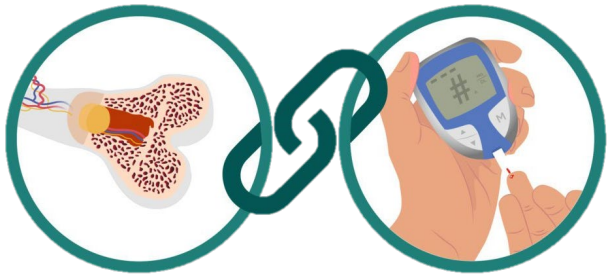
Società Italiana di Diabetologia | 1964-2024

ASSOCIAZIONE MEDICI DIABETOLOGI 1974

**Riunione annuale congiunta SID-AMD 2024**
**Napoli (NA), 5 ottobre 2024**
**HOTEL ROYAL CONTINENTAL**



# Diabete e Osso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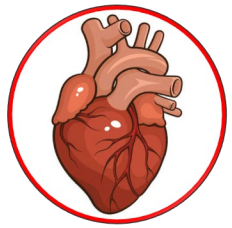
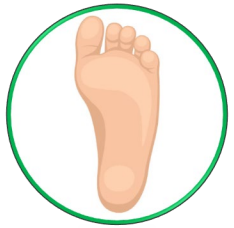
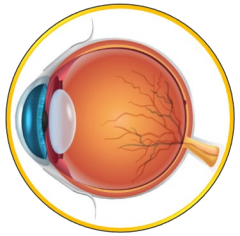
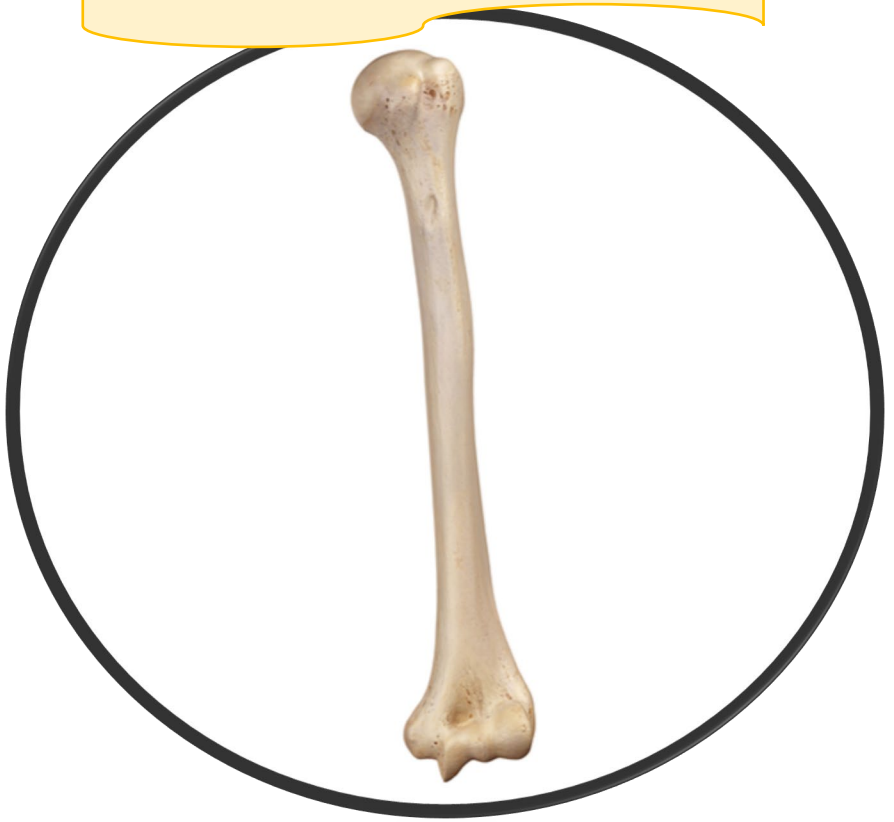
Università degli Studi della Campania *Luigi Vanvitelli*

