The Journal of Clinical Endocrinology & Metabolism, 2023, **00**, 1–11
https://doi.org/10.1210/clinem/dgad256
Advance access publication 15 May 2023
Mini-Review

New Insights in the Pathophysiology, Epidemiology, and Response to Treatment of Osteoporotic Vertebral Fractures

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Abstract

Context: Vertebral fractures (VFs) make up an important but challenging group of fractures often caused by osteoporosis. Osteoporotic fractures pose unique diagnostic challenges in generally requiring imaging for diagnosis. The objective of this narrative mini-review is to provide an overview of these recent advances in our knowledge of VF pathophysiology and epidemiology with particular focus on endocrine diseases, prevention, and treatment.

Evidence Acquisition: We searched PubMed on May 23, 2022, for studies of VFs in humans. Results were limited to papers available as full-text publications in English, published from 2020 and onward. This yielded 3457 citations. This was supplemented by earlier publications selected to add context to the recent findings.

Evidence Synthesis: Studies addressed VF risk in hyperthyreosis, hyperparathyroidism, acromegaly, Cushing syndrome, primary aldosteronism, and diabetes. For pharmaceutical treatment, new studies or analyses were identified for romosozumab and for weekly teriparatide. Several studies, including studies in the immediate pipeline, were intervention studies with vertebroplasty or kyphoplasty, including combination with stem cells or pharmaceuticals.

Conclusions: Endocrinologists should be aware of the high likelihood of osteoporotic VFs in patients with endocrine diseases. Though licensed treatments are able to substantially reduce the occurrence of VFs in patients with osteoporosis, the vast majority of recent or ongoing randomized controlled trials in the VF area focus on advanced invasive therapy of the fracture itself.

Key Words: osteoporosis, spine fracture, risk factors, epidemiology, treatment

Abbreviations: BMD, bone mineral density; BTM, bone turnover marker; CT, computed tomography; DSA, digital subtraction angiography; DXA, dual-energy x-ray absorptiometry; GSQ, Genant semiquantitative method; MSC, mesenchymal stem cell; nPHPT, normocalcemic primary hyperparathyroidism; PA, primary aldosteronism; PCKP, percutaneous curved needle kyphoplasty; PHPT, primary hyperparathyroidism; PKP, percutaneous kyphoplasty; PVP, percutaneous vertebroplasty; QoL, quality of life; RCT, randomized controlled trial; RRR, relative risk reduction; TBS, trabecular bone score; VAS, visual analog scale; VF, vertebral fracture.

Vertebral fractures (VFs) make up an important but challenging group of fractures often caused by osteoporosis (1). Osteoporotic fractures pose unique diagnostic challenges in generally requiring imaging for diagnosis or at least for confirmation. They may or may not cause classic acute symptoms, so in the absence of earlier imaging it can be hard to accurately classify them as new (incident) or old (or prevalent) fractures, though magnetic resonance imaging provides some clues as to the likely age of a VF. Further, VFs invariably heal with deformity, unlike the majority of other osteoporotic fractures. While early osteoporosis drugs went into randomized controlled trials (RCTs) primarily powered for VFs—we have more vertebrae than hips—the focus of the field increasingly moved from VFs to hip fractures. These are associated with higher mortality, are far easier to diagnose, and are usually readily captured in registers and claims databases. However, VFs are of huge importance to patients and a considerable health care burden to the community, and they make up a large proportion of the fracture burden in patients with endocrine diseases (2). VFs are also often the hallmark of familial osteoporosis though they are too common to warrant routine genetic screening (3). Fortunately, recent studies have provided important new insights into the natural history of VFs and how best to prevent and manage them. The objective of this review is to provide an overview of these recent advances in our knowledge of VF pathophysiology and epidemiology with particular focus on endocrine diseases, prevention, and treatment.

Search Strategy

We searched PubMed on May 23, 2022, using the search string (*vertebra*[Title/Abstract] OR spin*[Title/Abstract]) AND (fracture*[Title/Abstract]*). Results were limited to findings in humans, available as full-text publications in English, published from 2020 and onward. This yielded 3457

Received: 28 October 2022. **Editorial Decision:** 2 May 2023. **Corrected and Typeset:** 26 May 2023

citations. We selected relevant papers—reviews and original research articles—related to the topics of this review. This was supplemented by earlier publications purposely selected for adding context to the recent findings.

New Insights to Pathophysiology

Anatomically, the spine consists of 7 cervical vertebrae, 12 thoracic vertebrae, and 5 lumbar vertebrae (in addition to the sacrum and coccyx) (4). Each vertebra (except C1) consists of a body—with a trabecular bone center surrounded by an outer layer of cortical bone—and a posterior arch (4, 5). Within the trabecular part of the vertebral body, bone mineral density (BMD) is lower in the central vs the peripheral region, and in the anterior vs the posterior region. Furthermore, microarchitectural parameters indicate a more dense microstructure in the periphery of the trabecular bone compared to the center (6). A recent case-control study in 148 individuals evaluated the association between such intravertebral trabecular bone heterogeneity and prevalent moderate or severe VF. VFs between T4 and L4 (patients with mild VF or any L3 VF were excluded) were identified from computed tomography (CT) scans using semiquantitative grading. Measures of trabecular heterogeneity and spatial distribution were derived from quantitative CT (QCT) scans, using the unfractured L3 vertebra. It was found that a higher anterior-to-posterior trabecular volumetric BMD ratio was associated with a lower odds ratio for prevalent VF, adjusted for height, weight, and integral volumetric BMD. The authors speculate that a relatively higher anterior BMD may result in a better protection against fracture when bending forward (7).

