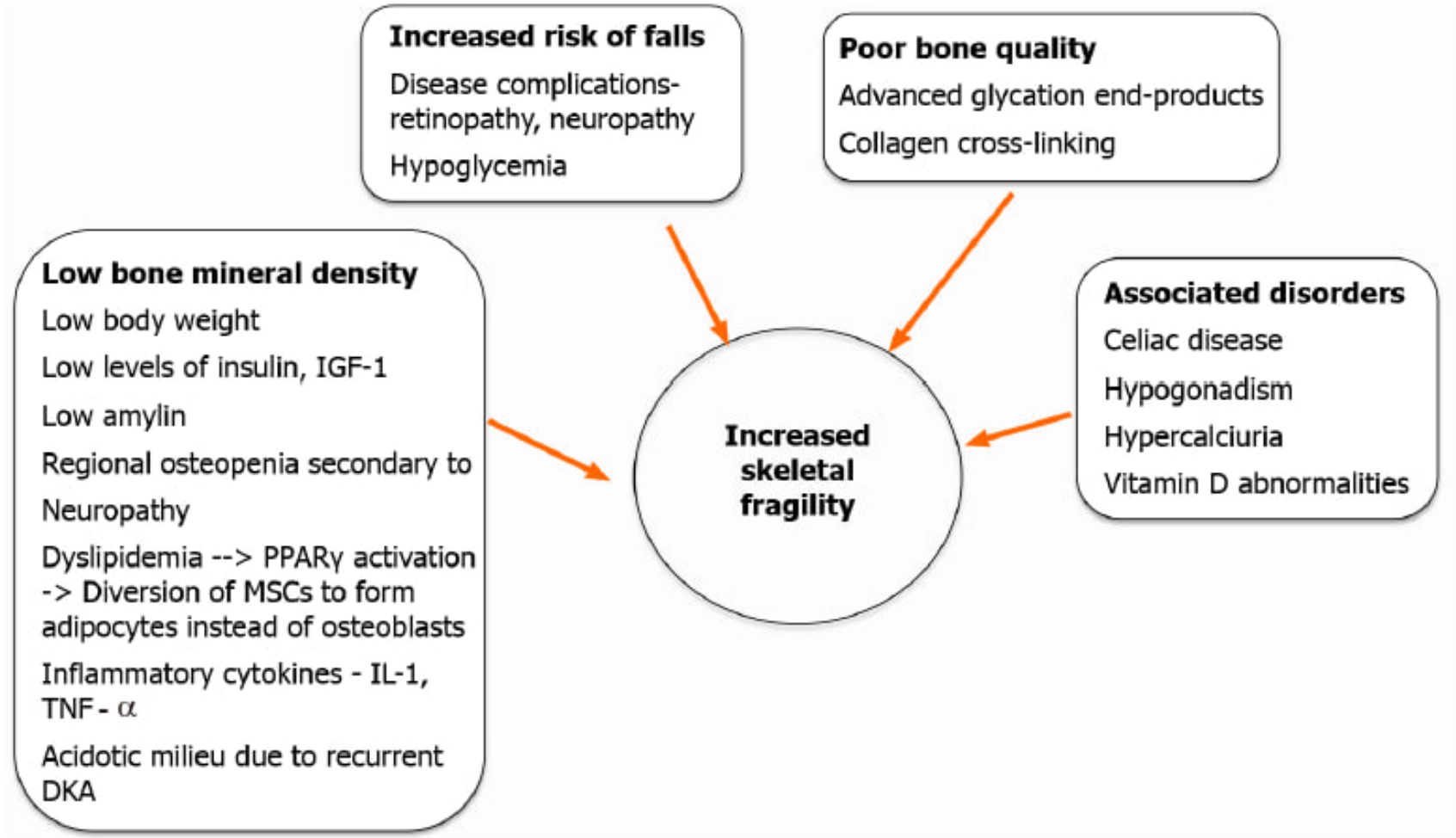
J Bone Miner Res 2015; 30: 2188-2199

Nonosseous factors contributing to bone fragility in T1DM

- Recurrent hypoglycemic episodes,
- Low body weight,
- Microvascular complications especially peripheral neuropathy,
- Autonomic neuropathy and retinopathy
- **Concomitant uncorrected:**
  - hypothyroidism,
  - celiac disease,
  - hypogonadism and
  - low IGF-1 levels
  - can also contribute to poor muscle strength.

Critical review of bone health, fracture risk and management of bone fragility in diabetes mellitus.
Palui R, Pramanik S, Mondal S, Ray S. *World J Diabetes* 2021; 12(6): 706-729