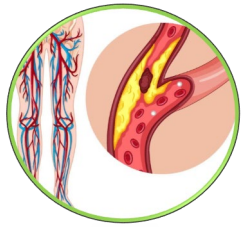



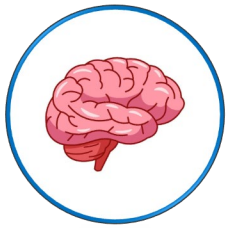


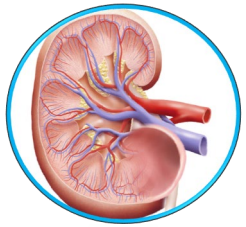


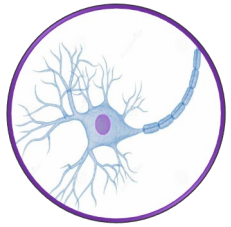
emerging organ targets












**meta-analysis of 25 prospective e retrospective studies: 7 185 572 individuals**

32% increased risk of any fractures in individuals with both type 1 and type 2 diabetes (RR 1.32, 95% CI 1.17 – 1.48)

| **Fracture risk in type 1 diabetes** | **Fracture risk in type 2 diabetes** |
|---|---|
| hip - 4.35 times<br>upper limb – 1.83 times<br>ankle – 1.97 times<br><br>**10-15 years earlier* | hip – 1.79 times<br>risk throughout life is 40–70% higher than in individuals without diabetes<br>increased also in the upper limbs and ankle<br><br>**despite normal or higher BMD* |

8% increased fracture risk per 1% rise in A1C level
(risk ratio [RR] 1.08 [95% CI 1.03–1.14])

BMJ Open 2019;9: e024067
Diabetes Care 2015;38:1913–1920
BMJ Open 2019;9:e024067
J Clin Endocrinol Metab 2019;104: 3303–3310
Osteoporos Int 2021;32:1693–1704

