

Caso clinico

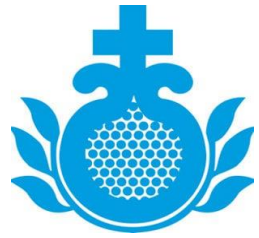
Fabiana Picconi

Unità Operativa Complessa di Endocrinologia Diabetologia
e Malattie del Ricambio

Ospedale S. Giovanni Calibita Fatebenefratelli, Roma

Università degli studi di Roma "Tor Vergata"

Dipartimento di Medicina dei Sistemi



la **MENOPAUSA**
da un'altra
prospettiva



Foto: Arte de Nina Millen

sabato 7 dicembre 2019

Bonus Pastor

via Aurelia, 208 - Roma

Maria, 68 anni insegnante



Diabetica Tipo 2 da circa 10 anni

Ipertensione Arteriosa dall'età di 57 anni

Diabete gestazionale

TIA all'età di 57 anni

Retinopatia diabetica non proliferativa

Familiarità per:

Malattia cardiovascolare

(padre IMA a 56 anni, madre ICTUS 68 anni)

Ipertensione (madre e fratello)

Diabete tipo 2 (padre e fratello)

Maria, 68 anni insegnante



BMI 31 Kg/m² , PA 130/85 mmHg

Menopausa fisiologica a 53 anni, no EP

Stile di vita sedentario

Fuma 10 sig/die

Non segue regime dietetico specifico

Terapia domiciliare

Repaglinide 2mg 1 cp x 3

**Glargine 20 UI la sera prima
di coricarsi**

Ramipril 5 mg 1 cp die

Acido acetilsalicilico 100mg

Atorvastatina 40 mg

Maria, 68 anni, Diabete Tipo 2 da circa 10 anni, controllo metabolico



Glicemia 178 mg/dl

HbA1c 8,5 % (69 mmol/mol)

Creatinina 0.8 mg/dl (eGFR 82ml/min/m²)

Col tot 173 mg/dl

HDL 61 mg/dl

Trigliceridi 130 mg/dl

LDL 86 mg/dl

Maria 68 anni, Diabete Tipo 2 da 10 anni



Diabete

Obesità

RD

Ipertensione arteriosa

Dislipidemia

Maria 68 anni, Diabete Tipo 2 da 10 anni

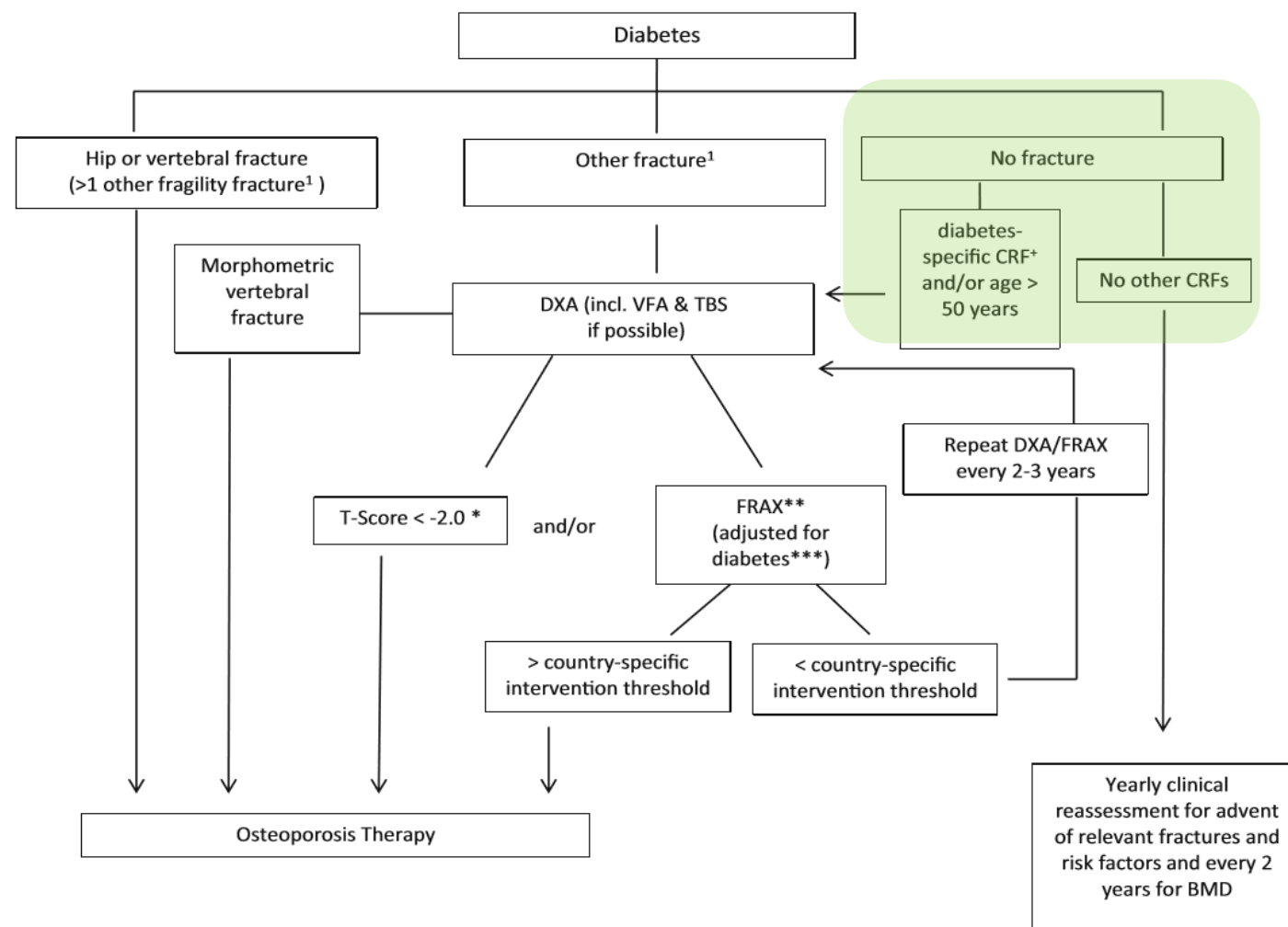
Come valutiamo il rischio osteoporotico di questa paziente?





Diagnosis and management of bone fragility in diabetes: an emerging challenge

S.L. Ferrari¹ · B. Abrahamsen^{2,3} · N. Napoli^{4,5} · K. Akesson⁶ · M. Chandran⁷ · R. Eastell⁸ · G. El-Hajj Fuleihan⁹ · R. Josse^{10,11} · D.L. Kendler¹² · M. Kraenzlin¹³ · A. Suzuki¹⁴ · D.D. Pierroz¹⁵ · A.V. Schwartz¹⁶ · W.D. Leslie¹⁷ · on behalf of the Bone and Diabetes Working Group of IOF



LABORATORIO

Bone markers were assessed

✓ 1 st level:

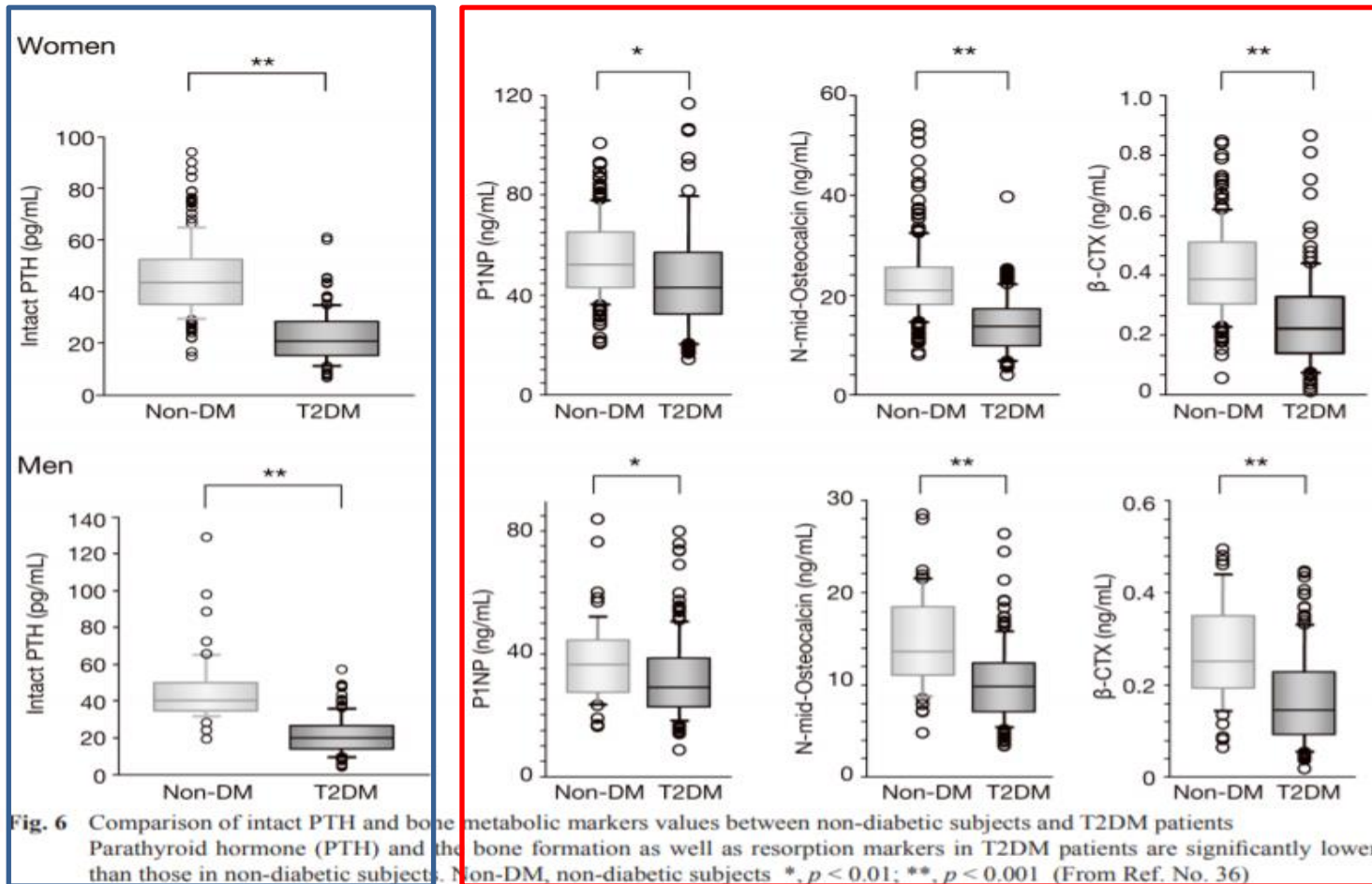
alkaline phosphatase, osteocalcin, serum β -cross
laps, PTH, 25OHD, 24h urine calcium

Secondary causes of osteoporosis were excluded

✓ 2 nd level:

TSH, ematology, renal and epatic function,
proteins, CA125, and CA15-3.