Summary:
Mechanisms of increased bone fragility in type 1 diabetes mellitus



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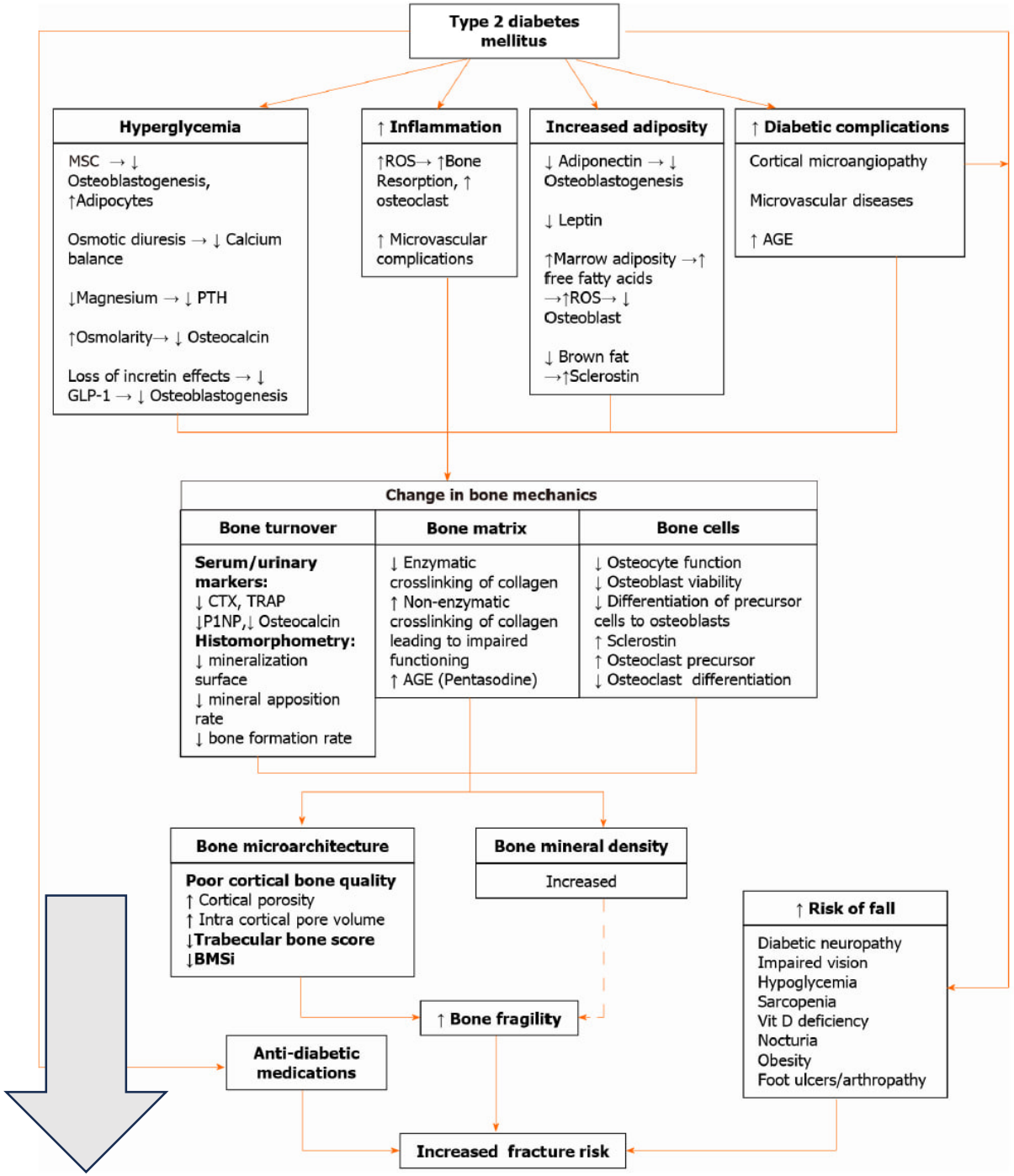