- Decreased bone quality
- Low bone turnover

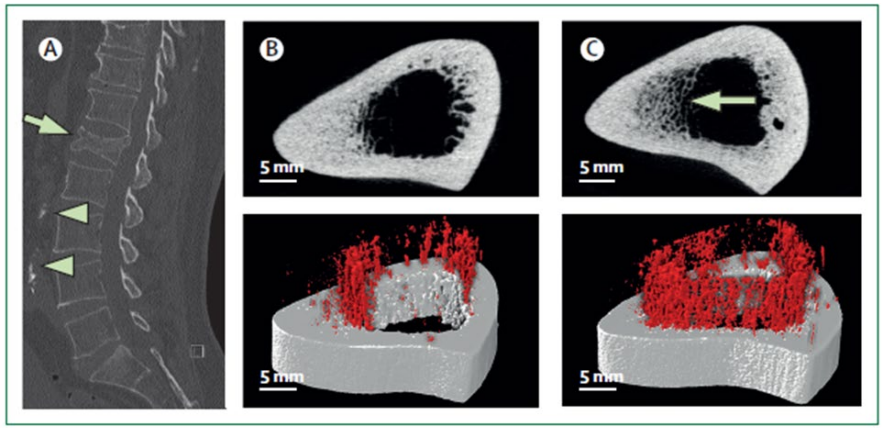
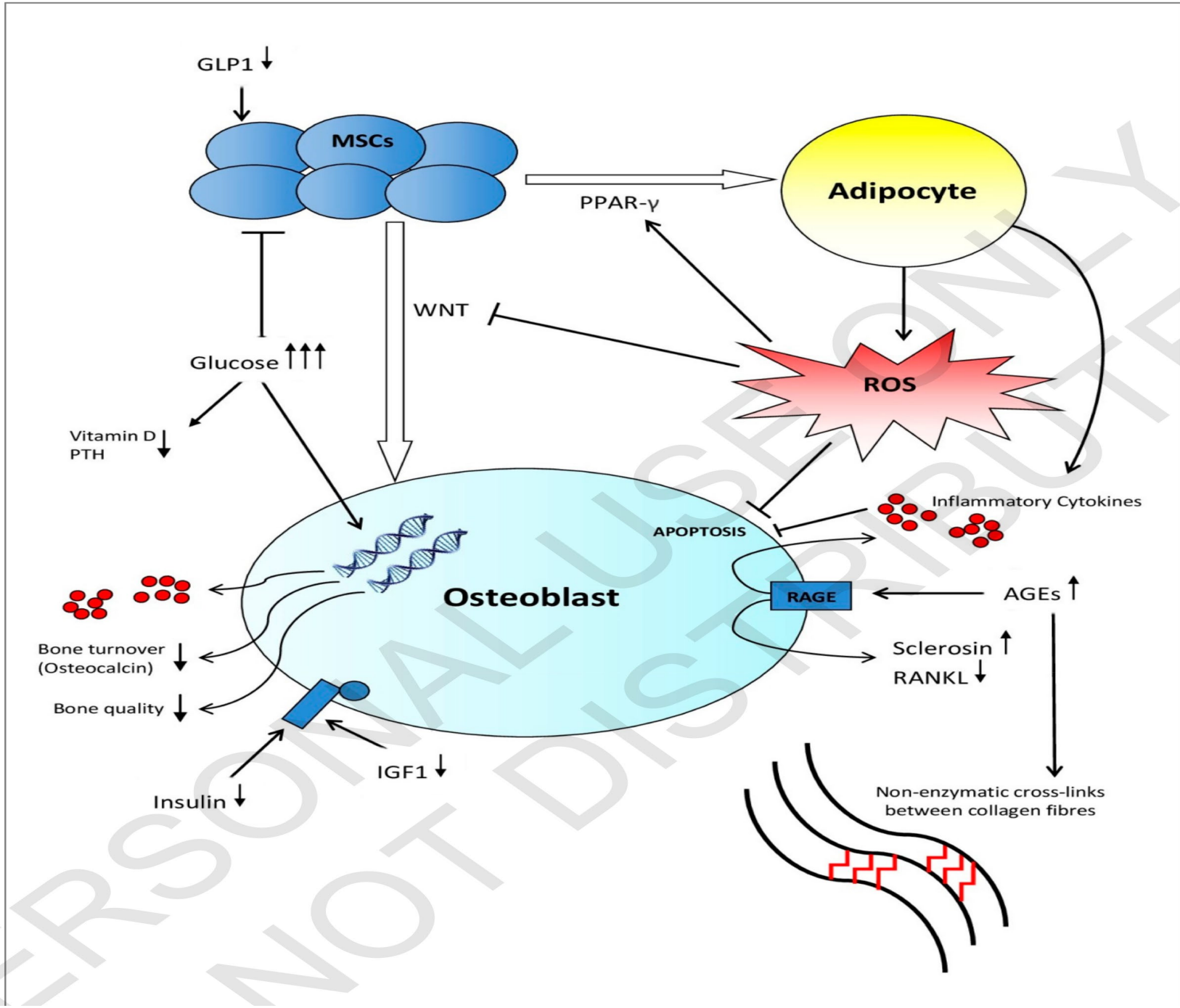



*Figure 2:* **Images of diabetic bone disease**
(A) CT scan of the spine (lateral view) demonstrating fracture of the first lumbar vertebra (arrow) in a 54-year-old man with poorly controlled type 2 diabetes for over 15 years after a fall from standing height. Dual-energy x-ray absorptiometry assessment revealed a T-score of −1·3. Vascular calcification is present (arrow heads). (B, C) High-resolution peripheral quantitative CT scan of mid-diaphyseal tibial cross-sections obtained from male organ donors. In contrast to the control case without diabetes (B), the individual with long-standing type 2 diabetes (C) shows trabecularisation of the cortical compartment (top panel, arrow) and a high amount of voids and canals reflecting increased porosity of the cortical compartment (bottom panel, red).