Other recent studies have focused on the effect of bone microarchitecture on the risk of VF, the importance of which is made tangible by the large proportion of patients with VF with nonosteoporotic BMD values (8, 9). A study of 33 patients undergoing an operative procedure for thoracolumbar VF and 33 patients without fractures undergoing spine surgery for other causes found no correlation between BMD from lumbar spine dual-energy x-ray absorptiometry (DXA) scans and measures of bone microarchitecture based on micro-CT scans of bone biopsies from unfractured lumbar (predominantly L3) vertebrae in individuals in the VF group. This suggests that lumbar spine BMD is not reflective of bone microarchitecture in patients with VF (8), though it should be emphasized that reductions in lumbar spine BMD per se are predictive of VF (10). In comparison, trabecular bone score (TBS)—derived from a pixel-to-pixel evaluation of gray-level texture variation on, for example, DXA scans—is correlated with microarchitectural features, and lower TBS is associated with an increased risk of VF (11). Recent studies have elaborated on factors associated with TBS, and the first has shown (in multivariable models, the results of which may differ from reported bivariate models) that greater height and current low mobility is associated with lower TBS in women, while higher weight and low childhood physical activity is associated with lower TBS in men. In both sexes, TBS is inversely associated with age, yet positively associated with lumbar spine T-score (12). Similar associations between higher femoral neck and lumbar spine BMD and higher TBS were shown in a Norwegian study in women, while increasing age, parental hip fracture, and daily alcohol consumption (yes vs no) were noted to be inversely associated with TBS. A higher TBS was associated with lower odds ratio of prevalent VF on VFA, though statistically significant only in a univariable model, and borderline significant in a multivariable model (13). While insights into the determinants of TBS and studies on its predictive capability continue to accumulate and may advance its future use, an example of its clinical application has emerged in terms of the TBS-adjusted FRAX score (https://www.sheffield.ac.uk/FRAX/).

Vertebral Fractures in Endocrine Disorders

In this section we review recent evidence on the relationship between endocrine disorders and VF. Covered elsewhere, and therefore not included here, are the topics of VFs in the context of diabetes (several newer meta-analyses and a review are available (14-16). In brief, type 2 diabetes seems to confer a modest increase—one meta-analysis reported a pooled OR of 1.55 (95% CI, 1.04-2.31)—in the risk of incident VFs, although this is not consistent across studies (14, 17, 18). Also, a higher risk of VFs has been reported in type 1 compared to type 2 diabetes (HR 1.33 [95% CI, 1.09-1.63] for type 1 vs type 2] (18)). As regards overweight/obesity, a meta-analysis showed reduced risk of VF in overweight, yet no overall effect of obesity on VF risk (a reduced risk was observed in subgroup analyses pooling large, high-quality studies) (19). Findings from recent observational studies are summarized in Table 1.

Thyroid diseases

In hyperthyroidism, an increase in bone turnover and fracture risk is well recognized (20, 21). Recently, this has been extended to include an association between Graves disease and prevalent VF, and while this association lost statistical significance in the fully adjusted logistic regression models (see Table 1 for details) (20), it certainly indicates that Graves disease—though patients would be expected to be hyperthyroid for relatively short time periods—is a significant risk marker for prevalent VF.

In recent years, a meta-analysis has shown an increased risk of VFs in subclinical hyperthyroidism—but not in subclinical *hypo*thyroidism—with a pooled relative risk of 1.97 (95% CI, 1.31-2.97). In subgroup analyses, the increased risk persisted in older (aged ≥70 years) but not in younger (aged <70 years) individuals, and in studies in women as well as women and men combined, but not in the single study in men only (RR 1.29 [95% CI, .18-9.32]) (22). A recent cohort study has, however, added to these findings, demonstrating a statistically significant, approximately 3 times higher risk of VF in older men with subclinical hyperthyroidism (23). Interestingly, another meta-analysis found a weak association between subclinical hyperthyroidism—compared to euthyroidism—and reduced femoral neck BMD in women, but not in men, while there was no discernible adverse influence on lumbar spine BMD in either sex (21). Together, these studies may indicate that while VF risk is increased in older individuals with subclinical hyperthyroidism, this is not consistently accounted for by changes in lumbar spine BMD. The suitability of using BMD—and lumbar spine BMD in particular—for case-finding of candidates for osteoporosis therapy should therefore be further evaluated among patients with subclinical hyperthyroidism.

Acromegaly

As reported in a prior meta-analysis, bone turnover is increased in patients with acromegaly, and more so in those with active vs controlled/cured acromegaly; BMD is

Table 1. Association between selected endocrine disorders and vertebral fractures from recent observational studies