Summary: Mechanisms underlying bone fragility in type 2 diabetes mellitus

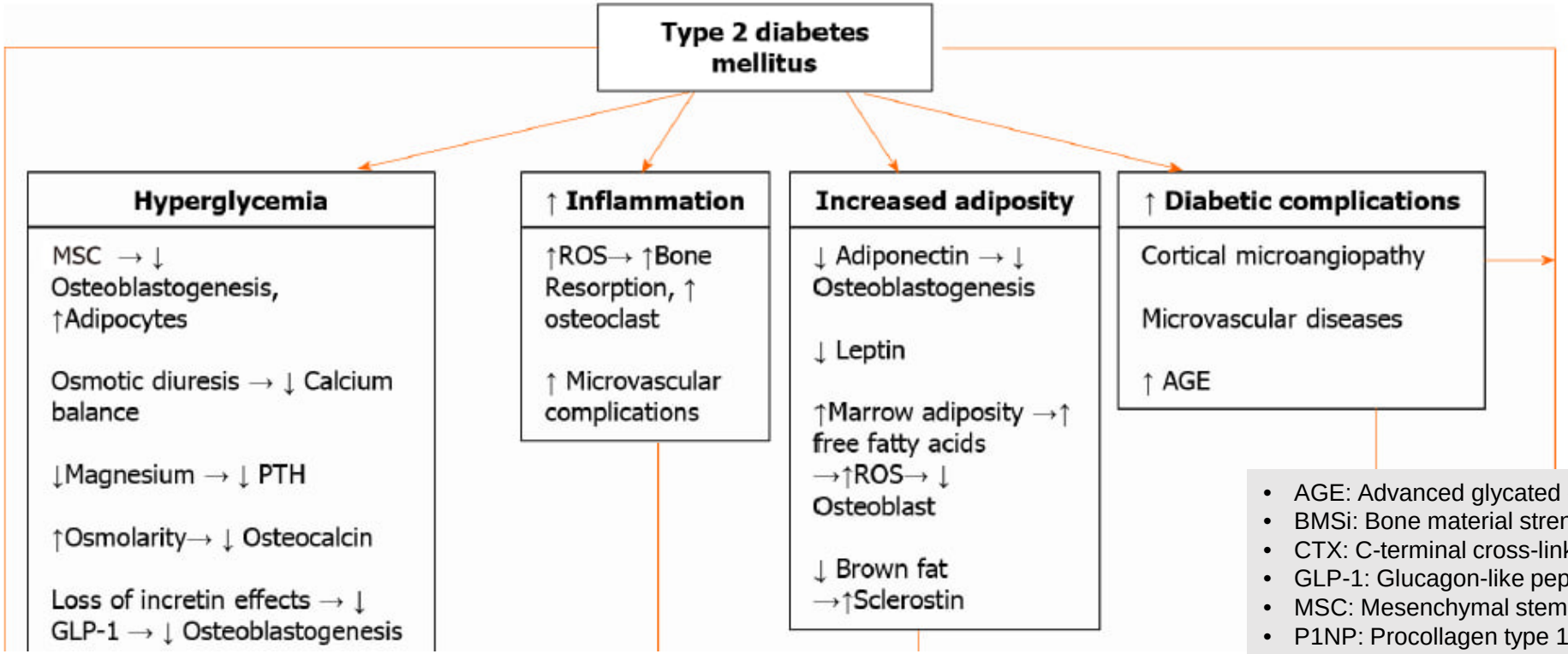
Bone formation markers	Bone resorption markers
Osteocalcin	C-Telopeptide of Collagen Cross-links (CTx)
Bone Specific Alkaline Phosphatase (BSAP)	N-Telopeptide of Collagen Cross-links (NTx)
Carboxyterminal propeptide of Type I Collagen (P1CP)	Pyridinolines
Aminoterminal propeptide of Type I Collagen (P1NP)	Deoxypyridinoline
	Tartrate-Resistant Acid Phosphatase (TRAP)

AGE: Advanced glycated end product;
BMSi: Bone material strength index;
CTX: C-terminal cross-linked telopeptide;
GLP-1: Glucagon-like peptide-1;
MSC: Mesenchymal stem cells;
P1NP: Procollagen type 1 N-terminal propeptide;
PTH:Parathyroid hormone;
ROS: Reactive oxygen species;
TRAP: Tartrate-resistant acid phosphatase.

Critical review of bone health, fracture risk and management of bone fragility in diabetes mellitus.
Palui R, Pramanik S, Mondal S, Ray S. *World J Diabetes* 2021; 12(6): 706-729

Mechanisms underlying bone fragility in type 2 diabetes mellitus

The increased fracture risk in T2DM is due to
increased bone fragility and **a greater risk of falls** in these patients.



- AGE: Advanced glycated end product;
- BMSi: Bone material strength index;
- CTX: C-terminal cross-linked telopeptide;
- GLP-1: Glucagon-like peptide-1;
- MSC: Mesenchymal stem cells;
- P1NP: Procollagen type 1 N-terminal propeptide; PTH: Parathyroid hormone;
- ROS: Reactive oxygen species;
- TRAP: Tartrate-resistant acid phosphatase.

- Sclerostin is produced primarily by the osteocytes and is a complex protein capable of uncoupling bone formation and bone resorption by inhibiting osteoblast function while stimulating bone resorption