Markers turnover osseo



RISULTATI

Maria 68 anni, Diabete Tipo 2 da 10 anni

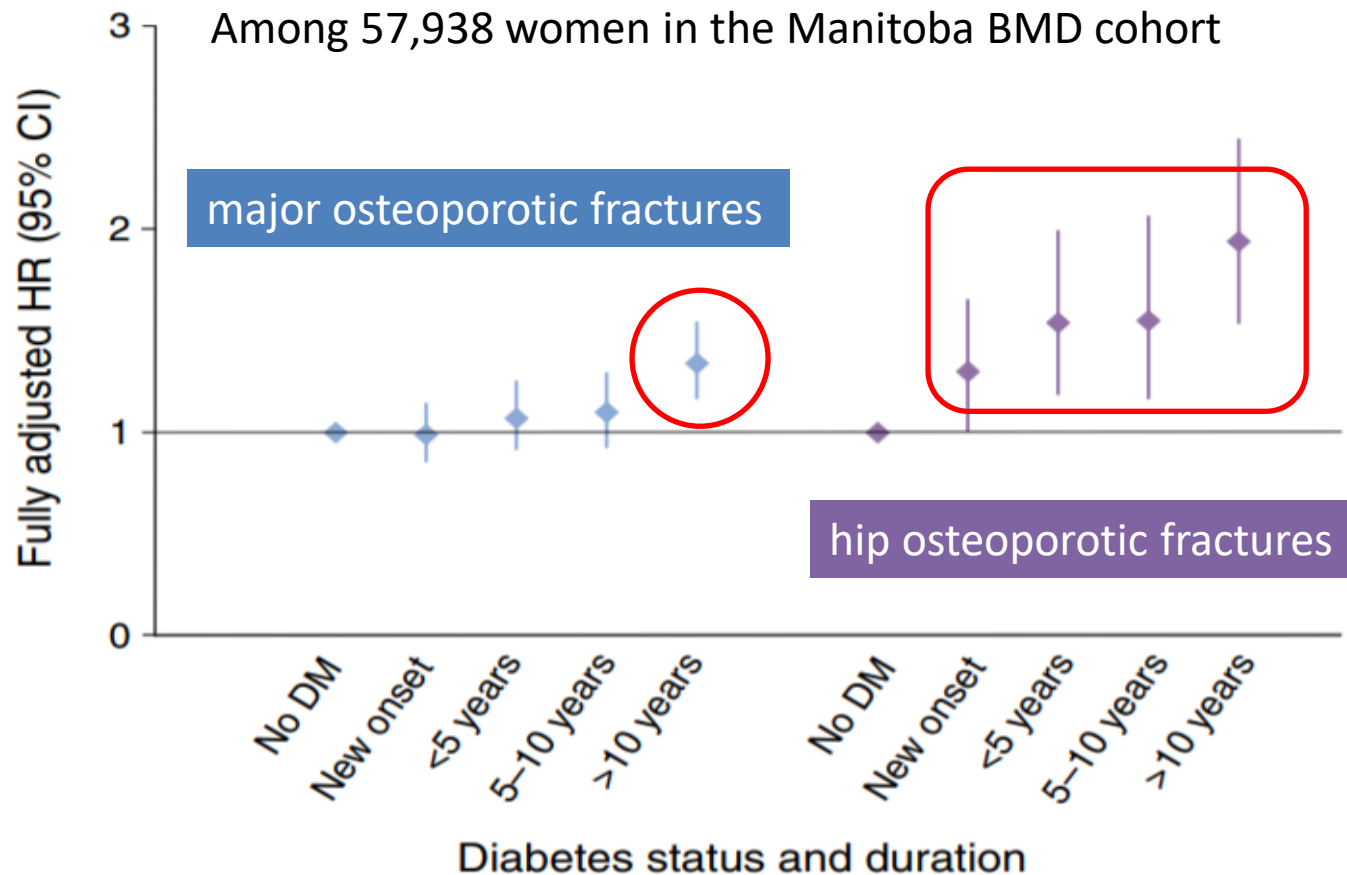
Tutti i parametri studiati
risultavano nell'ambito dei valori
di riferimento

***insufficienza: 25(OH)-vitamina D
19ng/ml***

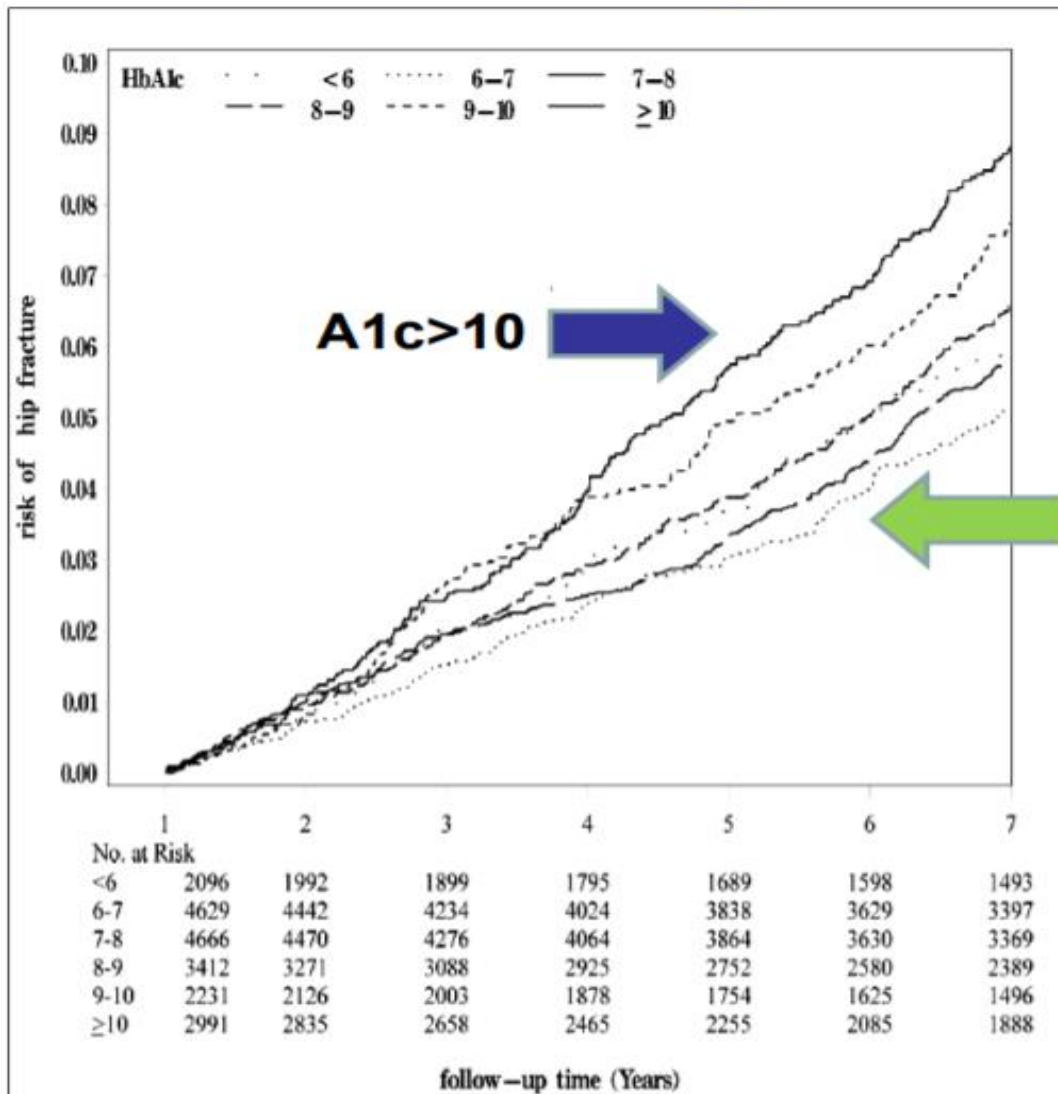
Fattori di rischio specifici DM

- Durata di malattia
- Controllo glicemico
- Presenza di complicanza (microvascolari)
- Effetto farmaci ipoglicemizzanti

Diabetes duration and risk factors for fracture



Linear increase in hip fracture incidence with increasing HbA1c.



20,025 older patients
with DM2 > 65

Li Ci et al
J Bone Miner Res. 2015

Glucose-lowering agents and fracture risk

Effects of glucose-lowering medications on BMD and fracture risk

Glucose-lowering medication	BMD	Fracture risk
Insulin	↑ (LC/NCC)	↑ (LC/NCC)
Sulfonylureas	??	↔ (LC/NCC/RCT AEs ^a)
Metformin	↔ (LC/NCC)	↔ (LC/NCC/RCT AEs ^a)
TZDs	↓ (RCT)	↑ (RCT AEs)
GLP-1 receptor agonists	??	??
DPP-4 inhibitors	??	↔ (RCT AEs)
SGLT2 inhibitors	↓/↔ (RCT)	↑/↔ (RCT AEs)