	Study	Population	Exposure	Comparator	VF metric(s)	Results
Thyroid diseases	Svensson et al, 2021 (23) Cohort study	Men, 69-81 y N = 1856 Median FU 9.8 y	Subclinical hyperthyroidism (S-TSH < .45 mIU/L)	S-TSH ≥ 0.45 mIU/L	Subject-reported incident VF, confirmed by review of radiology report	HR 2.83 (95% CI, 1.24-6.48; multivariable Cox model), when excluding individuals with serum free T4 > 22 pmol/L and/or treated with levothyroxine
	Takedani et al, 2020 (20) Cross-sectional study	Women, > 50 y and postmenopausal	Graves disease with no or <6 mo antithyroid treatment (n = 43)	Healthy age- and sex-matched controls (n = 86)	Prevalent VF	VF prevalence in Graves disease 35%, controls 17%; $P < .05$ OR 2.72 (95% CI, 1.13-6.54)[a]
Acromegaly	Pelsma et al, 2020 (25) Cohort study	Men and women Median FU 9.1 y	Acromegaly, controlled (n = 31)	None	Prevalent VF and incident/worsening radiographic VF at FU	27 (87%) individuals with VF at baseline 19 incident VFs in 11 (35.5%) individuals at FU
	Silva et al, 2021 (26) Cross-sectional study	Women, 30-50 y and premenopausal	Acromegaly (beyond this, pituitary function had to be normal; n = 30)	Healthy controls, matched for age, sex, and BMI (n = 53)	Prevalent VF	8/27 (30%) individuals with VF in acromegaly group vs 0 in control group (P N/A)
	Plard et al, 2020 (27) Cross-sectional study	Men and women ≤80 y	Acromegaly (n = 50)	None	Prevalent VF (GSQ) and prevalent vertebral deformities	VF prevalence 6% Vertebral deformity prevalence 92%
Primary aldosteronism (PA)	Yokomoto-Umakoshi et al, 2020 (28) Cross-sectional study	Women and men evaluated for hypertension at endocrine unit N = 210	PA, in subgroup analyses categorized as uPA or bPA	Aldosterone-to-renin ratio or captopril challenge test negative (ie, patients without PA)	Prevalent VF	VF prevalence in uPA 46%, bPA 20%, no PA 12%; $P < .001$ OR for VF in uPA 3.16 (95% CI, 1.12-8.92)[b]
Hypoparathyroidism	Cipriani et al (2021) (32) Cross-sectional study	Postmenopausal women	Chronic (≥1 y) postsurgical hypoparathyroidism (n = 50)	Healthy controls (women), matched on age (n = 40)	Prevalent VF	VF prevalence 16% vs 7.5% in hypoparathyroid individuals vs controls (P N/A)
Normocalcemic primary hyperparathyroidism	Palermo et al (2020) (35) Cross-sectional study	Women and men	nPHPT; normal calcium and increased PTH concentrations with secondary hyperparathyroidism ruled out (n = 47)	PHPT (n = 41) and controls with normal calcium, phosphate, and PTH concentrations (n = 39)	Prevalent VF	VF prevalence in nPHPT 28%, PHPT 60%, controls 23% OR (nPHPT vs controls) 1.32 (95% CI, .48-3.72)[c] OR (PHPT vs controls) 5.87 (95% CI 2.16-17.3)[c]
Cushing syndrome	Stachowska et al (2021) (40) Cross-sectional study	Women and men	Cushing syndrome (n = 19)	Age- and sex-matched controls (no symptoms/ signs of Cushing syndrome; n = 36)	Prevalent VF	VF prevalence in Cushing syndrome 53%; not evaluated in controls.
	Apaydin et al (2021) (41) Cross-sectional study; data sampled from medical records	Women and men	Cushing syndrome (n = 135)	Age-matched controls (n = 107), included in analyses of BMD only	Prevalent VF (radiological evaluations available for 81/135 patients)	VF prevalent in 61/81 (75%) patients with Cushing syndrome; not evaluated in controls
	van Houten et al (2021) (42) Cohort study; data sampled from medical records and by questionnaires	Women and men	Cushing syndrome, ≥ 18 y at diagnosis (n = 231)	None	1) Prevalent VF at diagnosis (VFA or x-ray imaging available for 86/231 patients)	1) VF prevalent in 17/86 (20%) patients 2) VF rate per 1000 patients per year[d]: 2-5 y before Tx: 9

(*continued*)

Table 1. Continued

	Study	Population	Exposure	Comparator	VF metric(s)	Results
					2) VF rate before and after treatment (Tx; assessed in 178/231 patients)	< 2 y before Tx: 96 < 2 y after Tx: 22 2-5 y after Tx: 9
Klinefelter syndrome	Vena et al (2020) (44) Cross-sectional study	Men, ≥ 18 y	Klinefelter syndrome (n = 87)	None	Prevalent VF	VF prevalent in 13/87 (15%) individuals
Pheochromocytoma/ paraganglioma	Yokomoto-Umakoshi et al (2020) (45) Cross-sectional study	Men and women	PPGL (n = 62)	Nonfunctional adrenal tumor (n = 61)	Prevalent VF (imaging available for 49/62 exposed individuals and 61/61 controls)	VF prevalent in 21/49 (43%) PPGL individuals and 10/61 (16%) control individuals ($P = .002$) OR (PPGL vs controls) 4.47 (95% CI, 1.76-11.3)[b]

Abbreviations: BMD, bone mineral density; BMI, body mass index; FU, follow-up; GSQ, Genant semiquantitative method; HR, hazard ratio; N/A, not available; nPHPT, normocalcemic primary hyperparathyroidism; OR, odds ratio; PA, primary aldosteronism (uPA, unilateral; bPA, bilateral); PHPT, primary hyperparathyroidism; PPGL, pheochromocytoma or paraganglioma; PTH, parathyroid hormone; T4, thyroxine; TSH, thyrotropin; Tx, treatment; VF, vertebral fracture; VFA, vertebral fracture assessment; y, years.
[a]Adjusted for age only. Five multivariate models were developed, each adjusting for age and one additional covariate (BMI, glycated hemoglobin A_{1c}, urine type 1 collagen cross-linked N-telopeptide, lumbar spine BMD, and femoral neck BMD, respectively); in these models, the OR was attenuated and lost statistical significance.
[b]Adjusted for age and sex.
[c]Adjusted for age.
[d]VF count includes both clinical and radiographic VF, and a substantial number of patients undergo VF assessment or radiological imaging at the time of diagnosis. Hence, the VF rate in the 2 years before treatment might be overestimated (personal correspondence with author, august 2022).