Critical review of bone health, fracture risk and management of bone fragility in diabetes mellitus.
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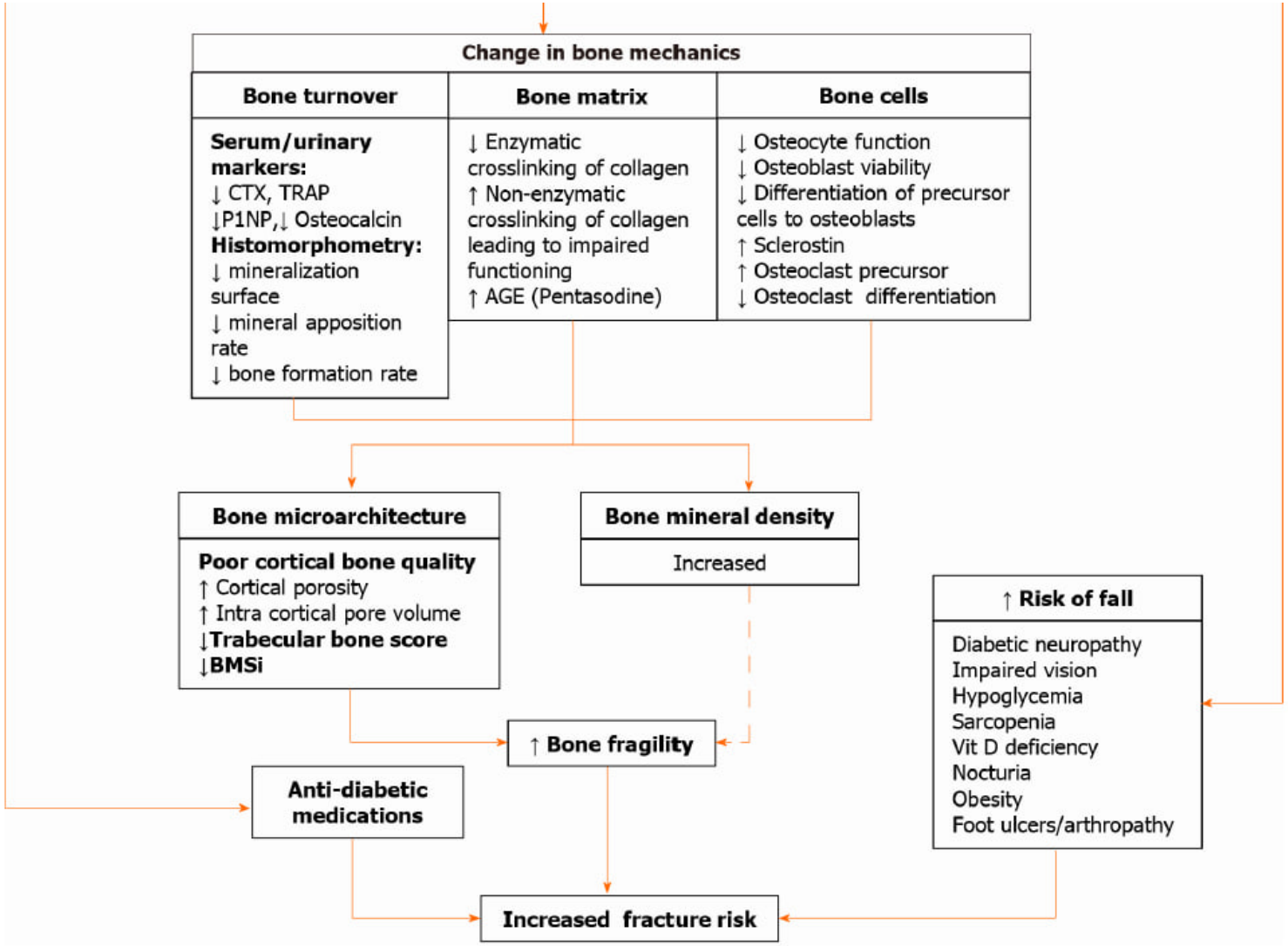
Mechanisms underlying bone fragility in type 2 diabetes mellitus



Critical review of bone health, fracture risk and management of bone fragility in diabetes mellitus. Palui R, Pramanik S, Mondal S, Ray S. *World J Diabetes* 2021; 12(6): 706-729

Summary:
Differences and similarities of bone effects in T1DM and T2DM

Diabetes mellitus type 1	Both types of diabetes mellitus	Diabetes mellitus type 2
Decreased BMD • An absolute deficiency of insulin secretion resulting in **insufficient bone mineralization** during adolescence • Low peak bone mass	**Impaired bone microarchitecture** • Low level of *C*-terminal cross-linked telopeptide (CTX) and osteocalcin • High level of sclerostin • Decreased IGF-1 • Increased AGEs leading to reduced collagen elasticity and inhibition osteoblasts • Microvascular disease inflammation	Normal to Increased BMD Insulin resistance and increased insulin secretion, resulting in **increased bone mineralization**
Significantly higher risk of hip fracture	• **Bone microarchitectural damage** • **Diabetes-induced falls**	**Increased fracture risk of hip, spine, and forearm fractures**

AGEs – advanced glycation end products, BMD – bone mineral density, IGF-1 – insulin-like growth factor-1.

Osteoporosis and diabetes - possible links and diagnostic difficulties. Tomasiuk JM, Nowakowska-Płaza A, Wisłowska M, Głuszko P. Reumatologia. 2023;61(4):294-304. doi: 10.5114/reum/170048. Epub 2023 Sep 3.

IMPACT OF DIABETES TREATMENTS ON BONE METABOLISM

Treatment	Animal *in vivo* studies				Human *in vivo* studies			
	Bone formation	Bone resorption	BMD	Fracture healing	Bone formation	Bone resorption	BMD	Fracture risk
Antidiabetic treatment								
Metformin	↑	↓	↑*	↑	↓/=	↓/=	↑/=	↓/=
Thiazolidinediones	↓	↑	↓/=	?	↓/=/↑	↑/=/↑	↓/=	↑/=
Insulin	↑	=	↑/=	↑	=	=	=	↑/=
Sulphonyl urea	↑	↓	↑	?	↑/=	↓/=	=	↑
Incretins	↓	↓	↑/=	?	↓/=	↓/=	↑/=	↓/=
SGLT2	=	↑/=	=	?	=	↑/=	=	↑/=

- Overall, metformin and glucagon-like peptide 1 analogs have a **beneficial effect on bone morphology.**
- Agents like sulfonylureas, dipeptidyl peptidase-4 inhibitors and sodium-glucose cotransporter-2 inhibitors **do not have any direct beneficial or detrimental effects on bone morphology**.
- To date, **only** pioglitazone and bariatric surgery have demonstrated an increased risk for fracture in a real-world setting.

*Only tested in type 1 diabetes; *[1]only tested in nondiabetics; #not yet approved.

