AGGARWAL CLINIC
(Estd. by Padam Shri Dr. N.D. Aggarwal)
1-E, The Mall, Patiala - 147001 Tel.: 0175-2212054

CLINICIAN NOTE

EVIDENCE SUMMARY

GLP-1 and obesity drugs: effect on bone

Bones before they break · lecture preparation · 18 October 2026 · For discussion, not a prescription



Dr Aditya Aggarwal

Bottom line: GLP-1 receptor agonists do not clearly raise or lower fracture risk in trials and meta-analyses. Large weight loss on semaglutide or liraglutide alone costs a little hip and spine bone density, and about a quarter of the weight lost is lean mass. Exercise, above all resistance training, prevents most of this bone loss. Older adults and postmenopausal women at fracture risk need a bone plan before starting. Tirzepatide and newer drugs have no bone trials yet.

HOW TO READ THE GRADES

- **LoE** (level of evidence): I = large randomised trial or meta-analysis of trials; II = smaller randomised trial or prospective cohort; III = retrospective cohort or post hoc analysis; IV = case series or mechanistic human study; V = expert opinion, narrative review or animal data.
- **Certainty** (High, Moderate, Low, Very low) is our GRADE-style reading of the cited sources.
- Most trials measure bone density (BMD) or bone turnover markers (P1NP = formation, CTX = resorption), not fractures. Fracture data come mainly from people with type 2 diabetes.

1. What changes practice

Bone plan

FIVE POINTS FOR THE LECTURE

- Pair every GLP-1 prescription with exercise. In a 52-week trial, liraglutide plus exercise kept hip and spine BMD at placebo levels while giving the largest weight loss; liraglutide alone lost more BMD than exercise alone [1].
- Prescribe resistance training (at least 2 days a week) plus aerobic exercise, and adequate protein, for everyone losing weight on these drugs [2,3,4].
- In older adults and postmenopausal women with fracture risk, expect small falls in hip and spine BMD on semaglutide [5]. Assess fracture risk before starting and treat osteoporosis on standard criteria.
- Do not tell patients these drugs protect bone. The protective signal in type 2 diabetes is from older trial data with few fractures, and cohort data conflict [6,7,8].
- Bariatric surgery carries a clear rise in fracture risk, more after malabsorptive procedures; GLP-1 drugs have not shown this [9,10].

CERTAINTY: LOW *Moderate for BMD effects in randomised trials; low for fracture effects; very low for tirzepatide and newer drugs.*

2. What the guidance says

Newest first

CONSENSUS AND ADVISORIES

No guideline dedicated to obesity drugs and bone was found. The statements below cover bone and muscle as part of wider obesity or nutrition advice.

GROUP, YEAR	POSITION RELEVANT TO BONE AND MUSCLE
International Delphi consensus, 2026 [11]	52 statements on nutrition and lifestyle with GLP-1-based therapy, covering body composition and physical activity. Built mostly on indirect evidence from bariatric nutrition guidance.
Swiss obesity guidance, 2026 [12]	Multimodal lifestyle care is the base of all weight management: nutrient-dense diet, 150 to 300 minutes of moderate aerobic exercise a week, plus resistance training. Advises body composition assessment.

GROUP, YEAR	POSITION RELEVANT TO BONE AND MUSCLE
ACLM, ASN, OMA and TOS joint advisory, 2025 [3]	Lists muscle and bone loss as a key challenge of GLP-1 therapy. Advises baseline muscle strength, function and body composition checks, and resistance training with appropriate diet to preserve muscle and bone.
Mechanick, strategy review, 2025 [2]	Muscle loss on incretin drugs can be about 10% or more of muscle mass over 68 to 72 weeks. Recommends protein, micronutrients and resistance training for all.
Endocrine Society vitamin D, 2024 [13]	Against routine vitamin D testing, including in obesity. Suggests empiric vitamin D for adults over 75. Does not replace treatment where there is an established indication.