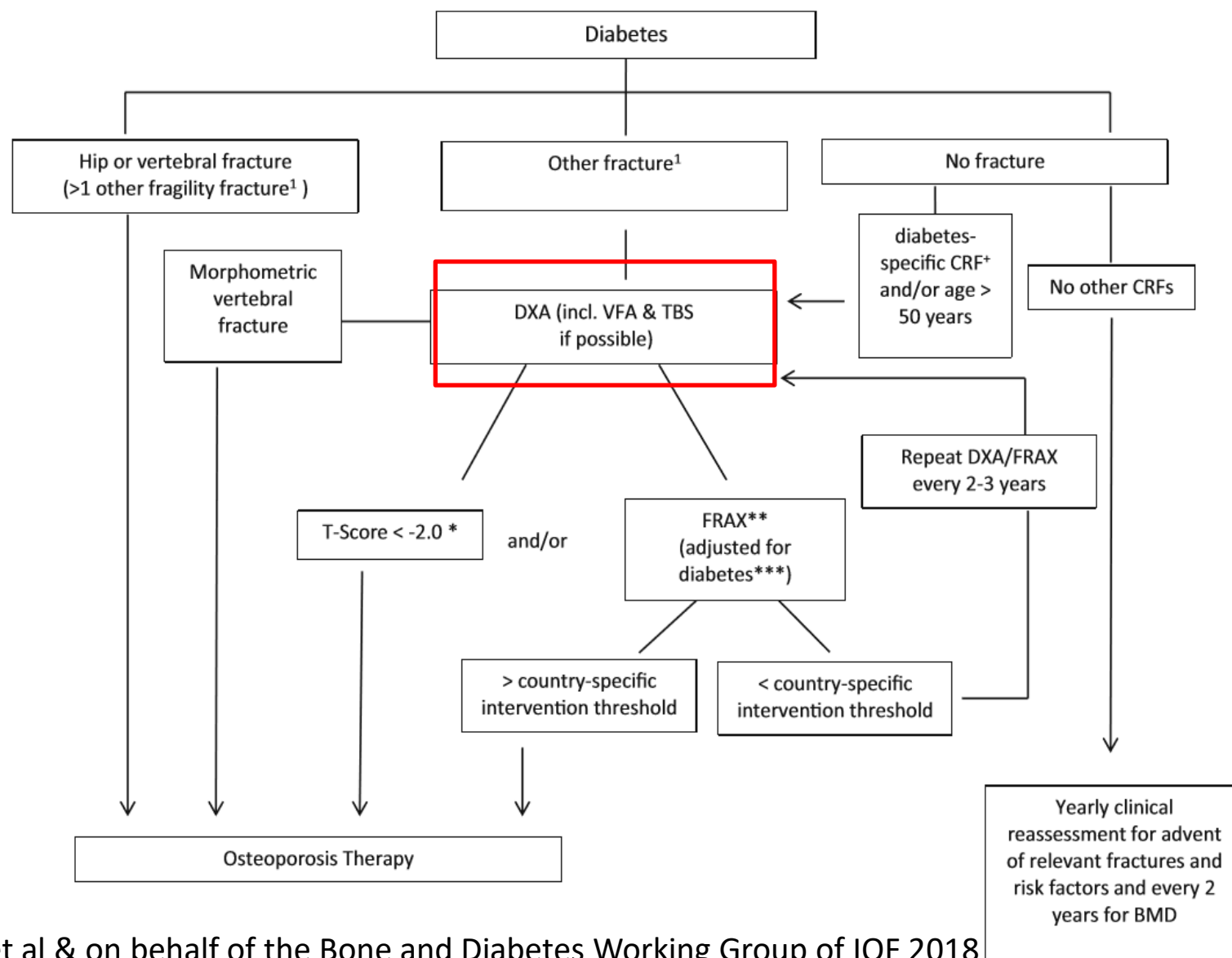
AEs, adverse events; LC, longitudinal cohort; NCC, nested case–control study

Arrows: decreased ↓; increased ↑; no ↔ effect of medication class

?? indicates insufficient evidence to evaluate the effect of the medication class

^aData on AEs from one RCT

Diagnosis and management of bone fragility in diabetes: an emerging challenge



Maria 68 anni , Diabete Tipo 2 da 10 anni



Esegue DXA lombare e femorale
che mostra:

BMD 0.878 lombare T score -2.4

BMD 0.845 femore collo T score-
2.1 tot T score -2.2

Alla luce dei dati densitometrici, quale considerazioni possiamo fare?



Risk of fracture in women with type 2 diabetes: the Women's Health Initiative Observational Study

TABLE 2. BMD measurements at spine and hip^a

	Spine BMD (g/cm ²)		Hip BMD (g/cm ²)	
	Diabetic women (n)	Nondiabetic women (n)	Diabetic women (n)	Nondiabetic women (n)
Baseline ^b	1.04 ± 0.19 (472)	0.97 ± 0.17 (5922)	0.90 ± 0.16 (469)	0.84 ± 0.14 (5915)
Year 3	1.06 ± 0.20 (331)	0.99 ± 0.17 (4839)	0.89 ± 0.16 (331)	0.84 ± 0.13 (4831)
Year 6	1.07 ± 0.21 (253)	1.00 ± 0.18 (4203)	0.87 ± 0.16 (261)	0.84 ± 0.13 (4262)
Year 9	1.12 ± 0.24 (91)	1.02 ± 0.18 (1608)	0.88 ± 0.17 (92)	0.82 ± 0.13 (1606)

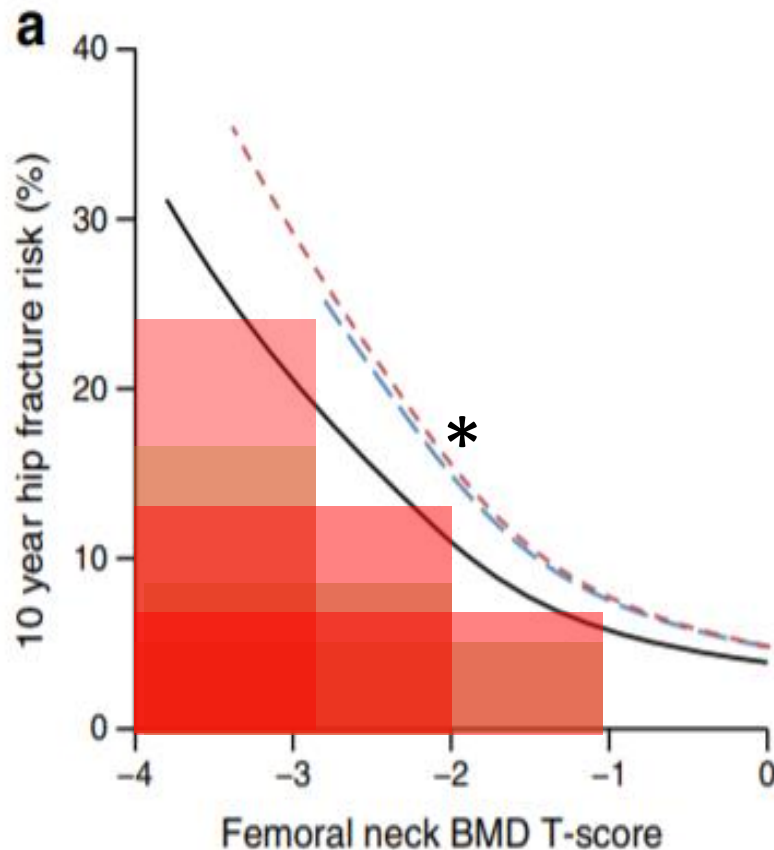
^a All comparisons of diabetic women *vs.* nondiabetic women were $P < 0.01$.

^b Corrected for the use of multiple scanners and the longitudinal nature of the data.

BMD 5-10% higher in diabetics

Prospective study of postmenopausal women with DM2 (n 93,676)

DXA T score BMD Diabete mellito tipo 2



Women 75 years

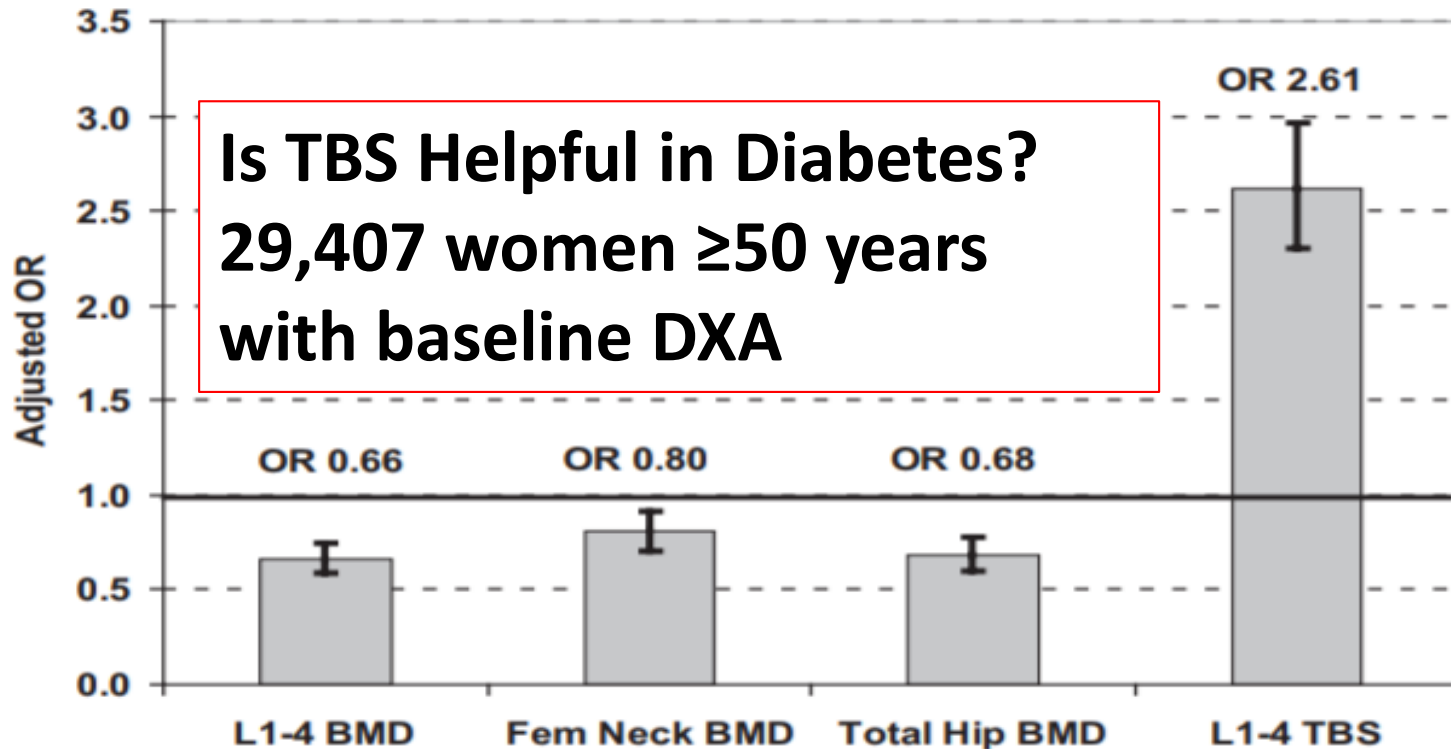
No DM2

DM2 insulin - - - -

DM2 no insulin - - - -

TBS (Trabecular Bone Score) and Diabetes-Related Fracture Risk

William D. Leslie, Berengère Aubry-Rozier, Olivier Lamy, and Didier Hans, for the Manitoba Bone Density Program