↓, decreased; ↑, increased; ?, not investigated; =, unaltered; BMD, bone mineral density; PTH, parathyroid hormone; SGLT2, sodium-glucose cotransporter 2.

Update on the impact of type 2 diabetes mellitus on bone metabolism and material properties.
Picke, A., Campbell, G., Napoli, N., Hofbauer, L. C., & Rauner, M. (2019).
Endocrine Connections, 8(3), R55-R70.

Insulin!

- However, whether insulin actually increases the fracture risk is controversial.

- Insulin-treated patients on average have **longer disease duration** and **a higher prevalence of micro-and macrovascular complications**.

- Thus, insulin use may just be **a surrogate for** severity or duration of T2DM, risk of hypoglycemia, presence of complications or increased risk of fall, which may explain the increased fracture risk in patients with T2DM.

IMPACT OF LOW BONE MASS TREATMENTS ON Diabetes Mellitus

Medication	Effect on glucose metabolism	BMD	Risk of fracture
Alendronate	Reduction in the risk of diabetes	Increase	NA/unchanged
Risedronate	Reduction in the risk of diabetes	Increase	NA
Etidronate	NA	NA	Unchanged
Denosumab	No effect on blood glucoselevels	Increase	Decrease
Raloxifene	Improves insulin sensitivity	NA	Decrease/unchanged
Teriparatide	No effect blood glucose levels	Increase	Unchanged

Treatment	Animal *in vivo* studies				Human *in vivo* studies			
	Bone formation	Bone resorption	BMD	Fracture healing	Bone formation	Bone resorption	BMD	Fracture risk
Anti-osteoporosis treatment								
Bisphosphonates	↓*	↓*	=*	↑*1	↓	↓	↑/=	↓
Anti-RANKL Ab	↓*	↓*	↑*	↑*1	↓*1	↓*1	↑*1	↓*1
Intermittent PTH	↑	↓	↑	↑	↑	↓	↑	↓
Anti-sclerostin Ab#	↑	↓	↑	↑	↑*1	↓*1	↑*1	↓*1

*Only tested in type 1 diabetes; *1only tested in nondiabetics; #not yet approved.

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Endocrine Connections, 8(3), R55-R70.

Evaluation of bone health in T1DM and T2DM

Risk assessment modalities

- The bone status and fracture risk in diabetic patients may be evaluated by different approaches:
  - BMD,
  - standard clinical risk factors (CRFs), ➡
  - Fracture probability,
  - Bone microarchitecture
  - Bone strength

•Advanced age.
•**Personal history** of fracture as an adult.
•Glucocorticoid therapy.
•History of fragility fracture in **a first-degree relative.**
•Low body weight.
•Cigarette smoking.
•Excessive alcohol consumption.
•Medical diseases.

BMD

- Studies have consistently demonstrated **lower BMD in patients with T1DM** and **higher BMD in patients with T2DM** compared to subjects without diabetes .

- Importantly, for patients with both T1DM and T2DM, the BMD T-score underestimates **the fracture risk**.

- Schwartz et al. showed that:
  - a T-score in a diabetic woman that is associated with **risk of hip fracture**
  - corresponds to a T-score of approximately 0.5 units lower in a nondiabetic woman.

- Though BMD underestimates the risk of fracture, **it stratifies the risk in elderly patients with T2DM**

Study of Osteoporotic Fractures (SOF) Research Group; Osteoporotic Fractures in Men (MrOS) Research Group; Health, Aging; and Body Composition (Health ABC) Research Group. Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes.Schwartz AV, Vittinghoff E, Bauer DC, Hillier TA, Strotmeyer ES, Ensrud KE, Donaldson MG, Cauley JA, Harris TB, Koster A, Womack CR, Palermo L, Black DM; *JAMA* 2011; **305**: 2184-2192

FRAX

- The FRAX algorithm allows for calculations of the 10year probability of fracture.
- The assessment is based on CRFs and the hip BMD T-score and permits for the incorporation of secondary osteoporosis for example in T1DM but not in T2DM.

Study of Osteoporotic Fractures (SOF) Research Group; Osteoporotic Fractures in Men (MrOS) Research Group; Health, Aging; and Body Composition (Health ABC) Research Group. Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes.Schwartz AV, Vittinghoff E, Bauer DC, Hillier TA, Strotmeyer ES, Ensrud KE, Donaldson MG, Cauley JA, Harris TB, Koster A, Womack CR, Palermo L, Black DM; *JAMA* 2011; **305**: 2184-2192

- A retrospective cohort study showed that **FRAX underestimated the risk of hip fracture and major osteoporotic fracture in a group of combined T1DM and T2DM patients**.

ORIGINAL ARTICLE

JBMR

FRAX Underestimates Fracture Risk in Patients With Diabetes

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FRAX underestimates fracture risk in patients with diabetes.
Giangregorio LM, Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA.
J Bone Miner Res 2012; **27**: 301-308

Bone microarchitecture and bone quality

- HRpQCT can be used to image and quantify volumetric BMD and bone microarchitecture including cortical porosity at a low radiation dose.
- Further, the estimated bone strength and failure load can be calculated.
- An association between **high cortical porosity** and T2DM was first described by Burghardt and others.
- Although the HRpQCT data is promising and could be a better fracture risk predictor than DXA, this research technique is unlikely to become widely available for routine clinical use.

