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#### Recommended Citation

Shah M, Appuswamy AV, Rao SD, and Dhaliwal R. Treatment of bone fragility in patients with diabetes: antiresorptive versus anabolic? *Curr Opin Endocrinol Diabetes Obes* 2021.

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# Treatment of bone fragility in patients with diabetes: antiresorptive versus anabolic?

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## Purpose of review

The pathogenesis of bone fragility in diabetes has not been fully characterized. The antifracture efficacy of available therapies remains unproven in patients with diabetes. We aim to collate current evidence of the treatment of diabetic bone fragility, and to provide a rationale for considering optimal therapeutic option in patients with diabetes.

## Recent findings

The antifracture efficacy of antiresorptive and anabolic therapies is well established in patients without diabetes. Studies in patients with osteoporosis have shown that anabolic therapies lead to faster and larger benefits to bone mineral density and offer greater protection against fracture than antiresorptive therapies. Available data suggest that antiresorptive and anabolic therapies have similar effect on bone density and fracture risk reduction in patients with and without diabetes. However, the evidence in diabetes is limited to observational studies and post hoc analyses of osteoporosis studies.

## Summary

There are no specific guidelines for the treatment of bone fragility in patients with diabetes. We offer a rationale for use of anabolic therapies in diabetes which is a low bone formation state, in contrast to postmenopausal osteoporosis that is characterized by increased bone turnover. Prospective studies evaluating the effect of available therapies on bone quality and fracture outcomes in patients with diabetes are needed.

## Keywords

anabolic, antiresorptive, bisphosphonate, bone quality, diabetes, fracture, osteoporosis

## INTRODUCTION

Diabetes and osteoporosis are common chronic conditions in older adults. The global prevalence of diabetes mellitus is estimated to be 463 million [1]. Recent data suggest that the estimated prevalence of osteoporosis in individuals with type 2 diabetes (T2D) has increased from 3.1% to 6.1% between 2005 and 2014 [2]. Both type 1 diabetes (T1D) and T2D are associated with an increased risk of hip fractures of up to 33% [3<sup>\*\*\*</sup>]. Hip fractures correlate with higher mortality in those with diabetes compared to those without diabetes [4]. Findings of a large cohort study indicate that this increased risk of fractures begins in childhood and extends across the lifespan of patients with T1D [5]. Further, fracture risk assessment in diabetes is challenging. The observed changes in bone mineral density (BMD) in patients with T1D and T2D fail to fully explain the increased fracture risk, since BMD is only modestly reduced in patients with T1D [6] and is usually normal or even higher in patients with T2D [7] than in those without

diabetes. Therefore, while BMD remains a strong predictor of fractures in patients with diabetes, BMD measurements alone tend to underestimate fracture risk in this population [6,8,9].

The bone deficits observed in patients with diabetes and the underlying mechanisms that cause these deficits have not been fully elucidated. Alterations in bone quality and bone strength of patients with diabetes are the detrimental consequences of insulin deficiency or resistance, hyperglycemia, advanced glycation of bone matrix proteins, excess cytokine production, and low bone turnover [10–

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**Curr Opin Endocrinol Diabetes Obes** 2021, 27:000–000

DOI:10.1097/MED.0000000000000645

## KEY POINTS

- The bone fragility observed in patients with diabetes is predicated on low bone turnover, impaired bone material properties, and reduced bone quality.
- There are no randomized controlled trials that have compared the efficacy of antiresorptive and/or anabolic therapies on bone density, turnover, strength, or fracture outcomes in patients with type 1 or type 2 diabetes.
- In the context of bone mineral density that is discordant to the increased fracture risk, and low bone turnover, anabolic therapies have a potential benefit for the treatment of bone fragility in patients with diabetes.
- Prospective studies focused on the determinants of and treatment for the bone fragility in patients with diabetes are needed for developing an optimal approach to the management of bone health in these patients.

12]. Other specific diabetes-related factors, such as increased risk of falls due to retinopathy and neuropathy and peripheral vascular disease, may also contribute to the greater fracture risk in these patients [9–13].