Lumbar spine TBS predicts osteoporotic fractures in those with diabetes, and **captures a larger portion of the diabetes-associated fracture risk than BMD.**

Alterazioni proprietà strutturali

1. Aumento porosità corticale
2. Riduzione strutturale trabecolare

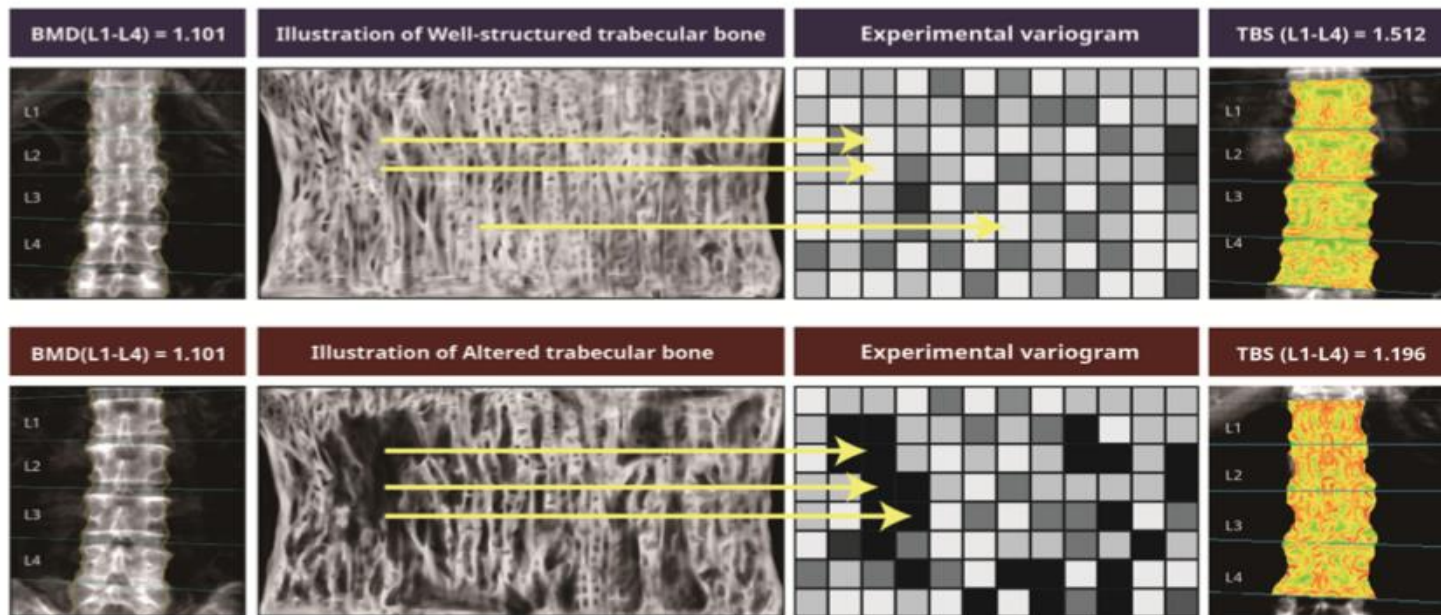
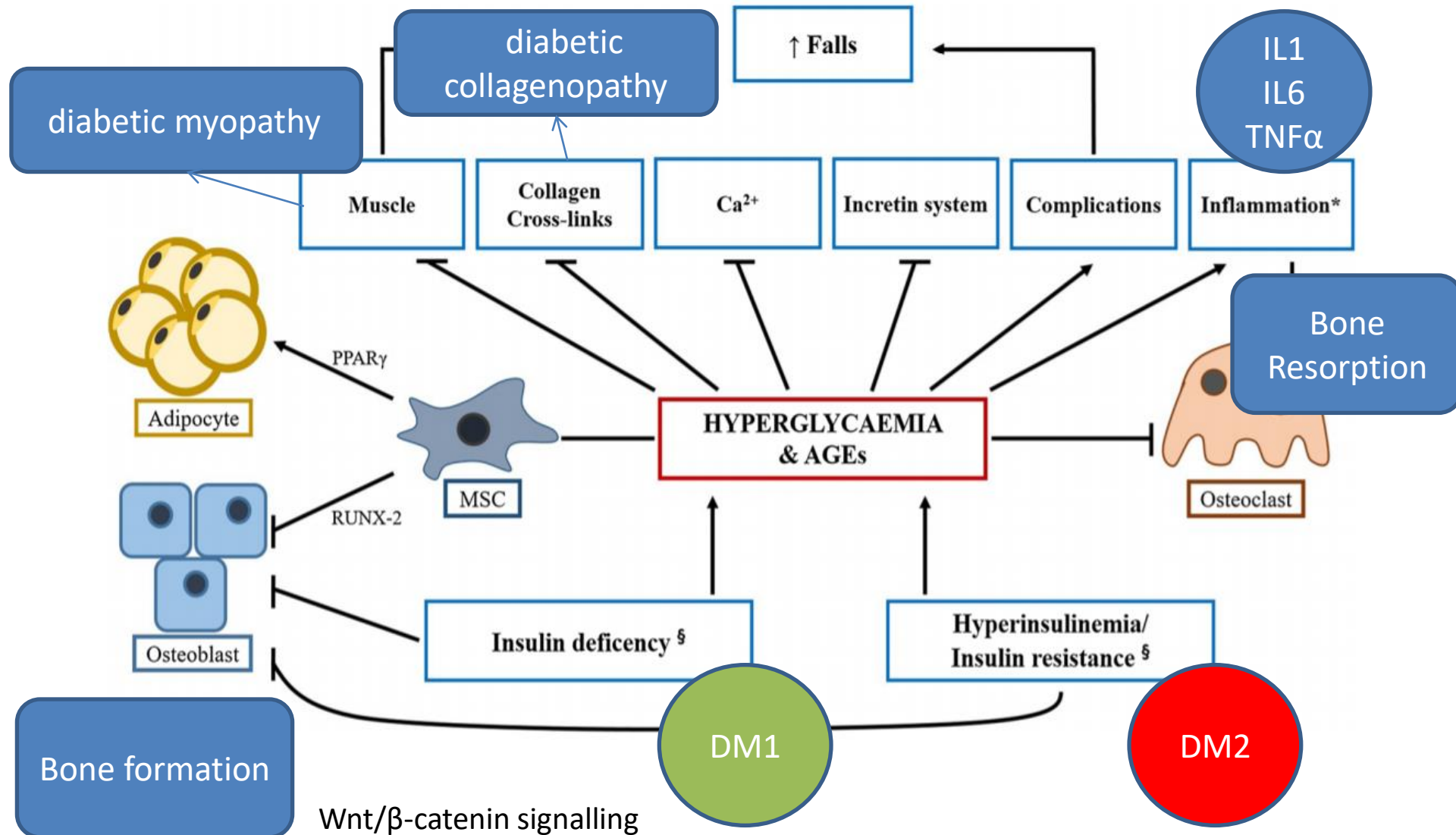
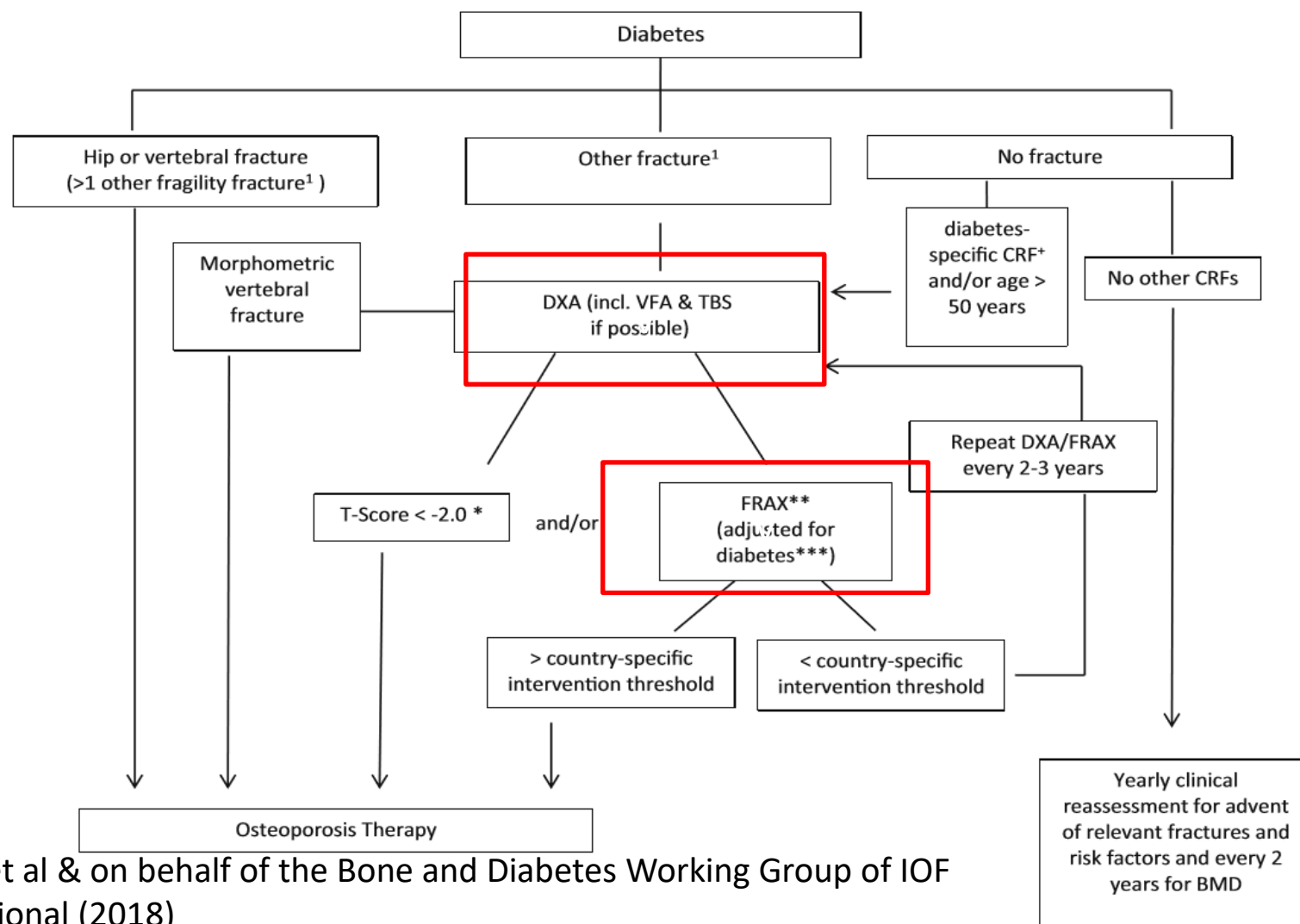


Fig. 4. Trabecular bone score assessed with software in lumbar spine.