increased at the femoral neck though not at the lumbar spine; and radiological VFs are generally held to be more common in acromegaly vs control individuals (OR 8.26; $P < .0001$), while VFs within the acromegaly group are found more commonly in active vs controlled/cured acromegaly, in men vs women, and in hypogonadal vs eugonadal patients (24). In patients with controlled acromegaly, a recent study (N = 31) showed a high VF incidence with 36% of patients experiencing new radiographic VF over a median 9.1 years follow-up, although the lack of a control group as well as a high rate of nonparticipation in the follow-up assessment among the original acromegaly cohort prevented firm conclusions on the causal association (25). Also consistent with a higher risk of VF, the quality of trabecular bone microarchitecture—as measured by high-resolution–peripheral QCT at the tibia and distal radius—has been shown to be deteriorated in acromegaly (26). Contrary to these findings, one small (N = 50) cross-sectional study recently reported a low prevalence of acromegaly patients with VF (6%) yet a high prevalence of patients with vertebral deformities (wedge-shaped vertebra[e], osteophyte formation, and/or narrowing of the disc space; 92%), with the authors suggesting that such deformations may have biased the VF findings in prior studies (27). While misinterpretation of vertebral deformities as fractures may cause an overestimation of VF prevalence, this novel hypothesis is based on a single, small study and will need to be further evaluated in other studies, preferably applying different diagnostic VF classifications head to head.

Primary aldosteronism

One recent, single-center study has assessed the association between primary aldosteronism (PA) and VF, in individuals undergoing evaluation for hypertension. They found a VF prevalence of 29% vs 12% ($P = .011$) in PA vs no-PA individuals (28). This essentially confirms a previous finding (29). The novelty of the recent study was a higher prevalence of VF in unilateral vs bilateral PA (46% vs 20%; $P = .02$), and the excess prevalence of VF in PA vs no-PA individuals remained significant only for those with unilateral PA, not bilateral PA. While evaluation for prevalent VF should still be considered in all patients with PA, this study indicates that extra attention should be given to patients with unilateral PA. Interestingly, the study also showed a numerically increasing prevalence of VF by increasing aldosterone-to-renin ratio tertile in a subset of individuals, although statistical significance was achieved only when comparing the highest and lowest tertiles (28). While this needs confirmation from larger studies, it does seem to strengthen the impression of causality between PA and VF. In that regard, a meta-analysis comparing PA and essential hypertension patients found higher levels of serum PTH and urinary calcium in PA, while serum calcium was similar between the groups. The authors speculate on the mechanism of action between PA and bone health, and suggest that while a direct link may be plausible, the negative bone effects may also be driven by excess cortisol secretion (30). Again, the PA-bone relationship needs further studying.

Parathyroid diseases

In the absence of replacement with PTH or agonists, the skeletal consequence of hypoparathyroidism is a low turnover,

high BMD state. Despite a higher BMD, observational studies have not consistently reported altered fracture risk, and it has been suggested that the beneficial effect of higher BMD may be offset by decreased mechanical competence of hypermature bone (31). Interestingly, a recent study found a VF prevalence of 16% in patients with chronic postsurgical hypoparathyroidism compared to 7.5% in healthy, age-matched controls, although no formal statistical testing was reported (32). These results have been incorporated into a meta-analysis that demonstrated more than a doubling of VF occurrence (clinical or radiographic) in individuals with hypoparathyroidism (OR 2.22; 95% CI, 1.23-4.03) in spite of a generally higher lumbar spine, femoral neck, and total hip BMD. In subgroup analyses, the increased VF occurrence remained statistically significant in nonsurgical (OR 2.31; 95% CI, 1.32-4.03) but not postsurgical (OR 2.58; 95% CI, .69-9.64) hypoparathyroidism (33).

The classical skeletal manifestations of primary hyperparathyroidism (PHPT) are a low BMD and high bone turnover state with increased propensity to fracture. Accordingly, a recent meta-analysis has eloquently summarized the risk of VF. Overall, the risk of VF was tripled in PHPT patients (OR 3.00; 95% CI, 1.41-6.37). This was even further exacerbated in subgroups of studies that compared PHPT patients to healthy controls (or population-based estimates), included only mild PHPT patients (ie, those with no complications from PHPT), and included only postmenopausal women, respectively (34).

The concept of normocalcemic PHPT (nPHPT) can be a challenging one, requiring careful exclusion of potential secondary hyperparathyroidism in individuals with elevated PTH levels and normal calcium levels (35, 36), something that generally requires long-term observation. A recent study in patients with nPHPT found a VF prevalence similar to control individuals (28% and 23%, respectively), yet numerically lower than in patients with PHPT (60%). This difference—albeit not statistically significant—was observed in a context of similar levels of PTH and lumbar spine (and femoral neck and total hip) BMD in nPHPT and PHPT, while microarchitectural parameters were not reported (35). For context, PHPT has been associated with impaired trabecular microarchitecture and reduced Bone Material Strength index in other publications (37, 38). Whether nPHPT and PHPT represents a continuum of the same disease or if different pathophysiological mechanisms are at play remains to be elucidated (37). Similarly, establishing the occurrence and consequences of VFs in nPHPT requires additional studies.