Int. J. Mol. Sci. 2019, 20, 4873

2024 Standards of Care in Diabetes

American Diabetes Association

# ASSESSMENT OF DIABETES-BONE HEALTH

General risk factors

- Prior osteoporotic fracture
- Age >65 years
- Low BMI
- Sex
- Malabsorption
- Recurrent falls
- Glucocorticoid use
- Family history
- Alcohol/tobacco abuse
- Rheumatoid arthritis

Diabetes-specific risk factors

- Lumbar spine or hip T-score ≤ −2.0
- Frequent hypoglycemic events
- Diabetes duration >10 years
- Diabetes medications: insulin, thiazolidinediones, sulfonylurea
- A1C >8%
- Peripheral and autonomic neuropathy
- Retinopathy and nephropathy


J Bone Miner Res 2005; 20: 1185–94
Bone 2004; 35: 375–82
Diabetes Care 2024; 47(Suppl. 1):S52–S76
N Engl J Med 2020; 382: 734–43

2024 Standards of Care in Diabetes

American Diabetes Association

# ASSESSMENT OF DIABETES-BONE HEALTH

**Type 2 diabetes**

BMD measurement is recommended after **5 years** of disease duration, with monitoring every 2-3 years

**Type 1 diabetes**

BMD measurement should be considered **after the 5th decade of life**

In youth, BMD should be evaluated in association with celiac disease because of the involvement of inflammatory pathways

- ≥ 65 y
- < 65 y + multiple risk factors
- diabetes duration (>26 years in type 1 diabetes and >10 years in type 2 diabetes)

- hypogonadism

- 25-OH vitamin D levels

**DXA** → T-score ≤-2.0 should be interpreted as equivalent to -2.5 in a person without diabetes

Lancet Diabetes Endocrinol 2022; 10: 207–20
J Clin Endocrinol Metab 2019; 104: 1645–54
Osteoporos Int 2019; 30: 1663–70
Eur J Endocrinol 2019; 180: 51–58

Nutrition, Metabolism & Cardiovascular Diseases (2021) **31**, 1375–1390

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

REVIEW

# Bone fragility in patients with diabetes mellitus: A consensus statement from the working group of the Italian Diabetes Society (SID), Italian Society of Endocrinology (SIE), Italian Society of Gerontology and Geriatrics (SIGG), Italian Society of Orthopaedics and Traumatology (SIOT)

**Table 1** Risk assessment and diagnosis of bone fragility.

The presence of traditional risk factors for osteoporotic fractures, as well as the presence of diabetes-specific risk factors, should be investigated at each follow-up diabetes visit, regardless of the type of diabetes.

| T1D | T2D |
|---|---|
| •T1D patients have low BMD and high risk of fracture at an early age<br>DXA remains the gold standard for the diagnosis of osteoporosis; being a technique that involves low X-ray emission, it can also be performed in paediatric patients, when the reference physician deems it appropriate.<br>•Densitometry by DXA should be performed:<br>o in all T1D patients after the age of 50 years, or<br>o even earlier in those with diabetes-specific risk factors such as:<br>• micro- or macrovascular complications,<br>• suboptimal glycaemic control (HBA1c >8% or 63.9 mmol/mol)<br>• family history of fragility fractures<br>• celiac disease<br>o As already indicated by the International Society for Pediatric and Adolescent Diabetes (ISPAD), a DXA scan should be considered in late adolescence, especially if the patient also has celiac disease.<br>Note: in patients aged <50 years, the z-score should be used instead of the T-score.<br>•It is important to investigate previous fractures and risk factors for bone fragility (intake of calcium, vitamin D, malabsorption, etc.) during each clinical assessment.<br>•Vertebral morphometry can be performed either by RX or DXA in a semi-quantitative way. This assessment should be reserved to patients with:<br>o clinical history of intense spinal pain,<br>o fragility fractures in other bone sites.<br>o patients with spine or hip T or Z-score < −2.0<br>•FRAX® and DeFRA can be useful for estimating the risk of fracture, but there are no specific thresholds for T1D. | •Patients with T2D have normal or increased BMD compared to healthy individuals of the same age<br>•BMD should be measured in all T2D patients with:<br>o Age >50 years<br>o Previous fragility fracture<br>o Chronic therapy with thiazolidinediones or canagliflozin<br>o General risk factors, independent of diabetes<br>•A correction factor of 0.5 can be applied in the interpretation of T-score (for example < −2.0 should be considered as < −2.5).<br>•In T2D patients undergoing bariatric surgery with a malabsorptive component, DXA should be performed before surgery and every two years thereafter to monitor BMD<br>•FRAX® can be used in the clinical evaluation of patients with diabetes, selecting the option for rheumatoid arthritis<br>•The Trabecular Bone Score showed a very good sensitivity in predicting the risk of fracture in T2D but further studies are needed to validate its use in clinical practice<br>•Vertebral morphometry can be performed either by RX or DXA in a semi-quantitative way. This assessment should be reserved to patients with:<br>o T-score < −2.0<br>o clinical history of intense spinal pain,<br>o fragility fractures in other bone sites.<br>o disease duration >5 years<br>o use of a TZD |