Alterazioni nella formazione e rimodellamento osseo



Diagnosis and management of bone fragility in diabetes: an emerging challenge



Fracture Risk Assessment Tool FRAX

The screenshot shows the FRAX Fracture Risk Assessment Tool interface. At the top, there is a red header with the FRAX logo and the text 'Fracture Risk Assessment Tool'. Below the header is a navigation bar with links: Home, Calculation Tool, Paper Charts, FAQ, References, and a language dropdown set to English. The main content area is titled 'Calculation Tool' and contains a questionnaire. The questionnaire asks for personal information (Country: Italy, Name/ID), age, sex, weight, height, and various medical conditions (Previous Fracture, Parent Fractured Hip, Current Smoking, Glucocorticoids, Rheumatoid arthritis, Secondary osteoporosis, Alcohol consumption, and Femoral neck BMD). There are radio buttons for 'No' and 'Yes' for most conditions. A 'Calculate' button is present. On the right side, there are sections for 'Weight Conversion' (Pounds to kg) and 'Height Conversion' (Inches to cm), each with a 'Convert' button. At the bottom right, there is a box with the number '00355816' and the text 'Individuals with fracture risk assessed since 1st June 2011'.

FRAX[®] Fracture Risk Assessment Tool

Home Calculation Tool Paper Charts FAQ References English

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: **Italy** Name/ID: [About the risk factors](#)

Questionnaire:

- Age (between 40 and 90 years) or Date of Birth
Age: Y: M: D:
- Sex
☐ Male ☐ Female
- Weight (kg)
- Height (cm)
- Previous Fracture ☒ No ☐ Yes
- Parent Fractured Hip ☒ No ☐ Yes
- Current Smoking ☒ No ☐ Yes
- Glucocorticoids ☒ No ☐ Yes
- Rheumatoid arthritis ☒ No ☐ Yes
- Secondary osteoporosis ☒ No ☐ Yes
- Alcohol 3 or more units/day ☒ No ☐ Yes
- Femoral neck BMD (g/cm²)
Select BMD

Weight Conversion

Pounds kg

Height Conversion

Inches cm

00355816
Individuals with fracture risk assessed since 1st June 2011

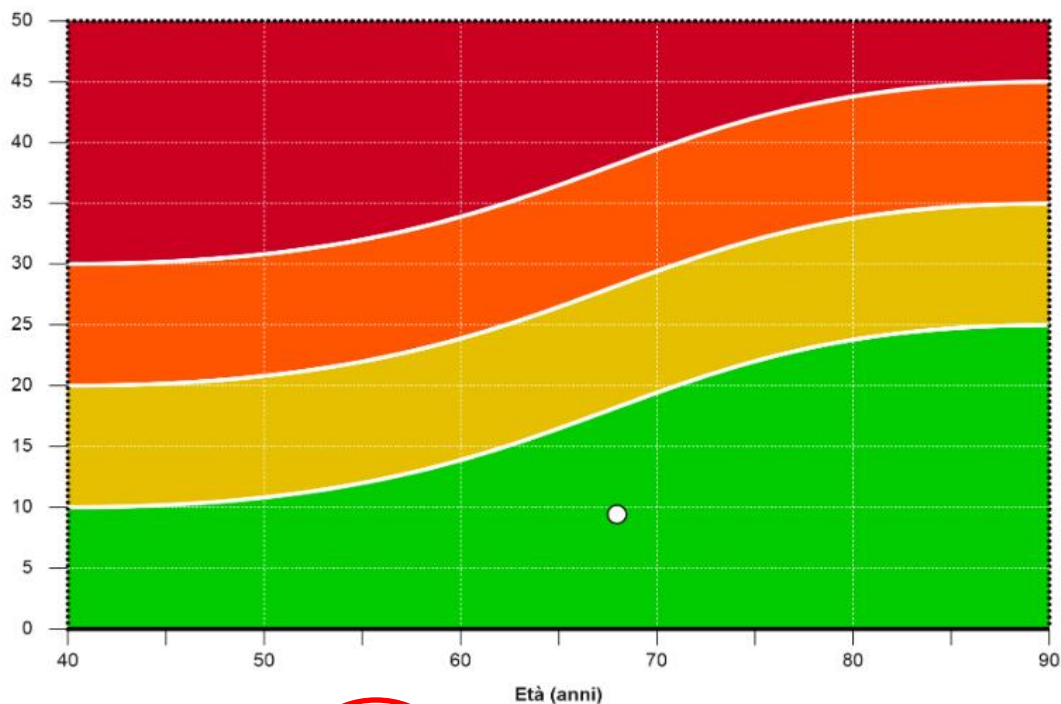
Diabetes is not currently included in the FRAX algorithm

FRAX is equivalent to adding 10 years of age or a crude adjustment of the FRAX score for individuals with type 2 diabetes include indicating 'rheumatoid arthritis'

DEFRACALC 79

Sesso ☐ M ☐ F

Carta del rischio DeFRACALC NOTA79



Eligibile nota 79: No

Rischio di fratture maggiori a 10 anni: 10%

DATA VISITA: 03/12/2019 16:33

CODICE
VISITA/PAZIENTE:

ETÀ: 68

SESSO: F menopausa

PESO: 85 Kg

ALTEZZA: 165 cm

STORIA FAMILIARE
FRATTURA FEMORE E
VERTEBRE: No

PREGRESSE FRATTURE
VERTEBRALI O DI
FEMORE: No

ALTRE PREGRESSE
FRATTURE
OSTEOPOROTICHE: No

FARMACI CHE
AUMENTANO IL
RISCHIO DI FRATTURA: No

COMORBILITÀ CHE
AUMENTANO IL
RISCHIO DI FRATTURA: Diabete

TSCORE FEMORE: -2,20

TSCORE COLONNA: -2,40

- 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 (\pm vitD), Risedronato, Zoledronato ^d ,	denosumab	-----
Trattamento in corso di blocco ormonale adiuvante in donne con carcinoma mammario o uomini con carcinoma prostatico	Alendronato (\pm vitD), Risedronato, Zoledronato ^d , Denosumab ^e	-----	-----
T-score colonna o femore ^e ≤ -4			
T-score colonna o femore ^e ≤ -3 + almeno una delle seguenti condizioni: 1) Familiarità per fratture di vertebre o femore 2) Comorbidità a rischio di frattura (artrite reumatoide o altre connettiviti, <u>diabete</u> , broncopneumopatia cronica ostruttiva, malattia infiammatoria cronica intestinale, AIDS, parkinson,	Alendronato (\pm vit.D), Ris	Denosumab ^e , d	