Cushing syndrome

In Cushing *disease*, a recent review suggested that VF prevalence exceeds 40% (39), while recent studies in patients with Cushing syndrome found prevalence estimates of 53%, 75%, and 20%, respectively (40-42). TBS is lower in patients with Cushing syndrome than in age- and sex-matched controls (40). A recent study showed improvements in BMD *z* scores after treatment of Cushing syndrome, along with a substantial drop in VF and non-VF rates (although limitations in VF data exist; see Table 1 for details) (42). While this should be interpreted with caution as investigations were performed only in subsets of patients and no control group was included for comparison (42), these data are consistent with a recent review and indicate the reversibility of diminished bone health following treatment of Cushing syndrome (43).

Other endocrinopathies

While few studies report on fracture risk in Klinefelter syndrome, one cross-sectional study found an overall VF prevalence of 15%. There was no difference in VF prevalence according to age at study entry (<50 vs ≥50 years), but median age at diagnosis of Klinefelter syndrome was significantly higher in those with vs without VF (age 33 vs 20 years; $P = .039$) (44). While the overall VF prevalence may not be excessive, the data indicate that early diagnosis (which would allow early treatment, if indicated) of Klinefelter syndrome may mitigate any excess risk of VF. Further studies are clearly required to evaluate this hypothesis.

Fracture risk in patients with pheochromocytoma or paraganglioma is grossly understudied. Our literature search yielded one study that demonstrated a 43% VF prevalence in patients with pheochromocytoma or paraganglioma. Compared to patients with nonfunctional adrenal tumors, the OR for prevalent VF was 4.47 ($P = .001$), adjusted for sex and age. Lumbar spine—but not femoral neck—BMD *z* score was lower in patients with pheochromocytoma or paraganglioma compared to controls (45). Additional studies are needed to firmly understand fracture risk in this patient group.

Vertebral Fractures in the Era of COVID-19

In our literature search, we identified only 4 publications on the interplay between COVID-19 and VF, of which 2 were original research articles (46, 47), 1 was a case report (48), and 1 a commentary (49). Both research articles evaluated VF prevalence and outcomes in patients admitted to Italian hospitals (46, 47). Di Filippo and colleagues (46) reported a high, 36% prevalence of thoracic (T4-T12) VF on chest x-rays performed on emergency department admission in COVID-19–positive patients. More patients with VF, compared to patients without VF, required noninvasive mechanical ventilation (48.8% vs 27.4%; $P = .02$), and had a borderline significant increase in mortality (22% vs 10%; $P = .07$), although these findings may have been confounded by a higher age as well as higher prevalence of hypertension and coronary artery disease in the VF group at baseline. In the other study, Battisti and colleagues (47) evaluated 501 emergency department patients admitted because of suspicion of COVID-19. In COVID-19–positive vs –negative patients, the prevalence of VFs was similar (22.2% vs 19%; $P = .5$). Within the COVID-19–positive group, crude 30-day mortality increased with the number of VFs (0 vs 1 vs 2+). However, the HRs for death at 30 and 120 days were similar across the VF groups when adjusting for age, sex, and trabecular bone density.

As VFs are associated with reductions in pulmonary function (50, 51), poorer outcomes of patients with the dual burden of COVID-19 and VFs might have been expected. Nevertheless, with the small number of publications available, more evidence is certainly needed to elucidate this potential link and how it may affect clinical care.

Prevention and Treatment of Osteoporotic Vertebral Fractures

All licensed antiosteoporosis medications have evidence for prevention of new VFs in postmenopausal women and,

depending on the type of medication, in other patient groups such as male osteoporosis and glucocorticoid-induced osteoporosis. Owing to the paucity of pipeline osteoporosis medications, the number of new insights into pharmaceutical prevention of VFs is limited; we identified 2 new reports of RCT data (summarized in Table 2, upper half), while we identified 9 notable RCTs addressing treatment of patients with osteoporotic VFs (see Table 2, lower half).

Prevention

The new RCT publications with incident VFs as the outcome both addressed the ability of bone anabolics to prevent morphometric VFs in postmenopausal women with osteoporosis. A new Japanese study (52) tested teriparatide and alendronate. While teriparatide was used not in the conventional 20 μg per day but 56.5 μg per week regimen, alendronate was used in the lower 5 mg per day (or 35 mg/wk) dose that is licensed for osteopenia in the United States and for osteoporosis in Japan. Postmenopausal women with high imminent fracture risk based on very low BMD or baseline fractures (see Table 2) were treated for 3 years and a 22% RRR was observed with weekly teriparatide over alendronate. While this strengthens proof of concept for weekly teriparatide, it is worth noting that the VERO study (53) found more than twice this effect size with daily teriparatide against risedronate, another widely used oral bisphosphonate.

Many readers will be familiar with the primary licensing FRAME and ARCH trials for romosozumab demonstrating superiority to placebo and alendronate, respectively, of romosozumab given for 12 months followed by antiresorptive treatment for another 12 months (54, 55). Additional information has been provided now (56) on the presence (in FRAME, in which 18% had baseline VFs) or severity (in ARCH, in which 96% had baseline VFs) of VFs in the 2 trials (Table 2, upper part) and on the question of whether outcomes differed according to baseline VF status. In brief, no significant interaction between treatment and presence of VF was observed in the FRAME study, while the higher risk ARCH study reported an interaction *P* value of .09 between treatment effect and presence of severe VF for new mild VFs. Romosozumab generally led to risk reductions for all 3 grades of new VFs except severe fractures at 24 months in the ARCH study. This provides reassurance that this anabolic treatment need not be confined to patients who have or have not experienced prior VFs, in contrast to teriparatide, where baseline VFs were required for inclusion in the Neer trial (57). For context, it is known from past analyses of the teriparatide trials that the VF risk reduction was independent of baseline FRAX risk score (58), though the trial participants as a whole were a high-risk population with preexisting VFs. For romosozumab, the risk reduction for VFs was independent of FRAX in the 12-month romosozumab treatment period of the FRAME study (59). This was not the case for nonvertebral fractures but this is outside the scope of this review.