OUTSIDE INDIA *Outside India: all statements come from the US, Europe or international panels. Not Indian data; use as a guide.*

3. How these drugs could affect bone — Mechanisms

GLP-1, GIP AND UNLOADING

- GLP-1 receptor: mice without the receptor have cortical osteopenia, bone fragility and more bone resorption. The effect ran through thyroid calcitonin, which exendin-4 raised in mice [14]. This is animal data; a calcitonin route has not been shown in humans.
- GIP: short GIP infusions in humans cut the resorption marker CTX by up to about 50 to 59%, independently of insulin and glucose, with no change in P1NP [15,16]. This is the rationale for hoping that GIP-containing drugs such as tirzepatide spare bone; there are no bone outcome trials to confirm it.
- Weight loss itself: less mechanical loading, lower intake of energy, protein and calcium, and hormonal shifts cause high-turnover bone loss after diet or bariatric surgery [10].
- Lab-model benefits of GLP-1 drugs on bone are seen at drug levels much higher than those in patients [10].

CERTAINTY: VERY LOW *Mechanistic and animal data; human relevance unproven.*

4. Bone density and turnover in trials — BMD and markers

RANDOMISED DATA

- Liraglutide 3.0 mg after diet-induced weight loss (Denmark, n=195, 52 weeks, no diabetes): the liraglutide-plus-exercise group lost the most weight (16.9 kg) with no BMD loss against placebo. Liraglutide alone lost more BMD than exercise alone at the hip (-0.013 g/cm², P=.03) and spine (-0.016 g/cm², P=.04) [1].
- Liraglutide 1.2 mg after a 12% diet weight loss (Denmark, n=37 women, 52 weeks): bone mineral content loss was about four times smaller than with diet alone; P1NP rose 16% and CTX did not change [17].
- Semaglutide 1.0 mg in people at increased fracture risk (Denmark, n=64, 55 postmenopausal women, 52 weeks): weight fell 6.8 kg; spine BMD fell 0.018 and total hip 0.020 g/cm² against placebo; femoral neck was unchanged. CTX rose; P1NP did not change [5].
- Meta-analysis of 25 trials in type 2 diabetes (2025): BMD at spine, femoral neck and hip was higher on GLP-1 drugs, with P1NP up and CTX down [18]. Larger 2026 meta-analysis of 60 studies (46 RCTs): no effect on BMD in the most-adjusted models [19].

OUTSIDE INDIA *Outside India: the BMD trials are Danish; the meta-analyses pool mainly Western and East Asian trials. Not Indian data; use as a guide.*

CERTAINTY: MODERATE *Consistent small BMD loss with large weight loss on a GLP-1 drug alone; trial sizes small (37 to 195).*

5. Lean mass — Muscle

WHAT IS LOST WITH THE WEIGHT

- Tirzepatide (SURMOUNT-1 DXA substudy, n=160, 72 weeks): weight fell 21.3%, fat mass 33.9% and lean mass 10.9%. About three-quarters of the weight lost was fat and one quarter lean mass [20].
- Across 60 studies, GLP-1 drugs reduced lean mass (SMD 0.52), mainly with liraglutide and semaglutide. Heterogeneity was very high (I^2 88%) and certainty low [19].
- Semaglutide 2.4 mg (STEP 1) gave 14.9% weight loss at 68 weeks against 2.4% on placebo; the scale of loss is the main driver of lean and bone loss [2,21].
- A 2026 review of 16 RCTs found lean mass loss in proportion to weight loss, and no trial that directly assessed bone health [22].

CERTAINTY: MODERATE *Lean mass loss is consistent; its effect on falls and fractures is not measured.*