Diabete

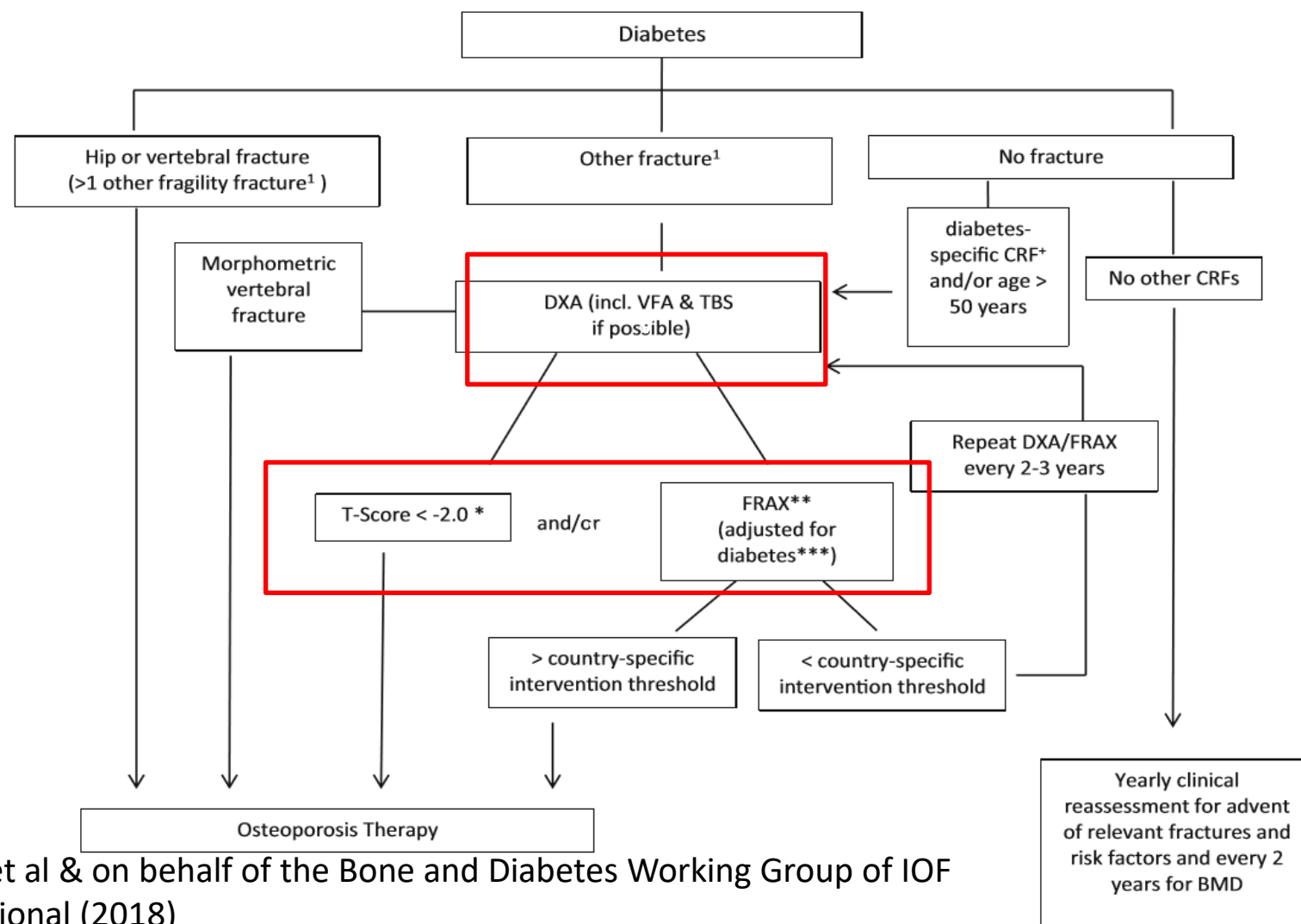
BMD 0.878 lombare

T score -2.4

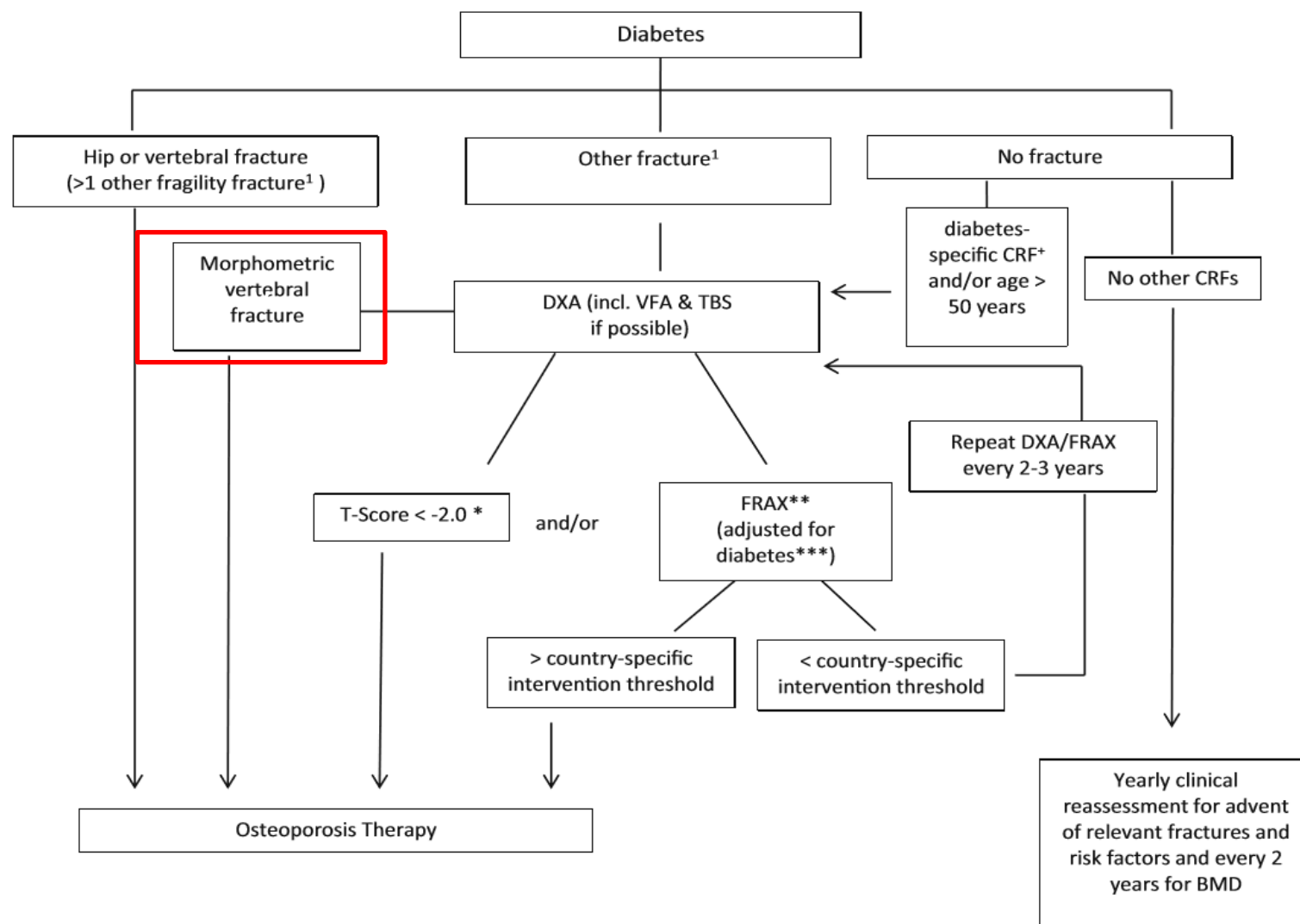
BMD 0.845 femore collo T score-2.1

tot T score -2.2

Diagnosis and management of bone fragility in diabetes: an emerging challenge



Diagnosis and management of bone fragility in diabetes: an emerging challenge



Esame morfometrico

Maria 68 anni , Diabete Tipo 2 da 10 anni

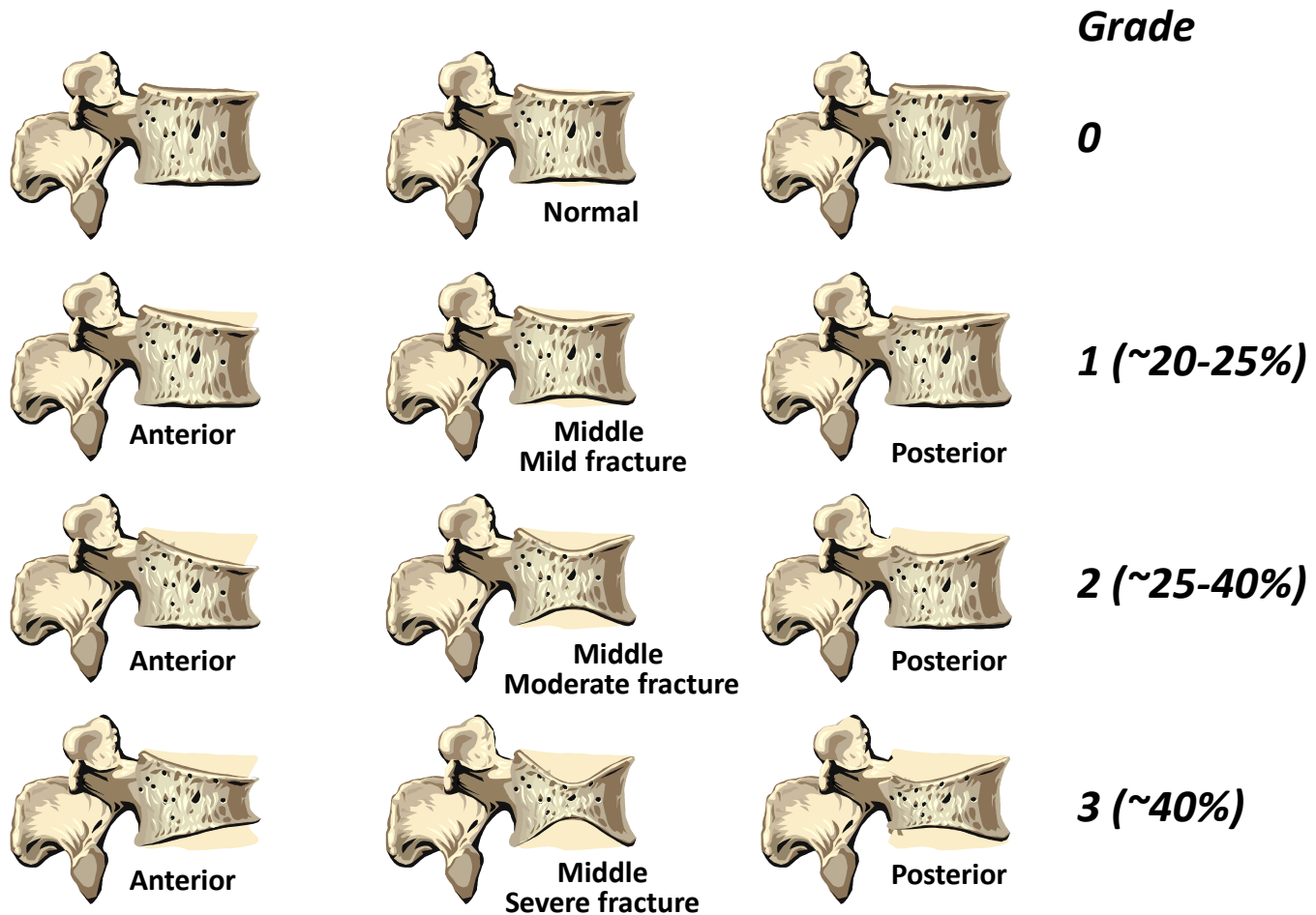


***L2 biconcave
(endplate) fracture***

25-40%

Middle/Mild

Semi-quantitative grading *(Genant et al 1993)*



(Source: Genant HK et al, JBMR 1993; 8:1137-1148)