A vertebral fracture diagnosis can be made using images acquired for other clinical problems such as a chest X-ray, CT or MRI [85,86].

**TBS** is a textural analysis resulting from a computed evaluation of pixel grey-level variations in previously obtained LS DXA images.

**An index of bone microarchitecture correlated with parameters of bone strength**.

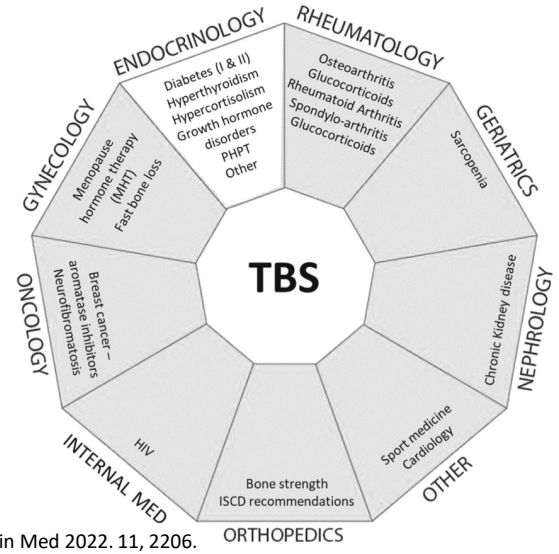
Higher values of TBS indicate a better microarchitecture, whereas lower values indicate a degraded microarchitecture.

TBS >1.31 normal microarchitecture

1.23< TBS <1.31 partially degraded microarchitecture

TBS <1.23 degraded microarchitecture

Several studies have also demonstrated the ability of TBS to **predict fragility fractures in secondary osteoporosis**




- Insuline-resistance
- Pre-diabetes
- Diabetes
- Visceral Fat

J Clin Med 2022. 11, 2206.

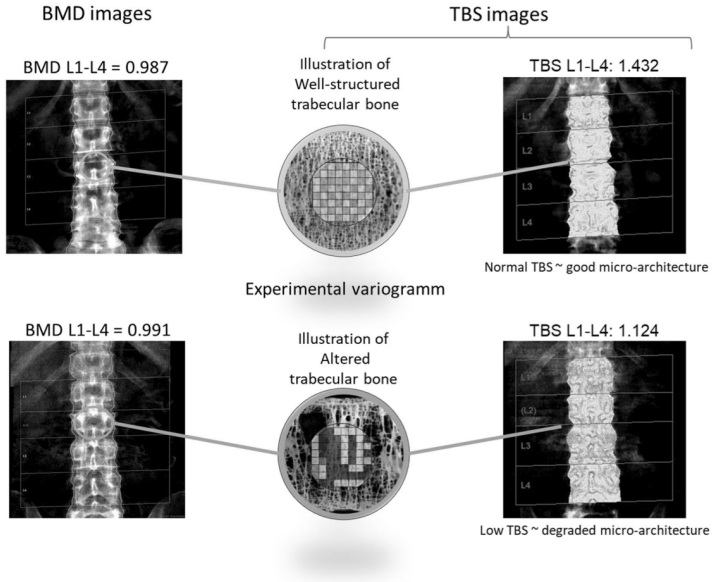



**Fig. 1** Concept of TBS. Two different patients with equivalent bone mineral density (BMD) but different trabecular bone score (TBS)

Trabecular bone score values adjusted for multiple covariates between subgroups.

