Guest Editorial

What's New in Osteoporosis: Emphasis on the Aging Athlete

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The contemporary treatment of osteoporosis has seen tremendous evolution. Today, we have access to powerful biologic agents for the treatment of osteoporosis and an improved understanding of their safety and how to use them[1]. It is now possible to "skeletally optimize" patients not just for life, but in preparation for sport or elective surgery.

This edition of "What's New in Osteoporosis" is as much focused on the changing demographic characteristics of our patients as it is on therapy. Contemporaneously with the increase in new drug therapies, we have seen a growing group of aging athletes ≥60 years of age[2,3]. Cultural shifts in athletic trends such as pickleball[4] illustrate an attitude toward an active lifestyle. Although age has been independently associated with injuries[5,6], the positive psychosocial and cognitive effects of an active lifestyle can substantially and positively impact overall health[7], with the resulting improved physical activity known to independently decrease fracture risk[8,9]. Data have suggested that impact sports have a positive, direction-specific effect on bone strength and structure, in many instances mitigating age effects[10]. "Biological age" compared with "chronological age"[11] continues to be a salient point of discussion in today's treatment of osteoporosis.

Stratifying Osteoporosis

We know that the density of skeletal bone and fracture risk are correlated. Dual x-ray absorptiometry (DXA) and bone-related laboratory markers are often used to assess the disease burden. However, despite advancements in imaging modalities, including quantitative or peripheral computed tomography (CT)[3], fracture risk still remains incompletely explained by these biomarkers.

Patient Case Scenarios

To illustrate the point, we present 2 case scenarios commonly seen in the clinic. The patients have the same bone mineral density (BMD) and Fracture Risk Assessment Tool (FRAX) scores, but they are expected to have different true fracture risks. A thorough history and physical examination focusing on identifying risk factors, such as social isolation[12,13], frailty[14], and physical performance[8,15], among others (Fig. 1), are critical for identifying and differentiating residual risk.

Patient 1: The Frail Patient

This patient is an 80-year-old woman. She is widowed and has no children. She rarely leaves home and has an 8-hour-per-day home attendant. She has a slow gait, is fatigued, and cannot perform a single-leg stance. She has a positive Gower sign.

DXA determined that the patient has T-scores of −3.0 for the lumbar spine and −2.8 for the femoral neck. The FRAX determined that the patient has a 50% risk of a major osteoporotic fracture and a 38% risk of a hip fracture.

Patient 2: The Aging Athlete

The patient is an 80-year-old woman. She is married with 2 nearby children. She loves to hike and travel and plays pickleball twice a week. She has a good build and a confident gait. She is stable performing a 12-second single-leg stance and can do an effortless squat.

DXA determined that the patient has T-scores of −3.0 for the lumbar spine and −2.8 for the femoral neck. The FRAX determined that the patient has a 50% risk of a major osteoporotic fracture and a 38% risk of a hip fracture.

High-Risk Patients on the Fracture Risk Continuum: Osteosarcopenia

There is currently no consensus on the optimal screening or interventional approach to primary prevention of fragility fractures[16]. In a summary statement of randomized controlled trials (RCTs), Gates et al. demonstrated that a 2-step screening using the FRAX plus BMD measurement has an area under the curve (AUC) predictive value of around 0.7 for the 5 to 10-year fracture risk, which, in 2024, still leaves room for improvement[16]. Newer imaging methods appear to help to circumvent this problem but have yet to change the standard of care. Sornay-Rendu et al., in a long-term subanalysis of the Os des Femmes de Lyon (OFELY) study[17] and in a study utilizing DXA finite element analysis[18], showed that osseous

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microarchitecture is critical in defining fracture risk. Szulc et al. has now linked bone architecture to a fracture risk that appears independent of chronological age[19]. Until we can better understand the causative link between osseous microarchitecture and fracture risk, which in the future will likely involve deep-learning algorithms[20], chronological age remains a critical screening item for patients at high risk for fracture today.