Treatment

We identified several potentially important new RCTs addressing 1) performance of vertebro- (PVP) and kyphoplasty (PKP) techniques, 2) the use of zoledronic acid as an adjunct to PVP and PKP, 3) role of teriparatide in treating acute VF, 4) stem cell therapy, and 5) physiotherapy and exercise therapy in patients with osteoporotic VFs (see Table 2, lower half).

The use of vertebral augmentation procedures in osteoporosis remains controversial. In 2019, the American Society for Bone and Mineral Research concluded that there was limited evidence on the efficacy and safety and the society does not endorse routine use of PVP or PKP (60), which is in contrast to a prior, more positive conclusion by the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) (61). There is the potential for further refinement of the methods that may improve efficacy and safety. In a new Italian study of 139 individuals with osteoporotic VFs, balloon kyphoplasty was associated with fewer adjacent level fractures than the simpler procedure of percutaneous vertebroplasty though there was no difference in pain visual analog score (VAS) score at 12 months, which was the planned primary outcome metric (62). It would be of importance to observe the longer-term outcomes, however, since additional VFs would be expected to adversely affect function, pain, and prognosis. Kyphoplasty procedures continue to evolve and improve. A new Chinese RCT indicated that for PKP, using a double-arm digital subtraction angiography (DSA)-guided technique provided significant benefits in terms of shorter procedure time, lower pain scores, less radiation exposure, and lower cement leakage volume (63). Further, the use of a curved needle rather than a bilateral straight needle approach might also reduce procedure time and radiation dose (64). Outcomes are also, perhaps unsurprisingly, improved by coadministration of a potent antiosteoporosis agent such as zoledronic acid. A single infusion of zoledronic acid shortly before PVP improved pain VAS score at 12 months (primary outcome) and reduced the incidence of new VFs in an RCT of 242 men and women (65). Three years of zoledronic acid following PKP confirmed a large and significant reduction in new VFs—in line with primary licensing trials for zoledronic acid—and also reduced the risk of recompression fracture by almost two-thirds (66). Taken together, these studies indicate that there is further research and development potential for these procedures and that large-scale, randomized studies with fracture, patient-reported outcomes, and functional outcomes are needed so that routine use of PVP or PKP could potentially then be endorsed in patients with painful osteoporotic VFs and targeted to those who will benefit most from interventional procedures.

We also identified new trials of pharmaceutical and stem cell treatment in patients following a vertebral osteoporotic fracture. In Japanese patients, mean age 80 years, a short, 12-week RCT in 96 patients failed to demonstrate major benefits of weekly teriparatide over weekly alendronate though QoL function metrics were better with teriparatide (67). The intervention may have been of too short a duration for definitive results. A phase 1/2a study evaluated mesenchymal stem cell (MSC) injection into the fractured vertebral body, followed by teriparatide for 6 months and then bazedoxifene alone for 6 month. The comparator group received the same medical treatment but no stem cells. One patient who received MSC injection developed a pulmonary embolism but also had a prior history of this, hence making a firm conclusion on causality difficult. Pain VAS score and physical function favored MSC injection, though these outcomes were secondary in the analysis plan (68).

Nonpharmacological intervention in the form of individually tailored manual therapy on an outpatient basis or exercise therapy at home in 615 men and women with VFs in the United Kingdom—the PROVE trial—reported that adherence was challenging and that no significant differences were seen at