TBS (trabecular bone score)

- The TBS is a parameter that **reveals bone microarchitecture** through analysis of DXA image pixel gray-level variations. TBS is DXA based and it can be accessed without the need of new equipment.

- Leslie *et al.* evaluated 2356 diabetic women (both T1DM and T2DM) and 27051 women without diabetes and revealed lower TBS in diabetic patients in comparison to controls in spite of higher lumbar spine and hip BMD in patients with diabetes.

- Current studies suggest the potential of TBS in fracture risk prediction for diabetic patients.

TBS (trabecular bone score) and diabetes-related fracture risk

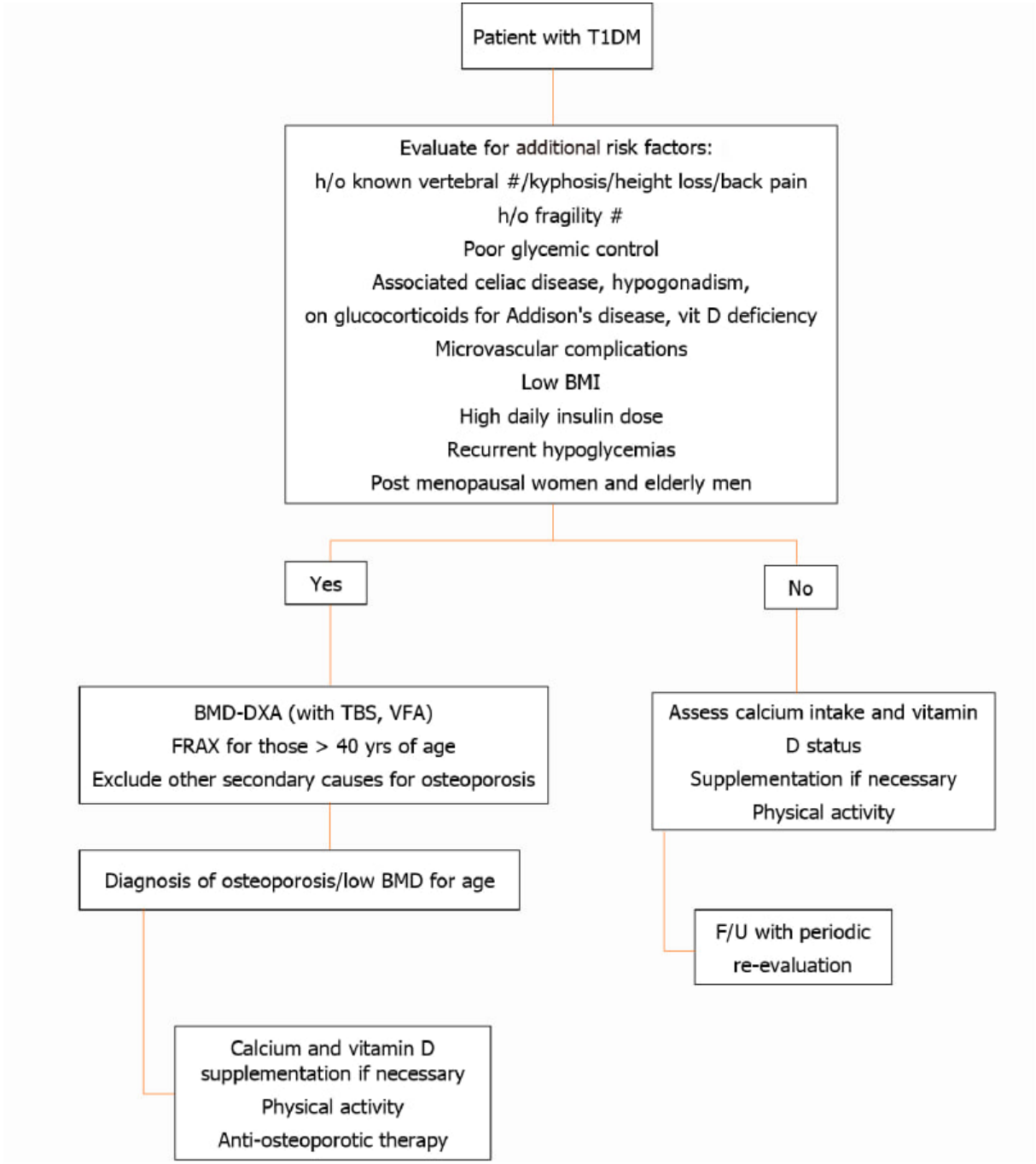
Leslie WD, Aubry-Rozier B, Lamy O, Hans D; Manitoba Bone Density Program. *J Clin Endocrinol Metab* 2013; **98**: 602-609**.**

- Clinical studies directly comparing differences in TBS between T1DM and T2DM are scarce.

- TBS is more helpful for predicting fracture risk when combined with BMD.