Regardless of advancements, in high-risk patients with a recent fracture, treatment duration and adherence in the United States continue to be poor, with recent data reporting a BMD testing rate of only 8.6% within 12 months of the index fracture, and a secondary fracture rate of 13.6% over a 2-year follow-up, in patients ≥50 years of age[21]. This highlights the continued systemic failure to appropriately capture, stratify, triage, and treat patients for primary or secondary fracture prevention. By extrapolation, we cannot yet rely on systems-based clinical pathways to replace a clinician's ability to identify and act upon risk; the doctor remains on the front line for fracture prevention.

Osteosarcopenia prevalence in the community is high, reportedly 21% in a recent systematic review and meta-analysis, which identified female sex (odds ratio [OR], 5.10; $p < 0.0001$), older age (OR, 1.12; $p = 0.008$), and prior fracture (OR, 2.92; $p = 0.0003$) as risk factors[22]. In a perspective article, Binkley et al. discussed how dysmobility syndrome, causing eventual fragility fracture and decline, intimately relates to the concept of osteosarcopenia[23]. In their original description of a "bone attack," in parallel with outcome similarities to a heart attack, critical items were listed in the initial workup of a patient, including prior low-energy fracture, sarcopenia, prior falls, diabetes, parental fracture history, and toxin exposure[23]. Vitamin D deficiency continues to be linked to functional decline in such high-risk patients. In a recent RCT subanalysis of 246 women residing in long-term care centers, Haeri et al. showed that every 5-ng/dL increase in serum 25-OH vitamin D was associated with an increase of 0.012 m/second in gait speed ($p = 0.0144$)[24]. Although some of these risk factors (parental fracture history and toxin exposure) are captured within the FRAX score, they made the important distinction, in the spirit of primary prevention, that such a method dependent on a high FRAX score is too little, too late in the capture of the at-risk patient.