| | Group 1a HbA1c ≥ 7.5% | Group 3 HbA1c ≤ 5.6% | | Group 1b HbA1c ≥ 6.5% and ≥ 5 yr | Group 3 HbA1c ≤ 5.6% | | Group 1c HbA1c ≥ 7.5% and ≥ 5 yr | Group 3 HbA1c ≤ 5.6% | |
|---|---|---|---|---|---|---|---|---|---|
| n | 42 | 160 | P-value | 63 | 160 | P-value | 30 | 160 | P-value |
| Unadjusted* model | 1.258 [1.227, 1.290] | 1.314 [1.298, 1.330] | **0.002** | 1.262 [1.236, 1.287] | 1.314 [1.298, 1.330] | **<0.001** | 1.244 [1.208, 1.280] | 1.314 [1.298, 1.330] | **< 0.001** |
| Model 1 Adjusted** for age, LS-BMD and BMI | 1.257 [1.231, 1.284] | 1.314 [1.301, 1.327] | **< 0.001** | 1.272 [1.250, 1.293] | 1.310 [1.297, 1.323] | **0.004** | 1.251 [1.221, 1.281] | 1.313 [1.300, 1.325] | **< 0.001** |
| Model 2 Adjusted** for age, LS-BMD and STT | 1.281 [1.255, 1.308] | 1.308 [1.295, 1.320] | 0.083 | 1.283 [1.262, 1.304] | 1.306 [1.293, 1.318] | 0.079 | 1.275 [1.244, 1.305] | 1.308 [1.296, 1.320] | **0.047** |

Higher HbA1c levels are associated with greater BMD in the hip and femoral neck, higher abdominal STT and lower TBS values. However, after adjusting for STT, TBS differences among groups disappeared, except in the subgroup of women with higher HbA1c levels and a longer disease duration.
These data indicate that the effect of abdominal soft tissue thickness should be considered when interpreting the TBS, particularly in subjects with T2D, in whom increased abdominal adiposity may artifactually reduce TBS values.

It’s possible through specific algorithms do an integrated assessment of BMD and more important risk factors, partially or totally independent of BMD, to allow a more accurate estimate of the risk of fragility fractures in the medium term.


One of the the most used algorithms today is **FRAX ®**. It was endorsed by the WHO and became available online and computes the 10-year probability of hip fracture or a major osteoporotic fracture.

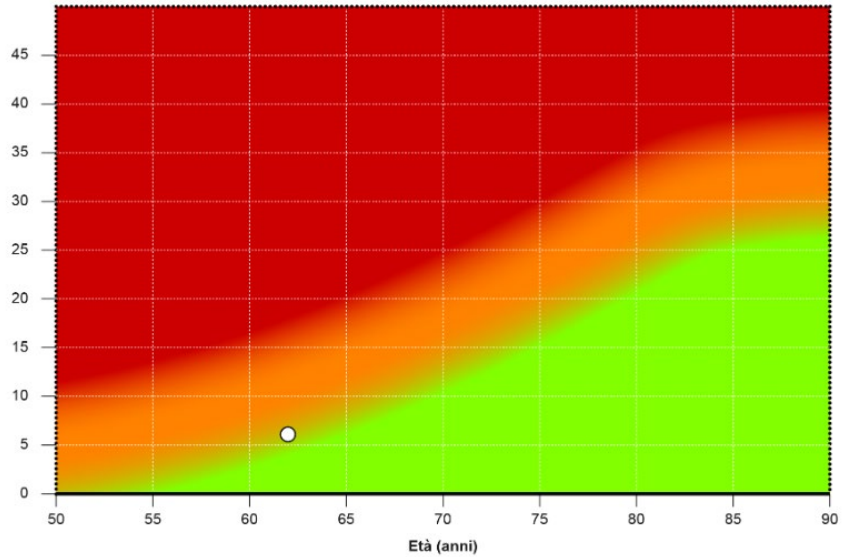
FRAX-determined fracture risk may more accurately reflect the true fracture risk in patients with T2DM by making any 1 of the 4 following adjustments: (i) adding 10 years of age; (ii) reducing BMD T-score by 0.5 SD; (iii) including rheumatoid arthritis as a substitute for T2DM; or (iv) by including TBS

To improve the accuracy of FRAX in Italy was created a **DeFRA**, which provides a risk estimate similar to FRAX® based only on continuous variables, but more accurate as it goes to evaluate other clinical risk factors in a more detailed and comprehensive manner.