Table 2. Recent findings on prevention and treatment of vertebral fractures

Study	Population	Intervention	Comparison	Outcome	Finding
Prevention of osteoporotic vertebral fractures					
Hagino et al (2021) (52)	1011 Japanese women with high risk of osteoporotic fracture based on low T-score < −3.3 and/or hip fracture and/or 2 VFs	Once weekly teriparatide 56.5 μg for 72 wk	Alendronate given as 5 mg daily, 35 mg once weekly or 900 μg IV every 4 wk for 72 wk	Morphometric VFs	Significantly lower event rate in teriparatide arm; IRR 0.78 (95% CI, .61-.99 ($P = .04$)
Geusens et al (2022) (56)	Post hoc analysis of 2 previously published romosozumab trials in postmenopausal women, FRAME N = 7180 and ARCH N = 4093	FRAME 12 mo romosozumab then 24 mo denosumab ARCH 12 mo romosozumab then 24 mo alendronate	FRAME 12 mo placebo then 24 mo denosumab ARCH 36 mo alendronate	Morphometric VFs, by grade (severe/moderate/mild)	FRAME Favors romozumab significantly for all grades of VF at 24 mo and all except mild fractures at 12 mo ($P = .26$), with no significant interaction ($P_{interaction}$ .18-.81) with prevalent VFs at baseline ARCH Favors romozumab significantly for all grades of VF at 24 mo and all except severe fractures at 12 mo ($P = .24$), no significant interaction with prevalent VFs at baseline, though there was borderline significant interaction with prevalent fractures for mild VF outcome at 24 mo only ($P_{interaction} = .09$, otherwise $P_{interaction}$ .12-.99).
Treatment of osteoporotic VFs					
Shim et al (2021) (68)	20 Korean postmenopausal women with recent osteoporotic VFs, 14 completed study (phase 1/2a study)	Mesenchymal stem cell injection into fractured vertebral body (with fibrin glue) plus 20 μg teriparatide once daily for 6 mo, followed by 20 mg bazedoxifene once daily for 6 mo	20μg teriparatide once daily for 6 mo, followed by 20 mg bazedoxifene once daily for 6 mo	Primary: safety and tolerability Secondary: Pain VAS, physical function, BMD, BTM	Overall good tolerability. One PE in intervention group in a patient with history of PE. Mild injection site reactions reported Favorable in terms of pain and function BMD and BTMs no significant difference
Ban et al (2020) (63)	60 Chinese men and women age >65 y with osteoporotic thoracolumbar (T12-L2) vertebral compression fractures	PKP, double-arm DSA-guided technique	PKP, C-arm–guided technique	Pain VAS-score, bone cement volume, leakage volume, surgery duration, radiation dose	Double-arm DSA group experienced significantly lower pain and had shorter procedure time and lower radiation dose. Volume of bone cement larger and leakage volume smaller
Griffoni et al (2020) (62)	139 men and women in Italy aged 55+ with osteoporotic fractures at T4-L5	PVP	Balloon kyphoplasty	Primary: pain VAS at 12 mo Secondary: Complications and new fractures. Standing lateral plain radiographs performed at baseline, postoperatively, and after 12 mo	No difference in pain at 12 mo PVP group developed significantly more incident adjacent-level fractures 11/64 vs 1/49; P = .0096
Hu et al (2020) (65)	242 men and women undergoing percutaneous vertebroplasty for osteoporotic vertebral compression fractures in China, mean age 69.5 y	Single infusion of zoledronic acid 2 d before PVP procedure plus oral calcium + PVP	PVP only	Primary: pain VAS at 12 mo Secondary: BMD and fractures	Lower pain VAS score at 12 mo in zoledronic group. Significantly higher BMD gain. New VF in 1.7% vs 10.7% (no P for fracture outcome reported but can be calculated as P = .003)

(*continued*)

Table 2. Continued

Prevention of osteoporotic vertebral fractures					
Study	**Population**	**Intervention**	**Comparison**	**Outcome**	**Finding**
Lu et al (2021) (66)	154 Chinese patients undergoing PKP for osteoporotic VFs, mean age 69 y	3 y of annual zoledronic acid after PKP	3 y of annual placebo after PKP	Primary: Recompression fractures and new VFs Secondary: BMD, pain VAS scores	Significant reductions in risk of recompression fractures (RRR 65%) and new VFs (RRR 73%). Better VAS and BMD outcomes in intervention arm, also smaller vertebral height loss
Wang et al (2021) (64)	72 patients mean age 76 y with osteoporotic vertebral compression fractures, China	PCKP	Bilateral PKP	Multiple outcomes: Procedure time, fluoroscopy time, cement volume, leakage, Cobb angle	PCKP procedure was faster, required a lower cement injection volume and fewer images with similar short-term effects (Cobb angle and anterior edge height). Authors also concluded PCKP was safer though this is not clear in the results. One case of intravascular leakage in traditional PKP arm, no intravascular leakage in PCKP arm but 3 cases of "leakage in the paravertebral body"
Barker et al (2020) (69)	615 men and women in UK, mean age 72 y, with osteoporotic VF and back pain	Individually tailored outpatient manual therapy over 12 wk (N = 203) Or Exercise therapy 45 min × 3-5 d/wk, at home with clinic sessions for instruction and FU (N = 216)	Single session of physiotherapy (N = 196)	Primary: Health related self-report questionnaire with 5 domains and timed loaded standing test at 12 mo	No significant difference at 12 mo; benefits over single session physiotherapy at 4 mo for endurance and balance. Adherence was challenging
Stanghelle et al (2020) (70)	149 women diagnosed with osteoporosis and VFs in Norway, mean age 74 y	12-wk resistance and balance exercise program	No intervention "life as usual"	Primary: 10-m habitual walking speed. Secondary: balance, strength, HRQoL, fear of falling, physical activity questionnaire	No difference in primary outcome. Better balance and strength in intervention group. HRQoL unchanged. No adverse events due to intervention
Ikeda et al (2020) (67)	96 Japanese patients with "acute" (ie, <1 wk) osteoporotic VF, mean age 80 y	56.5 µg teriparatide once weekly for 12 wk	Alendronate 35 mg once weekly for 12 wk	Vertebral collapse, BMD, prevention of delayed union, pain relief, and improvement of QOL	Improved QOL with teriparatide vs alendronate at 12 wk. No difference in other outcomes. No difference in VAS pain score

Abbreviations: BMD, bone mineral density; BTM, bone turnover marker; DSA, digital subtraction angiography; FU, follow-up; HRQoL, health-related quality of life; IRR, incidence rate ratio; IV, intravenous; PCKP, percutaneous curved needle kyphoplasty; PE, pulmonary embolism; PKP, percutaneous kyphoplasty; PVP, percutaneous vertebroplasty; QOL, quality of life; RRR, relative risk reduction; VAS, visual analog scale.

12 months despite benefits for endurance and balance at 4 months (69). A Norwegian intervention study in 149 women aimed at improving walking speed found no difference between the intervention and control groups for the primary outcome following a 12-week resistance and balance training program, though balance and strength improved more in the intervention group (70). Taken together, these studies suggest that these interventions could accelerate the recovery of patients after VFs whereas it is not clear that the long-term outcome is improved.