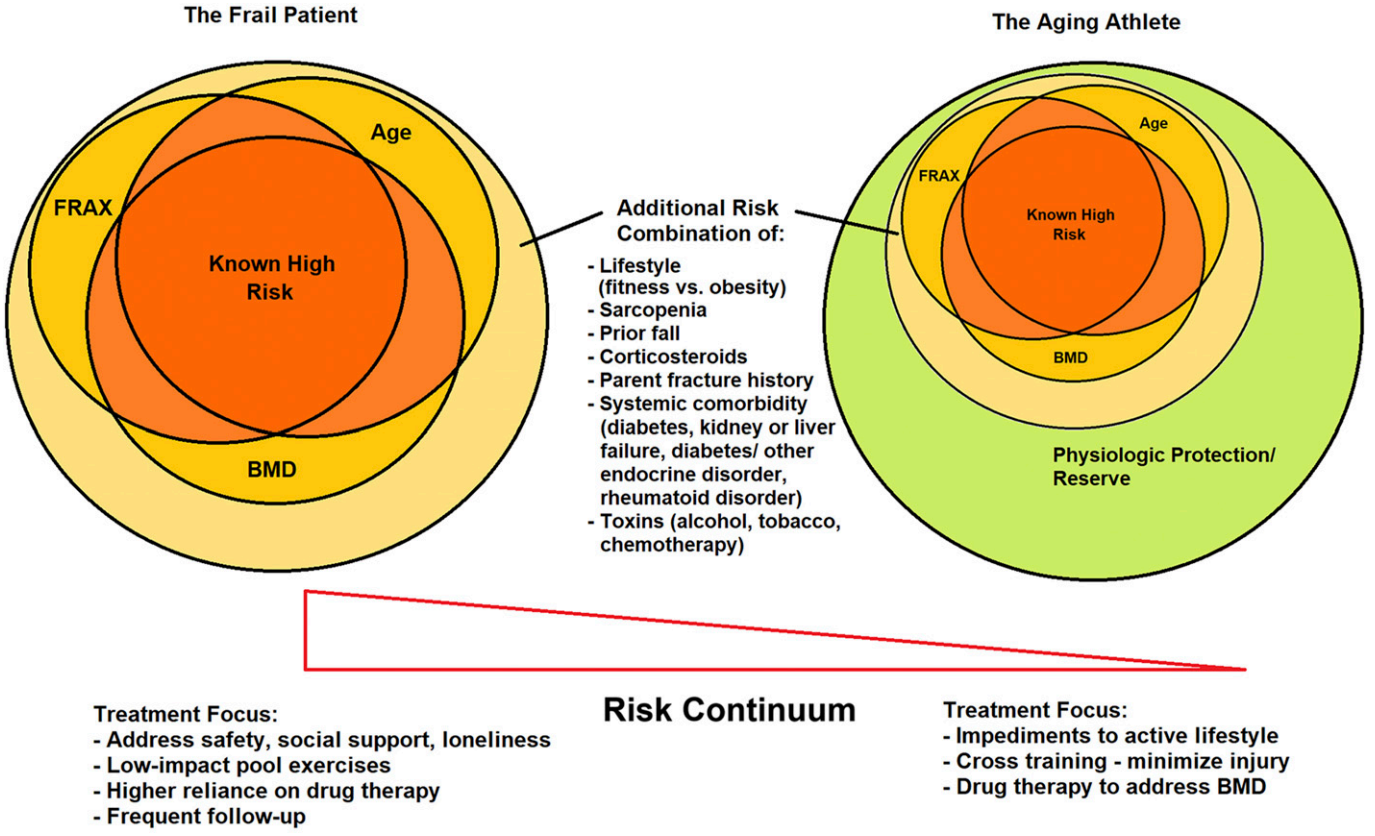

Fig. 1

Spectrum of disease in contemporary patients with osteoporosis and their respective treatment foci. Residual risk remains despite widespread use of age, FRAX, and BMD as primary screening tools for osteoporosis.

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Evidently, the FRAX score and BMD also do not tell the entire story. Visualizing this in a hypothetical Venn diagram demonstrates overlap of these 3 biomarkers but failure to explain residual risk (Fig. 1). FRAX adjustments for items such as fall history[25], diabetes[26], and corticosteroid dose exposure[27] have now been published, leading to the development of the FRAXplus score currently in beta testing[28]. For instance, a patient-reported history of fragility fractures is an independent risk factor for subsequent fractures at a higher rate than can be explained by BMD alone, with the effect being sex-independent[29]. This finding was corroborated by a recent meta-analysis by Vandenput et al. of 906,359 patients, finding that a fall history has independent implications for fracture risk regardless of BMD[30]. The implementation of fall prevention programs has been shown to lower the risk of fractures[31]. Patient safety thus becomes critical as a focus of treatment in high-risk patients (Fig. 1).

Low-Risk Patients on the Fracture Risk Continuum: Overoptimize

The aging athlete (Patient 2) has maintained a higher physiologic baseline, which has health benefits beyond just a demonstrable effect on longevity[32]. As patients now live well beyond the ninth decade, baseline skeletal optimization dictates the need to proactively minimize and maintain low skeletal disease burden during periods of good health, in anticipation for potential progression of osteoporosis 30 to 40 years later.

Early intervention is always the best intervention. The principal stimulus to osteoanabolic response is exercise[33]. Exercise intensity and duration are inversely correlated with fracture risk, especially in the hip[34,35]. However, spinal and upper-extremity fractures and physical activity do not relate in this way, suggesting that mechanical loading is protective against fractures only in the anatomic regions experiencing the loading[35]. Twisting or bending exercises placing patients at risk for compression fractures should be avoided, particularly given that the spine does not readily respond to weight-bearing exercise[36]. It should be mentioned at this juncture that the profound positive effect of anabolic agents on bone density in the spine compared with other body parts has been well documented[37-39], as was demonstrated by Händel et al. in a large network meta-analysis and meta-regression analysis of 69 RCTs[40]. Anabolic agents additionally improve trabecular architecture, based on a post hoc 3-dimensional (3D) modeling study on hip CT data from patients who received romosozumab from the FRAME (Fracture Study in Postmenopausal Women with Osteoporosis) and ARCH (Romosozumab vs Alendronate for Osteoporosis) trials[41], suggesting that anabolic drug treatment may be especially important in the active healthy patient with higher physical demands[42]. Taken together, it is possible that the aging athlete may especially benefit from anabolic agents, as the treatment effect is potentiated by mechanical input. The synergy between exercise and its anabolic effect in older athletes warrants further research, in order to highlight whether overoptimization may be a valid strategy in improving the patient baseline.