6. Fracture data

Fractures

TRIALS, META-ANALYSES AND COHORTS

SOURCE	POPULATION	FRACTURE RESULT
Cheng 2019, MA of 38 RCTs [6]	39,795 with type 2 diabetes	OR 0.71 (0.56 to 0.91); liraglutide OR 0.56; benefit only beyond 52 weeks
Tan 2025, MA of 25 RCTs [18]	Type 2 diabetes	RR 0.80 (0.47 to 1.36), not significant
Beaudart 2026, SR/MA, 60 studies [19]	1.25 million people	No effect on fracture in most-adjusted models
Hidayat 2019, MA of cohorts [23]	Observational	Any fracture RR 0.65 (0.24 to 1.74); hip RR 0.21 (0.04 to 0.98)
Hamad 2026, target trial emulation [8]	133,606 aged 50 to 90 with type 2 diabetes	HR 0.79 (0.76 to 0.83) vs DPP-4 inhibitors; NNT 126. Without diabetes: HR 1.13 (1.04 to 1.23)
Kasher Meron 2026, cohort, Israel [7]	46,177 aged 65 or more with type 2 diabetes	Fragility fracture HR 1.11 (1.01 to 1.21) vs SGLT2 or DPP-4 inhibitors
Hsu 2025, cohort [24]	66,329 per matched group	Tirzepatide vs other GLP-1 drugs: osteoporosis or fragility fracture HR 1.44 (1.22 to 1.69) at 14 months

Reading the table: randomised data lean towards neutral or slightly protective in type 2 diabetes, but fractures were rare secondary outcomes. Cohort studies conflict and are open to confounding; the signals of harm in older adults, in people without diabetes and with tirzepatide are hypotheses, not proof.

OUTSIDE INDIA *Outside India: the cohorts are from Israel and multinational US-led health record networks. Not Indian data; use as a guide.*

CERTAINTY: LOW *Few events in trials; conflicting observational studies.*

7. Other obesity drugs

Beyond GLP-1

ORLISTAT, OTHERS, NEWER AGENTS

- Orlistat: one small 1-year RCT (n=30) found no BMD difference from placebo, with a pattern of early negative vitamin D balance [25]. Bone changes with orlistat were no greater than with control in a review [26].
- Phentermine-topiramate: bone effect assumed negative but not well studied. Naltrexone-bupropion and setmelanotide: bone effects largely unknown [27].
- Dual and triple agonists and amylin analogues (the class of retatrutide and cagrilintide): only preclinical bone data, possibly positive [27]. No human bone outcome data were found for retatrutide or cagrilintide.
- Tirzepatide: no published trial with BMD or fracture endpoints was found; lean mass data above and one cohort signal are all that exist [20,24].

CERTAINTY: VERY LOW *Little or no human bone data for any of these drugs.*

8. Compared with diet and surgery

Context

HOW MUCH BONE DOES WEIGHT LOSS COST

- Hip BMD falls by about 1 to 1.5% with diet-induced weight loss and by 8 to 11% after gastric bypass [26].
- Bariatric surgery raises fracture risk: RR 1.20 (1.15 to 1.26) in observational and 1.16 (1.00 to 1.33) in interventional studies, higher after malabsorptive procedures [9]. Another meta-analysis found RR 1.29, and RR 1.68 for upper limb fractures [28].
- Calorie restriction and surgery cause high-turnover bone loss; GLP-1 drug effects on bone so far look smaller than those of surgery [10,27].

CERTAINTY: MODERATE *Consistent for surgery; diet-related BMD loss is small.*

9. Older adults and postmenopausal women

At-risk groups

WHERE CAUTION IS NEEDED

- The only trial in people at increased fracture risk (mostly postmenopausal women) showed hip and spine BMD loss and higher CTX on semaglutide over one year [5].
- In adults aged 65 or more with type 2 diabetes, one large cohort found an 11% higher fragility fracture rate on GLP-1 drugs [7].
- Exercise in dieting obese older adults (n=160, 6 months, about 9% weight loss): hip BMD fell 1% with combined and 0.5% with resistance training, against 3% with aerobic training alone; lean mass was also better kept [29].
- A review of obesity drugs in older adults advises resistance training to protect muscle and bone [30].

CERTAINTY: LOW *One small trial and one cohort; no fracture trial in this group.*

10. Protecting bone during treatment

Mitigation

PRACTICAL STEPS

- Exercise: WHO advice of 150 minutes of moderate aerobic activity weekly plus resistance training on at least 2 days is especially important during weight loss [4]. Combined training kept BMD in trials of liraglutide and of diet in older adults [1,29].
- Protein and micronutrients: adequate protein, micronutrients and resistance training for all patients on incretin drugs [2,3]. Exact protein targets in these papers rest on indirect evidence [11].
- Vitamin D and calcium: no routine vitamin D test is needed for obesity alone; empiric vitamin D is suggested over 75 years [13].
- Monitoring: baseline body composition and muscle function assessment is advised [3]. Interpretation (not a sourced finding): a baseline DXA is reasonable in postmenopausal women and older adults with fracture risk factors starting a GLP-1 drug.
- Antiresorptive: no trial has tested adding an antiresorptive to a GLP-1 drug. Interpretation (not a sourced finding): start one on standard osteoporosis criteria, not because of the obesity drug alone.