A search of ongoing and planned trials registered at clinicaltrials.gov and the European trials register identified a number of new VF augmentation trials, with and without combination with osteoporosis medications and MSCs. These are interesting prospects that could alter clinical practice over the next decade if successful and safe. The field could probably benefit from randomized studies comparing conventional PVP/PKP with injection of stem cells through the same route. By contrast, the only new osteoporosis drug currently registered in trials for prevention of VFs was the denosumab biosimilar RGB14 (trial NCT05087030), though there are also planned and ongoing trials of antiresorptives and teriparatide in specific conditions including chronic kidney disease for preventing VFs. There remains an unmet need for effective pharmaceutical treatments for patients who have sustained osteoporotic VFs but are unable to tolerate or safely use the currently licensed osteoporosis drugs, and the lack of a pipeline is a major concern.

Discussion

Severe clinical and personal consequences may arise in the aftermath of VFs, including back pain (71), physical/

functional limitations (72), and—as shown in a meta-analysis of patients with osteoporosis, comparing those with and without VF—a poorer physical health-related QoL (73). Also well recognized is the role of VFs as predictors of future fractures and mortality (74-76). In this review we have offered our perspective on recent findings relating to VFs in endocrine diseases and VF prevention and management.

On an overall note, we find it concerning that there is an extreme paucity of new osteoporosis pharmaceuticals in the pipeline, given the unmet treatment need (77) and the challenge of finding effective treatments to patients who are unable to tolerate or safely use the currently available classes of medications (78). As outlined earlier, new interventions currently in trial are aimed at treating the VF itself rather than underlying osteoporosis.

While a number of observational studies have evaluated VFs in endocrine diseases during recent years, as reviewed earlier, most of these face limitations, for example, a small number of participants (unsurprisingly, given the rarity of some of these endocrinopathies) (20, 25-28, 32, 35, 40, 44, 45), the lack of a control group (25, 27, 44), and/or by including only patients from a single clinical center (20, 25-28, 32, 40-42, 45). Prospective, multinational studies would be welcome in improving the understanding of VFs in rare endocrine disorders. For now, based on the evidence reviewed previously, the identification and management of VFs clearly remains an important task in the clinical workup of patients with subclinical hyperthyroidism, Graves disease, acromegaly, PA, PHPT, and hypoparathyroidism. It may be extended to also include Cushing syndrome, Klinefelter syndrome, and pheochromocytoma/paraganglioma, but as for now more evidence needed. It should be emphasized that VFs may also be highly pertinent in other endocrine diseases that were not subject to recent research; as such, the aforementioned list is not exhaustive.

Limitations pertinent to the study of VFs exist and, although beyond the scope of this review, should be highlighted. First is the lack of a common gold-standard method to diagnose VFs (79). Substantial differences in VF prevalence and predictive capabilities are evident across different methods, as highlighted in a study comparing the Genant semiquantitative method (GSQ) and the modified algorithm-based qualitative method (79). Thus, the choice of method to diagnose VFs holds consequences for VF epidemiology, and establishing a shared approach would be valuable to the field. The second aspect is the relevance of mild (grade 1) VFs diagnosed by the GSQ, which remain uncertain. Using data from men and women aged 50 years or older participating in the Canadian Multicentre Osteoporosis Study, mild GSQ VFs have been associated with future VFs but not future nonvertebral major osteoporotic fractures (exact point estimates not available) (79). Two recent studies have evaluated the association between VFs identified by lateral spine imaging on DXA machines and subsequent fracture risk (80, 81). One showed that women aged 75 to 80 years with mild VFs only, compared to those with no VFs, were at an increased risk of major osteoporotic fracture (adjusted HR 1.72 [95% CI, 1.08-2.76]), but not VF (HR 1.52 [95% CI, .71-3.25]). A borderline significantly increased risk of *any fracture* (HR 1.51 [95% CI, .98-2.34]) was observed (80). The other study showed that mild VFs, by the GSQ method modified to require end plate depression or cortical discontinuity to diagnose mild VFs, were not associated with subsequent hip, clinical spine, nor any low-trauma fractures in women aged 70+ years (81). Hence, research efforts should be directed at clarifying the relation between mild VFs and subsequent fractures.

There are limitations to this review: Since the mission was to provide an update on the latest new evidence, we did not include publications before 2020 unless they in our view provided essential background information needed to put the new studies into context. For space reasons we did not attempt to also incorporate a full discussion of VFs in the areas of diabetes and overweight/obesity, yet references were provided to relevant reviews on these topics.

In conclusion, endocrinologists should be aware of the high likelihood of osteoporotic VFs in patients with endocrine diseases. Though licensed treatments are able to substantially reduce the occurrence of VFs in patients with osteoporosis, the vast majority of recent or ongoing RCTs in the VF area focus on advanced invasive therapy for the fracture itself.

Disclosures

M.K.S. has received an educational grant, UCB; personal speaker fee; UCB; Institutional research grants from UCB/Amgen and Region Zealand Health Scientific Research Foundation; PhD scholarship, University of Southern Denmark; member of the board of the Danish Bone Society, and member of working groups of the Danish Bone Society and the European Calcified Tissue Society. B.A. has received grant support from Kyowa-Kirin (2019-2021), Pharmacosmos (2021), and UCB (2019-2022); consulted for Kyowa-Kirin and UCB; received speaker fees from Amgen and UCB; is president of the European Calcified Tissue Society, and a member of the Committee of Scientific Advisors, International Osteoporosis Foundation, and the Committee for Endocrinology and Metabolism, Novo Nordisk Foundation.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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