Abolishing toxic lifestyle habits such as smoking or excessive alcohol consumption needs to be addressed[43]. Nutrient counseling is critical for maintaining eucalcemia, especially in the setting of antiresorptive medications. There is an inverse relationship between body mass and bone mass and thus fracture risk[44], although it is now understood that muscle mass positively correlates with bone mass[45,46] and lower-extremity strength is protective against fracture[47], alluding to the potential for osteosarcopenia prevention through exercise. This has led to a change in the patient-doctor dialogue from "avoid too much weight loss" to "work on building muscle," as a way to take advantage of psychophysiologic empowerment.

In order to appropriately capture some of the above items, the Short Physical Performance Battery (SPPB) has been used with good success in the stratification of patients based on physical performance metrics, without a major ceiling effect[48]. These metrics include balance, walking speed, and repeated chair stand tests. The SPPB generally demonstrates good to excellent test-retest reliability and interrater reliability, but may present ceiling effects in athletes. The routine measurement of the SPPB requires an additional 10 minutes during a clinical visit and, although it represents additional patient and clinical burden, provides added value in the quantification of the physiologic protection and/or reserve (Fig. 1)[49], thus speaking to the elusive biological age[11] of the patient.

Osteoporosis Among Men

Although osteoporosis is often associated with the female sex, the mortality rate associated with fragility fracture in men is up to double the rate in women[50]. In men, fragility fracture risk increases after 70 years of age, increasing from 2.1% to 9.5% in men who are 80 years of age[51]. Although there are well-established guidelines for screening female patients for osteoporosis, the evidence for screening men in low-risk populations has been weak. Current guidelines state that men should be assessed for osteoporosis beginning at 70 years of age, although this age may decrease in the future based on improved risk factor analyses[52]. Lower morbidity but a potential for higher mortality in male patients in the setting of an osteoporotic fracture have led the osteoporosis community to call for raising awareness about osteoporosis screening in male patients[53].

Vertebral compression fractures are the most common type of osteoporotic fracture. Usually, the treatment focus for these fractures is to implement measures to prevent further collapse of the involved vertebral body, to prevent secondary fractures, and to improve pain and function in patients. In an RCT, Peris et al. identified that patient sex can influence the patient's outcomes regardless of the kind of treatment used (conservative or vertebroplasty)[54]. Male patients appear to have better outcomes in terms of pain and quality of life,

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independent of the treatment received[54]. However, in a retrospective study of 492 patients, Gutiérrez-González et al. showed that male sex is an independent predictor of mortality following a vertebral fracture[55], although this male predilection continues to be challenged by studies such as the Tromsø Study[56].

Drug Therapy for Osteoporosis: New Frontiers

Multidrug Sequence and Dosing

First-line treatment for osteoporosis is typically an antiresorptive agent such as bisphosphonates or denosumab, except in the setting of severe osteoporosis, in which case an osteoanabolic agent is preferred. Romosozumab is an antisclerostin antibody with both antiresorptive and anabolic effects resulting in up to 3 to 4 times the potency compared with denosumab and is especially potent when followed by an antiresorptive agent[57]. A summary of 4 RCTs[58] by Cosman et al. evaluated different romosozumab sequences and identified that initial treatment with romosozumab followed by an antiresorptive agent demonstrated the best BMD response. Patients who took denosumab for even a short period of time (1 year) before romosozumab saw smaller improvements in BMD. Generally, primary treatment with an anabolic agent followed by an antiresorptive agent appears to be preferable to the reverse.

Rebound osteoporosis is a well-described problem with discontinuation of denosumab. Inadvertent or intentional discontinuation is common in a real-world clinical setting; in 1 retrospective study, Cruchelow et al. reported 36% of patients having lapses in treatment and 10% of patients having discontinuation[59]. Rebound osteoporosis can be counteracted by using alendronate or zoledronic acid following discontinuation of denosumab and subsequently tracking C-terminal peptide levels to anticipate reentry into a resorptive state. Risedronate and raloxifene appear to be too weak to counteract this rebound effect[60,61]. Transitioning to a half-dose denosumab regimen was found by Khan et al. to prevent bone loss and prevent fractures in postmenopausal women with a moderate fracture risk, which presents an additional option for patients who do not tolerate the full-dose therapy[62].