The antifracture efficacy of osteoporosis medications is well established in individuals without diabetes [14]. In contrast, there remains uncertainty with regard to the role of antiresorptive versus anabolic therapies in the treatment of bone fragility within the context of diabetes. Herein, we review the available data on the efficacy of antifracture therapies in patients with diabetes to guide optimization of bone health in this growing population.

## ANTIRESORPTIVE THERAPIES

Antiresorptive agents reduce osteoclast-mediated bone resorption throughout the treatment period resulting in increased BMD, with a plateau effect in response after 2–3 years of treatment [15,16]. The net result is a reduction in fracture risk. Histomorphometry studies have demonstrated that in T1D and T2D, bone turnover is low with a lower bone formation rate in patients with fractures or with diabetic microvascular complications [17–21]. These findings have raised concerns that antiresorptive therapy may not be as effective in preventing bone loss and reducing fracture risk in patients with diabetes and may even further suppress bone turnover [22].

### Antiresorptive therapy in type 1 diabetes

The prevention and treatment of bone fragility in patients with T1D has become more clinically

relevant with the rising life expectancy in these patients. There is a dearth of data on the efficacy of antiresorptive therapy in T1D. Studies have demonstrated lower bone formation and increased osteoblast apoptosis in T1D [17,18]. In a preclinical study in which insulin-deficient mice had a lower bone formation rate at baseline than control mice, osteoblast apoptosis was decreased, and the bone formation rate was further reduced in insulin-deficient mice following treatment with alendronate [22]. Interestingly, the decrease in osteoblast survival in treated diabetic mice was similar to that in nondiabetic controls, and the difference in bone formation rate between treated diabetic mice and treated control mice was not significant. A few clinical studies have investigated the effects of anti-fracture treatment in patients with T1D. An observational study comparing the effect of risedronate and conventional treatment (calcium + vitamin D supplementation) over a 12-month period in 52 participants with T1D reported a significant increase in BMD at the spine and hip and in bone formation markers [23]. In a large Danish case-control study that included T1D and T2D patients, the fracture risk reduction at spine, hip, and forearm following alendronate therapy was similar to the risk reduction in those without diabetes [24], regardless of the type of diabetes.

There are no studies that have investigated the antifracture efficacy of denosumab, a human monoclonal IgG2 antibody that binds and inhibits RANKL, in patients with T1D.

### Antiresorptive therapy in type 2 diabetes

In contrast to the paucity of data in patients with T1D, more information about bone health management in patients with T2D is available. A post hoc analysis of three 48-week randomized control trials (RCTs) in patients with ( $n=52$ ) and without ( $n=832$ ) T2D showed that risedronate had similar effects on markers of bone resorption and formation and on lumbar spine BMD in both groups [25]. A post hoc analysis of the Fracture Intervention Trial (FIT) showed that, compared to placebo, alendronate decreased bone turnover markers (circulating levels of C-terminal telopeptide and bone-specific alkaline phosphatase) and improved BMD in women with T2D [26]. The positive effect of alendronate in the T2D cohort was similar to that observed in the nondiabetic group. One small observational study also showed no between-group differences in spine BMD response following treatment with alendronate in postmenopausal women with and without T2D [27]. With regard to fracture risk reduction, a post hoc analysis of two large RCTs (FIT and

the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial) estimated that in older women with T2D on bisphosphonate treatment, the relative risk of non-vertebral fractures was 0.52 (95% CI: 0.33–0.80) and that of vertebral fractures was 0.34 (95% CI: 0.18–0.67), compared to those in the placebo group [28]. Thus, evidence of the therapeutic benefit of bisphosphonates in patients with T2D is limited to post hoc analyses of RCTs and an observational study, but no prospective RCTs have evaluated the effect of antiresorptive therapies on fracture risk reduction in patients with diabetes.

Similarly, evidence for the antifracture efficacy of denosumab in T2D patients is limited to one post hoc analysis. In the Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) trial and its 7-year extension, 266 women with diabetes who received denosumab had higher BMD compared to the 242 women with diabetes who received placebo [29]. Further, those treated with denosumab had significantly fewer new vertebral fractures than the placebo group (1.6% versus 8%, RR:0.20, 95% CI 0.07–0.61;  $P=0.001$ ) but had an increased risk of nonvertebral fractures (11.7% versus 5.4%, HR:1.94, 95% CI 1.00–3.77;  $P=0.046$ ).