CERTAINTY: LOW *Exercise data are randomised; nutrition and monitoring advice is expert consensus.*

11. Indian context

Indian data

WHAT INDIAN STUDIES ADD

Scale of need: in ICMR-INDIAB-17 (n=113,043 adults across all states), 11.4% had diabetes, 15.3% prediabetes, 28.6% generalised obesity and 39.5% abdominal obesity [31].

NO INDIAN DATA *No Indian study of GLP-1 drugs, tirzepatide or other obesity drugs with BMD, bone marker, lean mass or fracture outcomes was found.*

OUTSIDE INDIA *Outside India: all bone and lean mass data above come from Europe, the US, Israel and multinational trials. Not Indian data; use as a guide.*

12. Key studies

Graded table

LOE, DESIGN, SIZE, EFFECT

STUDY	LOE, DESIGN	N; FOLLOW-UP	EFFECT
Jensen 2024 [1]	II, secondary analysis of RCT	195; 52 wk	Lira + exercise kept BMD; lira alone lost hip and spine BMD vs exercise
Iepsen 2015 [17]	II, RCT	37; 52 wk	Lira 1.2 mg: BMC loss 4x smaller; P1NP +16%
Hansen 2024 [5]	II, phase 2 RCT	64; 52 wk	Sema: hip -0.020, spine -0.018 g/cm²; CTX up
SURMOUNT-1 DXA [20]	II, substudy of RCT	160; 72 wk	Tirzepatide: lean mass -10.9%
Villareal 2017 [29]	II, RCT	160; 6 mo	Hip BMD -0.5 to -1% with resistance or combined vs -3% aerobic
Cheng 2019 [6]	I, MA of RCTs	38 RCTs; 39,795	Fracture OR 0.71
Tan 2025 [18]	I, MA of RCTs	25 RCTs	Fracture RR 0.80, NS; BMD up
Beaudart 2026 [19]	I, SR/MA (mixed)	60 studies; 1.25 million	No BMD or fracture effect; lean mass down
Hamad 2026 [8]	III, target trial emulation	133,606	HR 0.79 vs DPP-4i in diabetes

STUDY	LOE, DESIGN	N; FOLLOW-UP	EFFECT
Kasher Meron 2026 [7]	III, retrospective cohort	46,177; 35 mo	HR 1.11 in age 65 or more
Hsu 2025 [24]	III, retrospective cohort	66,329 per group; 14 mo	Tirzepatide HR 1.44 vs other GLP-1
Bariatric MA 2022 [9]	I-II, MA (mixed designs)	Observational and interventional	Fracture RR 1.20 and 1.16

Where the evidence is weak

FLAGS

WEAK OR LIMITED EVIDENCE

- No trial has a fracture endpoint for any obesity drug; trial fracture data are secondary outcomes in type 2 diabetes [6,18].
- BMD trials are small (37 to 195 people) and last one year or less [1,5,17].
- Tirzepatide, retatrutide, cagrilintide, setmelanotide, naltrexone-bupropion: no human bone outcome trials; the tirzepatide fracture signal is from one 14-month cohort with a composite outcome [24,27].
- Cohort findings conflict (protective in type 2 diabetes, harmful in older adults and in people without diabetes) [7,8].
- Nutrition and monitoring advice is consensus built on indirect evidence [11].
- Industry links: the semaglutide trial used drug supplied by the manufacturer [5].
- Corrections: published corrections exist for the 2025 joint advisory, the SURMOUNT-1 DXA substudy and the Endocrine Society vitamin D guideline; figures here are from the original abstracts [3,13,20].
- India: no Indian bone data for any obesity drug.