Dito et al.[63] reported their retrospective experience with patients who underwent drug switching from 24 months of teriparatide treatment to denosumab or zoledronic acid. Both regimens were found to improve BMD, and zoledronic acid was not found to be inferior to denosumab. These results demonstrate that bone mass consolidation after teriparatide can likely be performed with the use of any modern antiresorptive agent, although the decreased need for redosing and lower cost favors the use of zoledronic acid in this role.

Combination Drug Therapy

One option to address non-response is combination therapy. The DATA-HD (Combination Denosumab and High-Dose Teriparatide for Postmenopausal Osteoporosis) study[64,65] showed that combination therapy with high-dose teriparatide and denosumab is better than either drug alone. Rebound osteoporosis following this combination may be circumvented by transition to denosumab alone or a bisphosphonate. Patients who stop teriparatide alone do not experience rebound osteoporosis, but do experience persistent bone loss and also require treatment. In an extension of the DATA-HD trial, Ramchand et al.[66] identified that a single dose of zoledronic acid can maintain the BMD improvement resulting from the combined treatment for at least 12 months. They also identified that loss in BMD can occur up to 27 months after transition, and so repeat dosing with zoledronic acid may be required alongside long-term follow-up. In a second extension study[67], Ramchand et al. identified that a single dose of zoledronic acid is effective in maintaining large gains in BMD from combination therapy. However, this single dose does not prevent loss in the volumetric BMD and bone microarchitecture, which suggests that a follow-up dose of zoledronic acid or another treatment is needed in order to consolidate bone density[67].

Cyclic Teriparatide

Teriparatide treatment produces a nonlinear increase in BMD that is most rapid in the first 3 to 6 months of treatment, within what is known as the anabolic window[68]. In a randomized, open-label study of postmenopausal women, Ganapathy et al.[69] compared CT images following cyclic administration of teriparatide or regular daily administration for 24 months. The cyclic regimen consisted of 3 months of taking daily teriparatide followed by 3 months of not taking the medication. The regular regimen was daily teriparatide for 24 months. In the extension period of the study, patients undergoing cyclic dosing stayed on the cyclic regimen for 24 additional months, whereas the patients on the regular regimen switched to alendronate for 24 additional months. In the first 24 months, spine BMD improvement was significantly higher in the regular daily administration group than in the cyclic group: total bone density, 12% in the regular daily administration group compared with 8% in the cyclic group ($p < 0.001$) and vertebral strength, 22% in the regular daily administration group compared with 12% in the cyclic group ($p < 0.001$). Hip BMD improvements were found to be minimal but still favored the daily administration group. Comparing the 24-month daily administration and the 48-month cyclic administration regimen demonstrated no difference; the total spine density change was +12% for the 24-month group and +11% for the 48-month group, and the total hip density change was +2% for the 24-month group and +2% for the 48-month group (nonsignificant). Overall, the analysis did not show any benefit to the cyclic regimen. Improvement in BMD and bone strength with teriparatide appears to be related to the cumulative dose administrated rather than the regimen.

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Updates on Drug Therapy for Non-Osteoporotic Indications

Peri-Implant Bone-Healing

Supporting safety data for the use of newer agents including abaloparatide and romosozumab have continued to popularize osteoanabolics for use in perioperative skeletal optimization[70]. Mohanty et al.[1] studied patients with osteoporosis undergoing long spinal fusion who were treated with teriparatide and had follow-up of at least 2 years. They compared outcomes among patients with preexisting osteoporosis treated with teriparatide, patients with osteopenia, and patients with normal bone density. A lower 2-year reoperation rate was observed in patients with osteoporosis receiving teriparatide compared with the osteopenia group; OR, 0.45 ($p = 0.018$) in an unmatched cohort and OR, 0.45 ($p = 0.019$) in a matched cohort). Additionally, a lower pseudarthrosis rate was observed in patients with osteoporosis receiving teriparatide compared with patients with osteopenia. Pedicle screw loosening has similarly been linked to peripheral BMD[71], creating a possible role for point-of-care peripheral BMD testing in anticipation of spinal fusion surgery.