NOTA 79

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

- **Prevenzione secondaria in soggetti con pregresse fratture osteoporotiche**

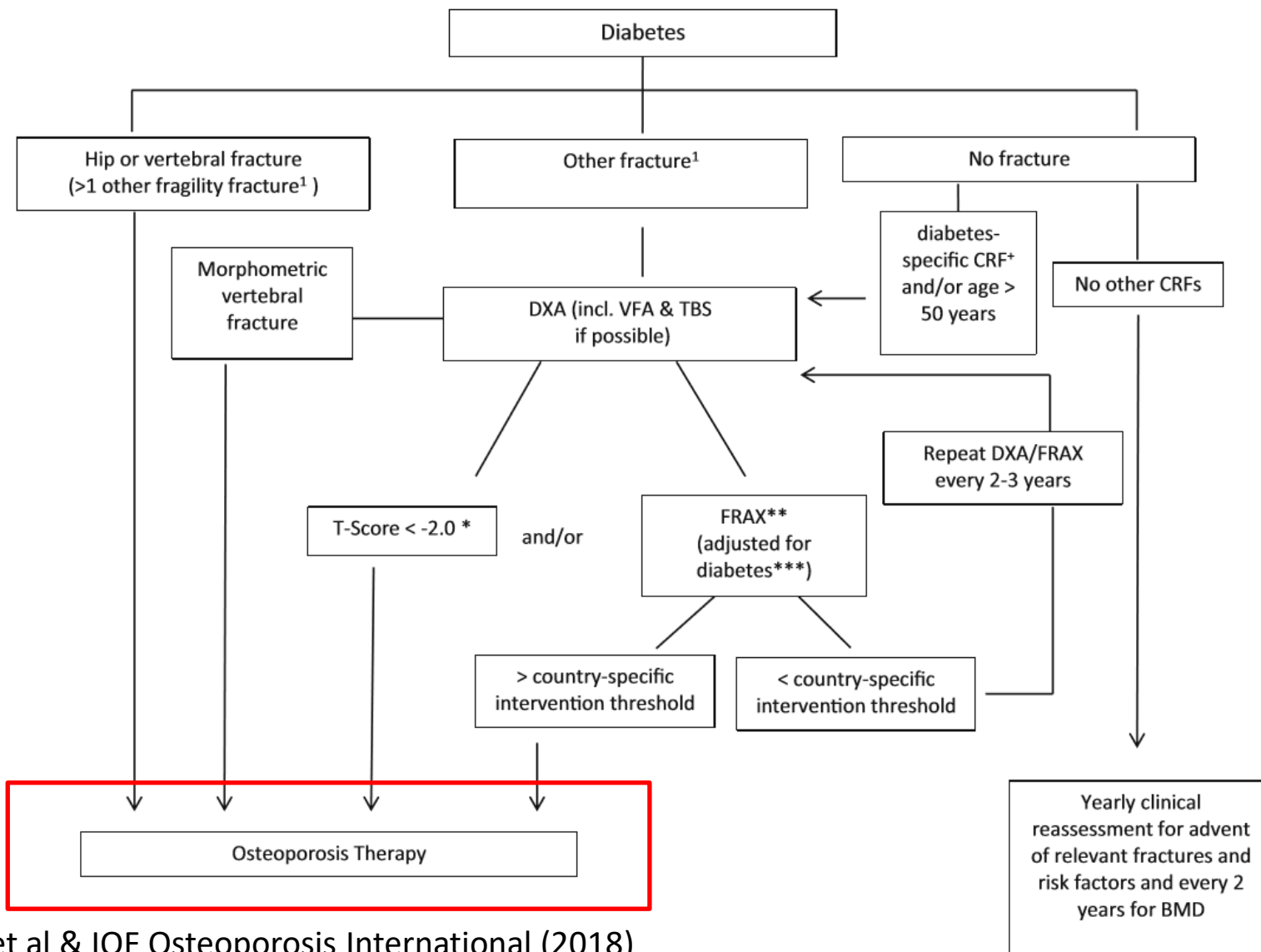
- **vertebrali o di femore**

Condizione	Trattamento I scelta ^a	II scelta	III scelta
1-2 fratture ^b	Alendronato (± vit.D), Risedronato, Zoledronato ^d ,	Denosumab ^e , Ibandronato, Raloxifene, Bazedoxifene	Stronzio ranelato ^f
≥ 3 fratture	Teriparatide ^g	Denosumab ^e , Zoledronato ^d	Alendronato (± vit.D), Risedronato, Ibandronato Stronzio ranelato ^f
≥ 1 frattura + T-score colonna o femore ^c ≤ -4			
≥ 1 frattura + trattamento > 12 mesi con prednisone o equivalenti ≥ 5 mg/die			
Nuova frattura vertebrale o femorale nonostante trattamento in nota 79 da almeno 1 anno			

- **non vertebrali e non femorali**

+ T-score colonna o femore ≤ -3	Alendronato (± vit.D), Risedronato, Zoledronato ^d ,	Denosumab ^e , Ibandronato, Raloxifene, Bazedoxifene	Stronzio ranelato ^f
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Diagnosis and management of bone fragility in diabetes: an emerging challenge



Anti-osteoporosis treatments in diabetic patients

Effects of osteoporosis medications on BMD and the risk of fracture in type 2 diabetes

Medications	BMD	Risk of fracture	
Alendronate [89–91]	↑	NA/=	Fracture Intervention Trial (FIT)
Etidronate [91]	NA	=	
Risedronate [92]	↑	NA	Post hoc analysis of phase III trials in Japan
Raloxifene [91, 93, 94]	NA	↓/=	MORE trial/ RUTH trial
Denosumab	NA	NA	
Teriparatide [95]	↑	=	DANCE study

↑ increase, ↓ decrease, = unchanged, NA not available, BMD bone mineral density

No randomized clinical trials have directly evaluated the antifracture efficacy of osteoporosis treatment in diabetic patients

New! Abaloparatide (bone formation) Romosozumab (Ab anti-sclerostin)

Effect of denosumab, a human monoclonal antibody of receptor activator of nuclear factor kappa-B ligand (RANKL), upon glycemic and metabolic parameters

Effect of denosumab on glycemic parameters

Table 2

Glycemic parameters, metabolic parameters, and T-scores at baseline and 26/52 weeks after denosumab administration in the study cohort.

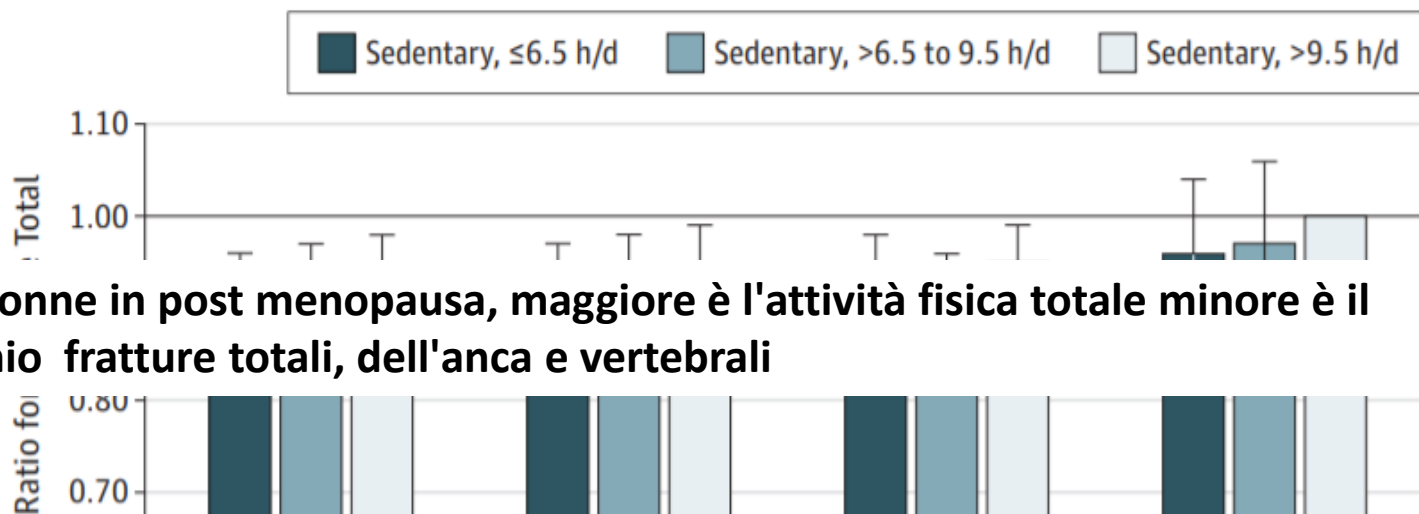
	n = 20				
	Baseline	26 weeks after	P (vs baseline)	52 weeks after	P (vs baseline)
BMI (kg/m ²)	23.6 ± 4.1	22.7 ± 5.6	.168	23.4 ± 4.1	.161
FPG (mg/dL)	116.7 ± 21.5	119.0 ± 22.0	.273	109.3 ± 18.5	.048
HbA _{1c} (%)	6.52 ± 0.56	6.48 ± 0.60	.284	6.32 ± 0.61	.019*
HOMA-β	59.9 ± 56.0	41.8 ± 25.3	.051	44.2 ± 25.1	.070
HOMA-IR	2.00 ± 1.21	1.66 ± 0.98	.066	1.38 ± 0.76	.008*
LDL-C (mg/dl)	107.8 ± 16.8	108.8 ± 20.1	.391	105.5 ± 20.8	.204
HDL-C (mg/dl)	64.1 ± 15.3	66.8 ± 17.4	.069	65.1 ± 15.2	.314
TG (mg/dl)	111.9 ± 38.2	113.8 ± 46.7	.422	108.1 ± 40.2	.231
AST (U/L)	22.7 ± 5.7	22.9 ± 5.6	.404	20.9 ± 4.8	.014*
ALT (U/L)	19.2 ± 8.1	18.4 ± 7.4	.190	16.6 ± 6.6	.004*
γ-GTP (U/L)	25.5 ± 16.8	26.7 ± 16.0	.279	23.7 ± 14.5	.123
T-score (lumbar spine)	-1.35 ± 1.39	N.A.	–	-0.91 ± 1.55	<.001 [#]
T-score (femoral neck)	-2.81 ± 1.00	N.A.	–	-2.45 ± 1.02	.001 [#]

Altre misure terapeutiche

- Attività fisica
- No fumo o alcol
- Apporto di Vitamina D
- Apporto di calcio 1000 mg/die (dieta)
- Controllo glicemico meno stringete nei pazienti anziani (ipoglicemie)
- Utilizzare ipoglicemizzanti con effetto neutro o positivo sul metabolismo osseo (metformina/incretine)