- However, there is a lack of evidence demonstrating **how post-treatment TBS improvement can decrease fracture risk.**

Evaluation of bone health, Fracture risk and strategies for treatment



Algorithm for evaluation of bone health in type 1 diabetes mellitus

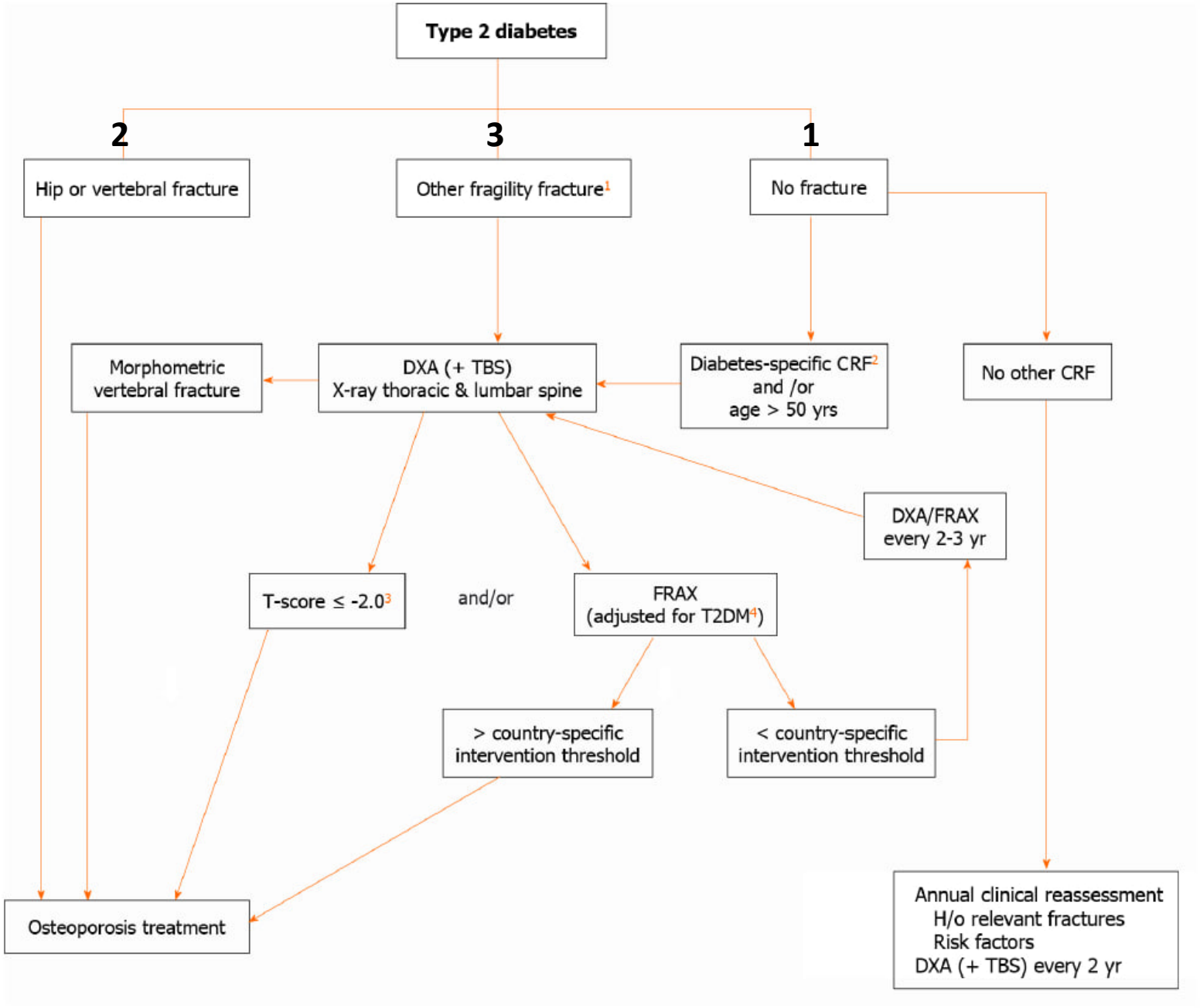
POINTS:

- In adult patients with T1DM, the first densitometry should be performed five years after the diagnosis of the diabetes mellitus and repeated every 2–5 years.
- The FRAX tool is not appropriate for assessing the fracture risk in **young patients** with T1DM.

BMI: Body mass index; BMD-DXA: Bone mineral density by dual energy X-ray absorptiometry; F/U: Follow up; FRAX: Fracture Risk Assessment Tool;
H/o: History of; T1DM: Type 1 diabetes mellitus; TBS: Trabecular bone score; VFA:Vertebral fracture assessment.

Critical review of bone health, fracture risk and management of bone fragility in diabetes mellitus.
Palui R, Pramanik S, Mondal S, Ray S. *World J Diabetes* 2021; 12(6): 706-729