Fracture-Healing

Recent articles continue to show the positive impact of parathyroid hormone (PTH) receptor analogs on fracture-healing. Yang et al.[72] retrospectively compared 16 patients treated with teriparatide for 6 months and 15 patients who underwent cement sacroplasty and found that the teriparatide group showed greater improvements in pain and the Oswestry Disability Index at 1, 3, and 6 months. Gou et al.[73] retrospectively evaluated patients treated for acute osteoporotic compression fractures. They compared patients who underwent cement augmentation and patients who received recombinant human PTH, rhPTH(1 to 34), 20 μg daily for 6 months. They reported that the PTH group had improved pain control and better health-related quality of life. Also, these patients had substantial improvements in BMD after 12 months.

Although treatment with romosozumab is theoretically beneficial for fracture-healing due to its dual antiresorptive-osteoanabolic action, Schemitsch et al. previously showed that it did not improve fracture-healing following intertrochanteric hip fractures[74]. In a retrospective study, Hayashi[75] evaluated the effect of 3 different formulations of teriparatide as well as romosozumab on bone healing and pain following a vertebral compression fracture, finding that a daily teriparatide injection led to greater improvement in bone union (84.4%; $p = 0.0029$) than romosozumab (40.0%). When comparing the teriparatide and romosozumab groups, Hayashi also found greater improvement in low back pain in the groups receiving teriparatide daily (84.4% compared with 25.0%; $p = 0.0001$), twice a week (78.3% compared with 25.0%; $p = 0.0009$), and weekly (62.5% compared with 25.0%; $p = 0.0341$).

Delayed Union and Stress Fractures

The treatment of subchondral or stress fractures using anabolic agents is also relevant to the discussion of the aging athlete, although data are limited. In a multicenter study, Gariffo et al.[76] retrospectively analyzed 20 patients presenting with delayed union of long-bone fractures at a mean age of 55 years. They found that using daily teriparatide in an off-label manner yielded complete fracture-healing in 85% by 6 months. Byun et al.[77] performed a systematic review and meta-analysis that showed a lower rate of delayed union in teriparatide-treated atypical femoral fractures compared with untreated controls (OR, 0.23; $p < 0.01$). The untreated group exhibited a longer healing time, by 1.78 months, but did not demonstrate a difference in the overall rates of nonunion or reoperation. Bisphosphonates, selective estrogen receptor modulators (SERMs), and hormone replacement therapy have been shown to be safe to continue in the setting of fracture-healing[78]. Nevertheless, due to the potential for interference with intramembranous bone healing and a potential detrimental effect on osteocytes[79], especially following primary fixation using a stiff orthopaedic construct, surgeons should still consider pausing bisphosphonates in favor of switching to a PTH receptor analog for patients with a fracture who were undergoing bisphosphonate therapy, especially for those with suppressed osteoanabolic serum markers[80,81].

Summary

As patients and treatment regimens evolve together and push the boundaries of what is possible in active aging individuals, clinicians remain central in their orchestration. Optimistically, advancing research may finally teach us how to summarily measure risk and tailor patient-centered treatments. Until then, the doctor remains the first and last line of defense in our patients' fight against osteoporosis and, perhaps more importantly, in their maintenance of healthy physical independence.

Evidence-Based Orthopaedics

The editorial staff of *JBJS* reviewed a large number of recently published studies related to the musculoskeletal system that received a higher Level of Evidence grade. In addition to articles cited already in this update, 4 other articles were identified that are relevant to osteoporosis. A list of those titles is appended to this review after the standard bibliography. We have provided a brief commentary about each of the articles to help guide your further reading, in an evidence-based fashion, in this subspecialty area.

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Evidence-Based Orthopaedics

Huang HK, Chuang AT, Liao TC, Shao SC, Liu PP, Tu Y, Lai EC. Denosumab and the risk of diabetes in patients treated for osteoporosis. *JAMA Netw Open.* 2024 Feb 5;7(2):e2354734.