References

VERIFIED BY PMID AND DOI · VANCOUVER STYLE

1. Jensen SBK, Sørensen V, Sandsdal RM, et al. Bone Health After Exercise Alone, GLP-1 Receptor Agonist Treatment, or Combination Treatment: A Secondary Analysis of a Randomized Clinical Trial. JAMA Netw Open. 2024. PMID 38916894; doi:10.1001/jamanetworkopen.2024.16775

2. Mechanick JI, Butsch WS, Christensen SM, et al. Strategies for minimizing muscle loss during use of incretin-mimetic drugs for treatment of obesity. Obes Rev. 2025. PMID 39295512; doi:10.1111/obr.13841

3. Mozaffarian D, Agarwal M, Aggarwal M, et al. Nutritional priorities to support GLP-1 therapy for obesity: A joint Advisory from the American College of Lifestyle Medicine, the American Society for Nutrition, the Obesity Medicine Association, and The Obesity Society. Obesity (Silver Spring). 2025. PMID 40445127; doi:10.1002/oby.24336

4. Jiang BC, Villareal DT. The Benefits of Exercise Training in Combination With Weight Loss Therapies. Diabetes. 2025. PMID 40627343; doi:10.2337/dbi25-0001

5. Hansen MS, Wölfel EM, Jeromdesella S, et al. Once-weekly semaglutide versus placebo in adults with increased fracture risk: a randomised, double-blinded, two-centre, phase 2 trial. EClinicalMedicine. 2024. PMID 38737002; doi:10.1016/j.eclinm.2024.102624

6. Cheng L, Hu Y, Li YY, et al. Glucagon-like peptide-1 receptor agonists and risk of bone fracture in patients with type 2 diabetes: A meta-analysis of randomized controlled trials. Diabetes Metab Res Rev. 2019. PMID 30974033; doi:10.1002/dmrr.3168

7. Kasher Meron M, Hornik-Lurie T, Twig G, et al. GLP-1 receptor agonists and the risk of fragility fractures in older adults with type 2 diabetes. J Clin Endocrinol Metab. 2026. PMID 41665888; doi:10.1210/clinem/dgag056

8. Hamad CD, Wiener J, Golzar A, et al. Glucagon-Like Peptide-1 Receptor Agonists and Fragility Fracture Risk in Type 2 Diabetes. JAMA Netw Open. 2026. PMID 42496972; doi:10.1001/jamanetworkopen.2026.25141

9. Chaves Pereira de Holanda N, de Lima Carlos I, Chaves de Holanda Limeira C, et al. Fracture Risk After Bariatric Surgery: A Systematic Literature Review and Meta-Analysis. Endocr Pract. 2022. PMID 34563701; doi:10.1016/j.eprac.2021.09.007

10. Paccou J, Gagnon C, Yu EW, et al. Effects of weight-loss interventions on bone health in people living with obesity. J Bone Miner Res. 2025. PMID 41042228; doi:10.1093/jbmr/zjaf135

11. Sievenpiper JL, Ard J, Blüher M, et al. Nutritional and lifestyle supportive care recommendations for management of obesity with GLP-1 - based therapies: An expert consensus statement using a modified Delphi approach. Obes Pillars. 2026. PMID 41502845; doi:10.1016/j.obpill.2025.100228

12. Gerber PA, Collet TH, Favre L, et al. Swiss obesity clinical practice guidance. Swiss Med Wkly. 2026. PMID 42312974; doi:10.57187/5415

13. Demay MB, Pittas AG, Bikle DD, et al. Vitamin D for the Prevention of Disease: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2024. PMID 38828931; doi:10.1210/clinem/dgae290

14. Yamada C, Yamada Y, Tsukiyama K, et al. The murine glucagon-like peptide-1 receptor is essential for control of bone resorption. Endocrinology. 2008. PMID 18039776; doi:10.1210/en.2007-1292

15. Nissen A, Christensen M, Knop FK, et al. Glucose-dependent insulinotropic polypeptide inhibits bone resorption in humans. J Clin Endocrinol Metab. 2014. PMID 25144635; doi:10.1210/jc.2014-2547