Evaluation of fracture risk in patients with type 2 diabetes mellitus

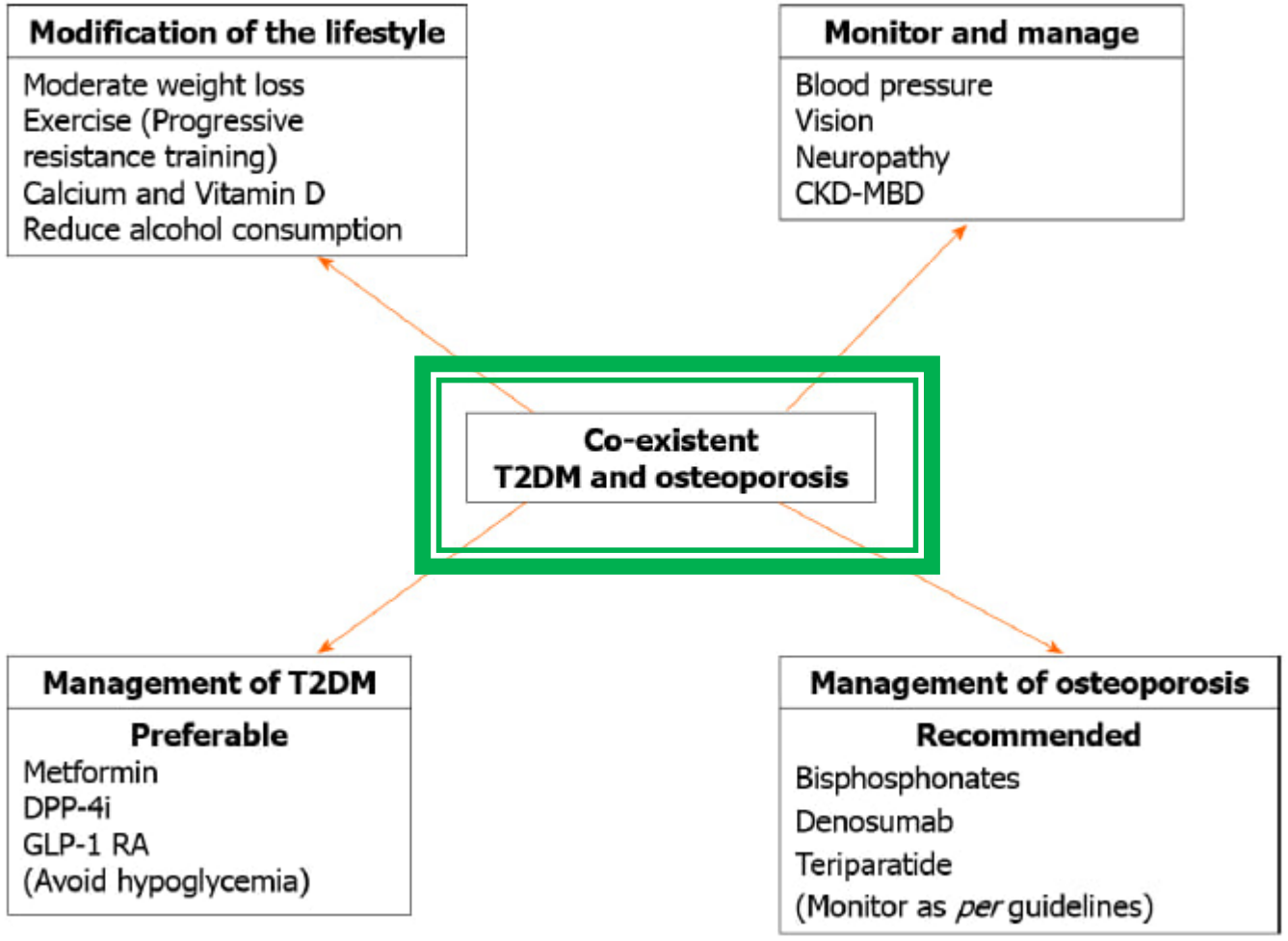


Critical review of bone health, fracture risk and management of bone fragility in diabetes mellitus.
Palui R, Pramanik S, Mondal S, Ray S. *World J Diabetes* 2021; 12(6): 706-729

1: ≥ 1 nonvertebral nonhip fragility fracture might be required to initiate therapy;
2: Diabetes-specific clinical risk factors (diabetes duration, antidiabetic medications,, hemoglobin A1c and microvascular complications);
3: In diabetes, fracture risk at T-score < -2 equivalent for nondiabetes at T-score < -2.5;
4: CRF: **Clinical risk factor**;
TBS: Trabecular bone score;
DXA: Dual energy X-ray absorptiometry; T2DM: Type 2 diabetes mellitus; FRAX: Fracture Risk Assessment Tool; H/o: History of.

Bone and Diabetes Working Group of IOF. Diagnosis and management of bone fragility in diabetes: an emerging challenge. *Osteoporos Int* 2018; 29:2585-2596.Copyright ©The Author(s) 2018. Published by Springer Nature.
Modified from Ferrari *et al*: Ferrari SL**,** Abrahamsen B,Napoli N, Akesson K, Chandran M, Eastell R, El-Hajj Fuleihan G, Josse R, Kendler DL, Kraenzlin M, Suzuki A, Pierroz DD, Schwartz AV, Leslie WD;

Strategies for treating type 2 diabetes mellitus and concurrent osteoporosis



CKD-MBD: Chronic kidney disease–mineral and bone disorder; DPP-4i: Dipeptidyl-peptidase 4 inhibitor; GLP-1: Glucagon-like peptide-1; T2DM: Type 2 diabetes mellitus.

Critical review of bone health, fracture risk and management of bone fragility in diabetes mellitus.
Palui R, Pramanik S, Mondal S, Ray S. *World J Diabetes* 2021; 12(6): 706-729