In a large Taiwanese cohort study, Huang et al. evaluated data from 68,510 patients. They found a lower cumulative incidence of diabetes in patients undergoing denosumab treatment compared with a propensity-matched control cohort. Their age-stratified analysis identified an association between decreased diabetes risk and denosumab treatment, specifically in adults ≥65 years of age. Although confounding bias is always possible, this is nevertheless an exciting development in the osteoporosis literature.

These new data suggest a lower risk for diabetes in patients receiving denosumab and may favor its use in specific at-risk populations.

Lyu H, Zhao SS, Zhang L, Wei J, Li X, Li H, Liu Y, Yin P, Norvang V, Yoshida K, Tedeschi SK, Zeng C, Lei G, Tang P, Solomon DH. Denosumab and incidence of type 2 diabetes among adults with osteoporosis: population based cohort study. *BMJ.* 2023 Apr 18;381:e073435.

This propensity-matched retrospective cohort study comparing 4,301 patients treated with denosumab and 21,038 patients treated with oral bisphosphonates demonstrated a lower incidence of type 2 diabetes with a hazard ratio of 0.68 (95% confidence interval [CI], 0.52 to 0.89). This study utilized a U.K. database, which suggests that the positive glycemic effect of denosumab may be conserved across populations. It was hypothesized that the mechanism of action is driven by improved glucose metabolism through suppression of receptor activator of nuclear factor kappa-B ligand (RANKL) signaling. Prior randomized controlled drug trials on the effect of denosumab on osteoporosis did not detect this effect, likely because of their underpowered study designs for this secondary outcome.

The complementary data on the lower incidence of type 2 diabetes in patients receiving denosumab in the United Kingdom add to the evidence that denosumab may have consistent antiglycemic effects.

Snyder PJ, Bauer DC, Ellenberg SS, Cauley JA, Buhr KA, Bhasin S, Miller MG, Khan NS, Li X, Nissen SE. Testosterone treatment and fractures in men with hypogonadism. *N Engl J Med.* 2024 Jan 18;390(3):203-11.

Male patients with low levels of testosterone due to hypogonadism benefit from testosterone replacement therapy. In a secondary analysis of a previous study of the effect of testosterone treatment on cardiovascular events in middle-aged men with hypogonadism, Snyder et al. evaluated the effect of testosterone treatment in lowering the risk of fractures. The authors found that, among middle-aged men and older men with hypogonadism, testosterone replacement compared with placebo did not result in a lower incidence of clinical fracture.

Hormone replacement therapy is historically known to be clinically ineffective in older women in treating osteoporosis and preventing fractures. This study demonstrates that testosterone replacement in men is also ineffective.

Tsai WH, Sung FC, Muo CH, Tsai MC, Wu SI. Antiosteoporosis medications and cardiovascular disease: a population-based nationwide nested case-control study. *Front. Pharmacol.* 2023 Oct 10;14:1220174.

In a report of the possible cardioprotective effects of anti-osteoporosis medications from Taiwan, Tsai et al. performed a nested case-control study utilizing the National Health Insurance Research Database. The study included 41,102 patients with a new diagnosis of osteoporosis undergoing treatment with no drug, denosumab, teriparatide, bisphosphonates, or hormone replacement therapy. When compared with patients who had no drug treatment, the adjusted ORs of cardiovascular disease incidence were 0.13 (95% CI, 0.12 to 0.15) for denosumab users, 0.52 (95% CI, 0.45 to 0.61) for teriparatide users, and 0.80 (95% CI, 0.76 to 0.85) for bisphosphonate users. In contrast, patients who used hormone replacement therapy demonstrated higher odds of developing cardiovascular disease (OR, 1.36 [95% CI, 1.25 to 1.47]), which, when interpreted in context, acts as a validation cohort for the statistical methods used. This large odds reduction in favor of denosumab contradicts prior meta-analyses suggesting its net-neutral effect on cardiovascular risk.

The literature has been mixed on the topic of cardioprotective effects of denosumab. However, recent data across multiple studies have suggested a positive and durable effect of denosumab on cardiovascular health. This may favor its use in patients with known risk factors for cardiovascular disease.