The use of DeFRA allows an objective assessment of the severity and impact of osteoporosis, improving the perception of risk by both the patient and other healthcare professionals.

DEFRACALC 79

Carta del rischio




Rischio di fratture maggiori a 10 anni: 5,95%

**Table 2. Diabetes medications and their associated effects on BMI and fracture risk**

| Medication | Associated BMD | Associated fracture risk |
|---|---|---|
| Metformin | • ↔/↑ [66, 67] | • ↓/↔ any fracture [66, 67] |
| Sulphonylureas | • ↔ [68] | • ↑ nonvertebral fractures in men [69]<br>• ↔ vertebral fractures [70]<br>• ↓/↔ any fracture [66, 67] |
| Thiazolidinediones | • ↓ [71, 72] | • ↑ in women [71, 73] |
| DPP-4 inhibitors | • ↑ [74] | • ↓ [75, 76]<br>• ↑/↔ with saxagliptin [77, 78] |
| GLP1-RA | • ↔/↑ [79] | • ↓ [80]<br>• ↑/↔ with exenatide [81] |
| SGLT2-i | • ↑ with canagliflozin [82]<br>• ↔ with dapagliflozin [83] | • ↑ [84]/↔ [85] with canagliflozin<br>• ↔ [86-88] |
| Insulin | • ↑ | • ↑ [9, 21] |

# INTERVENTION

**Lifestyle**
weight loss
physical activity

**prevent sarcopenia*

**Supplementation**
serum levels <20 ng/ml

**from 400-800 UI to 4000 UI per day*


**Supplementation**
nutritional uptake <1.2 gr per day


**Romosozumab**

**Biphosphonates**


**Denosumab**

**Teriparatide**

# Effect of Alendronate on Bone Mineral Density and Biochemical Markers of Bone Turnover in Type 2 Diabetic Women

The Fracture Intervention Trial

*Diabetes Care* 27:1547–1553, 2004

**RESULTS** — In diabetic women, 3 years of ALN treatment was associated with increased BMD at all sites studied, including 6.6% at the lumbar spine and 2.4% at the hip, whereas women in the placebo group experienced a decrease in BMD at all sites except the lumbar spine. The safety/tolerability of ALN was similar to placebo, except for abdominal pain, which was more likely in the ALN group.

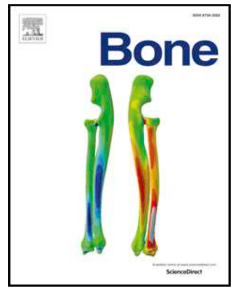
**CONCLUSIONS** — ALN increased BMD relative to placebo in older women with type 2 diabetes and was generally well tolerated as a treatment for osteoporosis. Increases in BMD with ALN therapy compared with placebo were similar between women with and without diabetes.

Bone 134 (2020) 115268

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone



Full Length Article

# Denosumab in postmenopausal women with osteoporosis and diabetes: Subgroup analysis of FREEDOM and FREEDOM extension

*Results:* Of 7808 subjects in FREEDOM, 508 with diabetes received denosumab ($n$ = 266) or placebo ($n$ = 242). Among those, BMD increased significantly with denosumab versus placebo in FREEDOM, and continued to increase during the Extension in long-term (continuing denosumab) and crossover (placebo to denosumab) denosumab subjects. In FREEDOM, denosumab-treated subjects with diabetes had significantly lower new vertebral fracture rates (1.6%) versus placebo (8.0%) (RR: 0.20 [95% CI 0.07–0.61]; $p$ = .001). Nonvertebral fracture incidence was higher with denosumab (11.7%) versus placebo (5.9%) (HR: 1.94 [95% CI 1.00–3.77]; $p$ = .046), although there were fewer hip fractures with denosumab (World Health Organization, 2017 [1]) than placebo (4; nonsignificant). During the first 3 years in FREEDOM Extension, new vertebral and nonvertebral fracture incidences were low in long-term and crossover denosumab diabetic groups (≤6%), consistent with the overall Extension population; yearly nonvertebral fracture incidence was comparable to the FREEDOM placebo group.