16. Christensen MB, Lund A, Calanna S, et al. Glucose-Dependent Insulinotropic Polypeptide (GIP) Inhibits Bone Resorption Independently of Insulin and Glycemia. J Clin Endocrinol Metab. 2018. PMID 29099978; doi:10.1210/jc.2017-01949

17. Iepsen EW, Lundgren JR, Hartmann B, et al. GLP-1 Receptor Agonist Treatment Increases Bone Formation and Prevents Bone Loss in Weight-Reduced Obese Women. J Clin Endocrinol Metab. 2015. PMID 26043228; doi:10.1210/jc.2015-1176

18. Tan Y, Liu S, Tang Q. Effect of GLP-1 receptor agonists on bone mineral density, bone metabolism markers, and fracture risk in type 2 diabetes: a systematic review and meta-analysis. Acta Diabetol. 2025. PMID 39985672; doi:10.1007/s00592-025-02468-5

19. Beaudart C, Malréchauffé Y, van Heden S, et al. GLP-1 Receptor Agonists and Musculoskeletal Outcomes: A Systematic Literature Review and Meta-Analysis. Drugs. 2026. PMID 42730869; doi:10.1007/s40265-026-02365-3

20. Look M, Dunn JP, Kushner RF, et al. Body composition changes during weight reduction with tirzepatide in the SURMOUNT-1 study of adults with obesity or overweight. Diabetes Obes Metab. 2025. PMID 39996356; doi:10.1111/dom.16275

21. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021. PMID 33567185; doi:10.1056/NEJMoa2032183

22. de Paulo RS, Bonifácio DB, de Carvalho MHL, et al. Dietary Strategies and Nutritional Management in Patients Receiving GLP-1 and Dual GIP/GLP-1 Receptor Agonists as Adjuncts to Lifestyle Interventions: A Systematic Review of Randomised Clinical Trials. Diabetes Obes Metab. 2026. PMID 42037117; doi:10.1111/dom.70779

23. Hidayat K, Du X, Shi BM. Risk of fracture with dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors in real-world use: systematic review and meta-analysis of observational studies. Osteoporos Int. 2019. PMID 31134305; doi:10.1007/s00198-019-04968-x

24. Hsu YH, Liang YC, Chan KC, et al. Association of tirzepatide use with risk of osteoporosis compared with other GLP-1 receptor agonists: A retrospective cohort study using the TriNetX database. Diabetes Res Clin Pract. 2025. PMID 41218687; doi:10.1016/j.diabres.2025.112995

25. Gotfredsen A, Westergren Hendel H, Andersen T. Influence of orlistat on bone turnover and body composition. Int J Obes Relat Metab Disord. 2001. PMID 11486790; doi:10.1038/sj.ijo.0801639

26. Harper C, Pattinson AL, Fernando HA, et al. Effects of obesity treatments on bone mineral density, bone turnover and fracture risk in adults with overweight or obesity. Horm Mol Biol Clin Investig. 2016. PMID 27665425; doi:10.1515/hmbci-2016-0025

27. Anastasilakis AD, Paccou J, Palermo A, et al. The effects of anti-obesity medications on bone metabolism: A critical appraisal. Diabetes Obes Metab. 2025. PMID 40555693; doi:10.1111/dom.16541

28. Zhang Q, Chen Y, Li J, et al. A meta-analysis of the effects of bariatric surgery on fracture risk. Obes Rev. 2018. PMID 29334691; doi:10.1111/obr.12665

29. Villareal DT, Aguirre L, Gurney AB, et al. Aerobic or Resistance Exercise, or Both, in Dieting Obese Older Adults. N Engl J Med. 2017. PMID 28514618; doi:10.1056/NEJMoa1616338

30. Henney AE, Wilding JPH, Alam U, et al. Obesity pharmacotherapy in older adults: a narrative review of evidence. Int J Obes (Lond). 2025. PMID 38710803; doi:10.1038/s41366-024-01529-z

31. Anjana RM, Unnikrishnan R, Deepa M, et al. Metabolic non-communicable disease health report of India: the ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17). Lancet Diabetes Endocrinol. 2023. PMID 37301218; doi:10.1016/S2213-8587(23)00119-5