Original Investigation | Public Health

Association of Physical Activity and Fracture Risk Among Postmenopausal Women

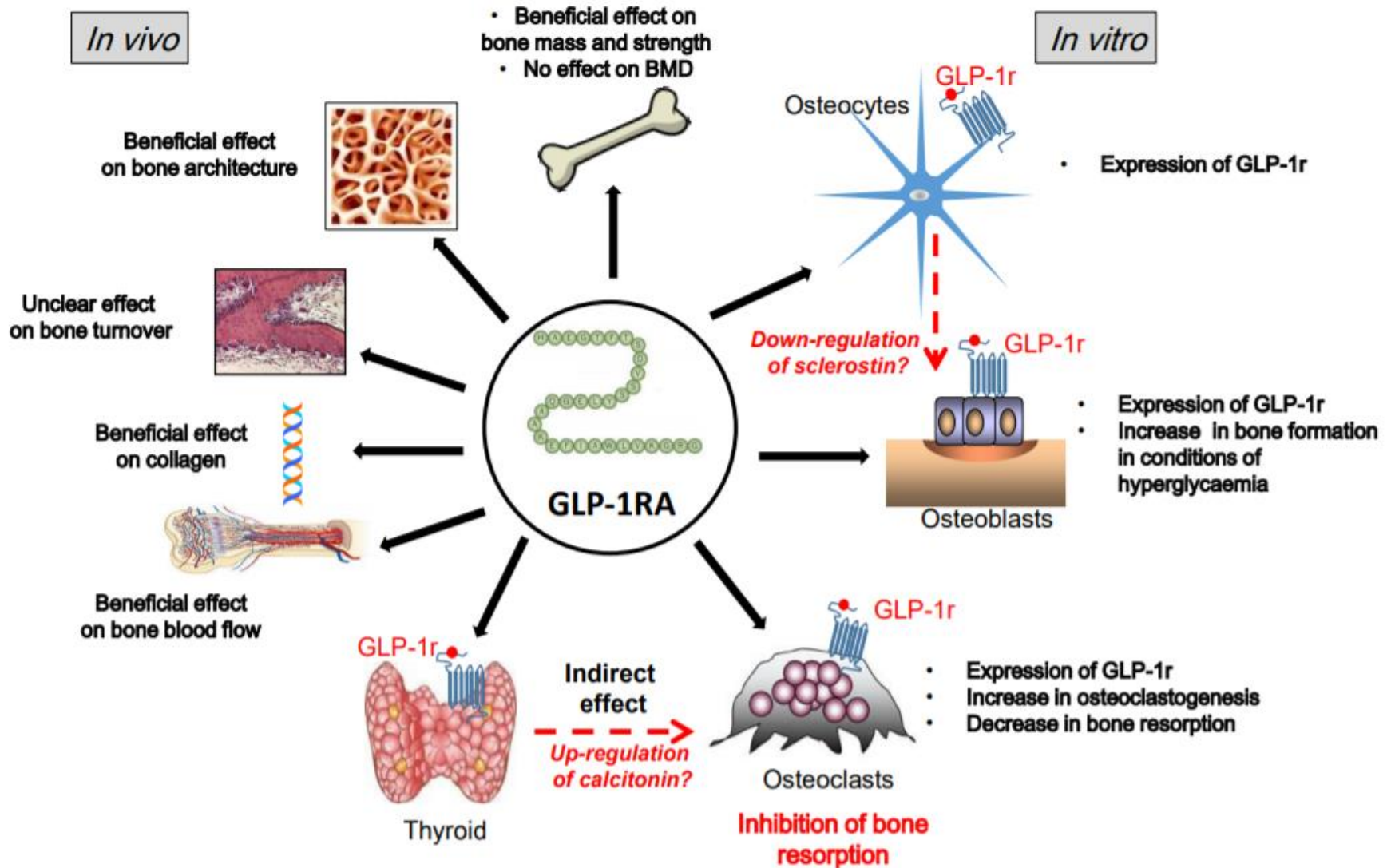


In donne in post menopausa, maggiore è l'attività fisica totale minore è il rischio fratture totali, dell'anca e vertebrali

Anche attività fisiche di lieve intensità (cammino) sono in grado di ridurre il rischio di frattura

La sedentarietà aumenta il rischio di frattura indipendentemente dall' attività fisica, per un tempo sedentario >9,5 h verso <6,5 h al giorno

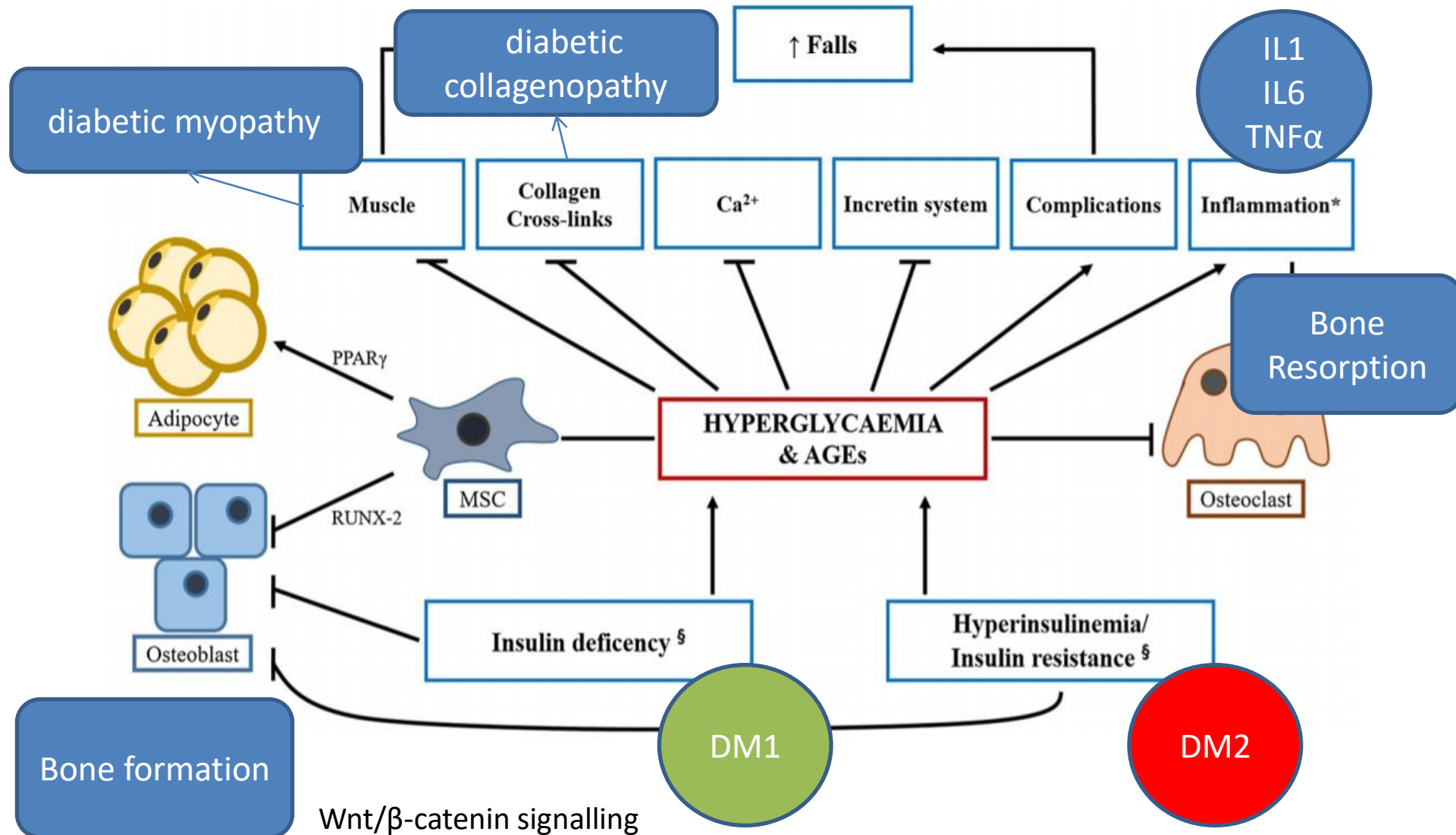
Novel skeletal effects of Glucagon-like peptide-1 (GLP-1) receptor agonists

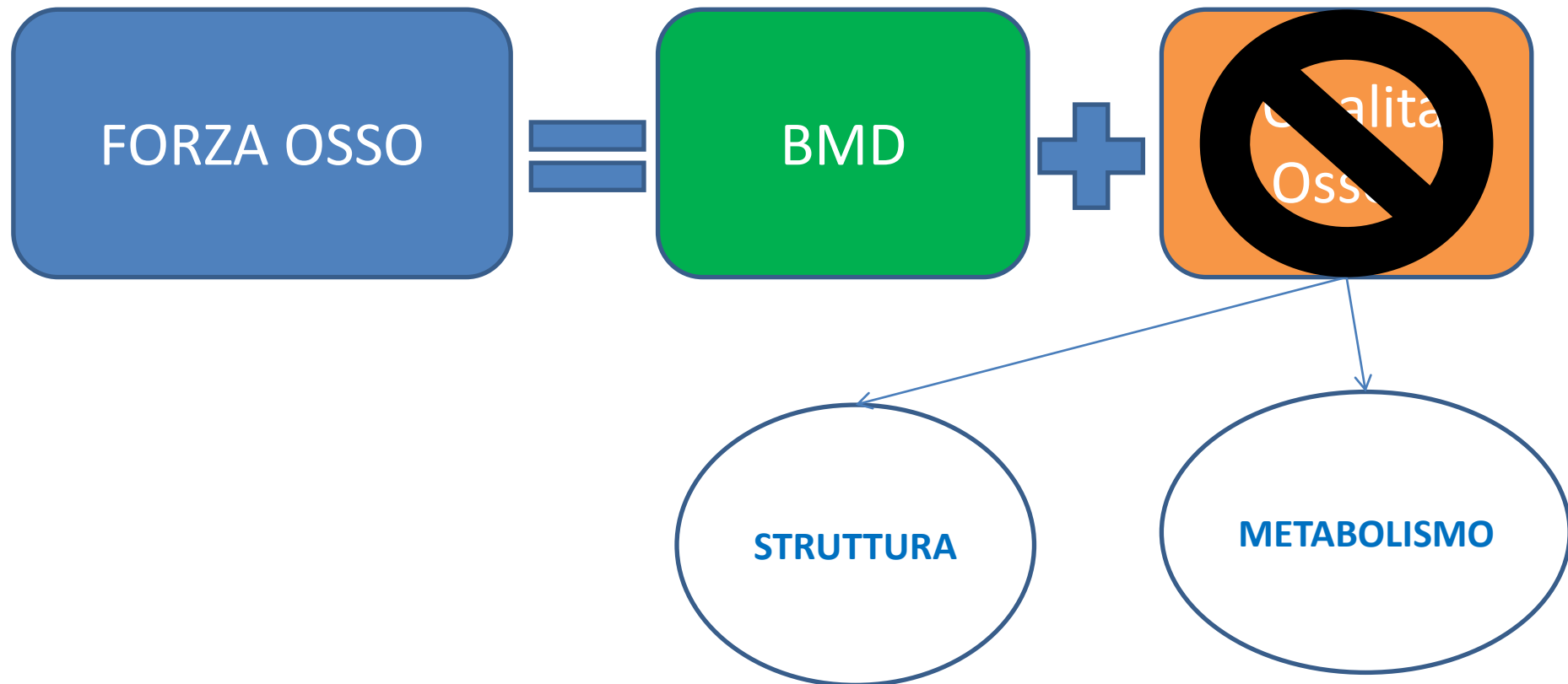


Conclusioni

- Il diabete nelle donne in menopausa **aumenta il rischio di fratture** da fragilità
- La fragilità ossea è caratterizzata da alterazioni predominanti nella **qualità ossea** (microarchitettura, proprietà dei materiali) con o senza riduzioni di BMD
- La fragilità ossea aumenta con lo scarso controllo della glicemia, la durata del diabete, le complicanze microvascolari, la necessità di insulina e alcuni antidiabetici orali
- **Specifici markers** di rischio di fratture nel diabete, specialmente di tipo 2, che riflettono le alterazioni della «qualità ossea» devono essere sviluppati
- Mancanza degli effetti dei farmaci per l'osteoporosi sulla riduzione della fragilità ossea nel diabete

Alterazioni nella formazione e rimodellamento osseo





Increased cortical porosity in T2DM with fractures

high-resolution peripheral quantitative computed tomography (HR-pQCT)