*Conclusion:* Denosumab significantly increased BMD and decreased vertebral fracture risk in subjects with osteoporosis and diabetes. No reduction in nonvertebral fractures was observed.

DOI: 10.1111/dom.15708

ORIGINAL ARTICLE

WILEY

# Denosumab, for osteoporosis, reduces the incidence of type 2 diabetes, risk of foot ulceration and all-cause mortality in adults, compared with bisphosphonates: An analysis of real-world, cohort data, with a systematic review and meta-analysis

**Results:** Denosumab (vs. bisphosphonates) was associated with a lower risk of incident T2D over 5 years (hazard ratio 0.83 [95% confidence interval {CI} 0.78-0.88]). Secondary analysis showed significant risk reduction in all-cause mortality (0.79 [0.72-0.87]) and foot ulceration (0.67 [0.53-0.86]). Also, pooled results from four studies (three observational, one randomized controlled trial) following meta-analysis showed a reduced relative risk (RR [95% CI]) for incident T2D in patients prescribed denosumab (0.83 [0.79-0.87]) ($I^2 = 10.76\%$).

**Conclusions:** This is the largest cohort study to show that denosumab treatment is associated with a reduced RR of incident T2D, as well as an associated reduced RR of all-cause mortality and microvascular complications, findings that may influence guideline development in the treatment of osteoporosis, particularly in patients who are at a high risk of T2D.

2024 Standards of Care in Diabetes

American Diabetes Association

**primary prevention**

type 2 diabetes and a T-score below –2.0 (equivalent to a T-score below –2.5 in people without diabetes) should receive antiresorptive treatment with either bisphosphonates or denosumab, according to comorbidities, renal function, and patient preference.

**secondary prevention**

diabetes and a recent vertebral or hip fracture, indicating high or very high risk of fracture, anabolic therapy (teriparatide, abaloparatide, or romosozumab with caution) can be considered.

anabolic treatment in people with diabetes should be followed by antiresorptive therapy.

in people with diabetes hospitalised for fragility fractures a rehabilitation plan should be considered.

Endocr Rev 2019; 40: 333–68
Diabetes Care 2004; 27: 1547–53
Bone 2020; 134: 115268
JBMR Plus 2020; 4: e10346

# NOTA 79

La prescrizione a carico del SSN è limitata alle seguenti condizioni di rischio di frattura osteoporotica:

- **Prevenzione primaria in donne in menopausa o uomini di età ≥50 anni a rischio elevato di frattura a causa di almeno una delle condizioni sottoelencate:**

| Condizione | I scelta[a] | II scelta | III scelta |
|---|---|---|---|
| Trattamento in atto o previsto per >3 mesi con prednisone equivalente ≥5 mg/die | Alendronato (± vit.D), Risedronato, Zoledronato[d] | Denosumab[e] | _____ |
| Trattamento in corso di blocco ormonale adiuvante in donne con carcinoma mammario o uomini con carcinoma prostatico | Alendronato (± vit.D), Risedronato, Zoledronato[d] Denosumab[e] | _____ | _____ |
| T-score colonna o femore[c] ≤-4 | Alendronato (± vit.D), Risedronato | Denosumab[e] Zoledronato[d] Ibandronato, Raloxifene, Bazedoxifene | |
| T-score colonna o femore[c] ≤-3 + almeno una delle seguenti condizioni:<br>1) Familiarità per fratture di vertebre o femore<br>2) Comorbilità a rischio di frattura (artrite reumatoide o altre connettiviti, diabete, | | | |

# Take-home messages

- ✓ La fragilità ossea è una complicanza cronica del DM (osteopatia diabetica)
- ✓ La valutazione è complessa (fattori di rischio generali e specifici; DEXA + TBS; FRAX modificato)
- ✓ Farmaci anti-diabete hanno variabili effetti sullo scheletro (no insulina, SU, TZD, canaglifozin)
- ✓ Farmaci anti-osteoporosi efficaci e sicuri anche nei pazienti con DM

*Grazie per l'attenzione*