In summary, available evidence suggests similar efficacy of antiresorptive therapy in patients with and without diabetes, although data for T1D are sparse and limited to post hoc or secondary analyses of studies in which neither patients with T1D or T2D were the focus population. Nonetheless, BMD is an inadequate marker of fracture risk in diabetes, and whether an increase in BMD translates into clinically meaningful fracture risk reduction in this population is not known. It is speculated that antiresorptive treatments, by further reducing pre-existing low bone turnover in patients with diabetes, may have a detrimental effect on bone quality; although, an associated increase in fracture risk remains to be established. A population-based study of patients with diabetes (T1D and T2D) and age- and sex-matched controls showed that further reduction in bone turnover by antiresorptive therapy is not associated with an increase in fracture risk [24]. Notably, the patients with diabetes in this study had good glycemic control, which may have prevented detrimental effects of antiresorptive therapy on bone turnover and quality. Given the paucity of data on antiosteoporosis therapies in diabetes, it is prudent to treat bone fragility in T1D and T2D patients based on available guidelines until more data emerge [30]. Prospective studies investigating bone remodeling, bone quality, and fracture outcomes in patients with T1D and T2D are needed.

## ANABOLIC THERAPIES

Available anabolic treatments include parathyroid hormone (PTH) analog, teriparatide and PTH-related peptide (PTH-rp) analog, abaloparatide. Intermittent administration of PTH stimulates both osteoclast-mediated bone resorption and osteoblast-mediated bone formation, resulting in high bone turnover with a net gain in bone mass [31]. In addition, anabolic agents activate the canonical Wnt signaling pathway and significantly increase both modeling- and remodeling-based bone formation, thereby causing a marked increase in bone formation [32,33]. The pathophysiology of bone fragility in patients with diabetes is characterized by impaired differentiation and maturation of osteoblasts and decreased bone formation. Thus, in theory, osteoanabolic therapies should be superior to antiresorptive therapies in diabetes. However, the literature on the efficacy and safety of anabolic therapies in patients with diabetes is scarce compared to that for antiresorptive therapies.

### Anabolic therapy in type 1 diabetes

In studies of insulin-deficient mouse models that show a reduced BMD phenotype, treatment with intermittent PTH results in increased BMD and bone formation rate [34,35]. Similarly, intermittent PTH administration in mice with diabetes has been demonstrated to improve trabecular bone structure and strength through the anabolic effects of PTH on osteoblast differentiation and improved osteoblast survival [36]. Interestingly, the anabolic effects of PTH on trabecular bone were observed independent of BMD, which remained lower in mice with diabetes than in controls. In another study, short-term treatment with PTH-rp restored bone mass and remodeling in mice with diabetes to the levels similar to those in controls [37]. To date, there are no clinical studies (observational or prospective) that have assessed the efficacy of osteoanabolic treatment in patients with T1D. Further, post hoc analyses of data from osteoporosis RCTs are not feasible because these studies primarily focused on investigating postmenopausal or age-related osteoporosis, and patients with T1D are likely excluded from these trials.

### Anabolic therapy in type 2 diabetes

By contrast, the effect of anabolic therapies in patients with T2D has been assessed in preclinical and clinical studies, although studies are limited in number. Evidence from rodent studies indicate that PTH improves bone mass and skeletal homeostasis in the setting of diabetes [38,39]. Teriparatide has

been demonstrated to increase osteoblast number and function on trabecular bone in the vertebrae and increase trabecular bone mass, BMD, and mechanical strength of vertebrae [39]. Further, teriparatide was shown to improve cortical bone structure and BMD in this study.

The Direct Analysis of Nonvertebral fractures in Community Experience (DANCE) study was an observational study of patients treated with teriparatide for up to 24 months and followed for an additional 24 months after cessation of treatment [40]. Post hoc analyses of the DANCE study showed a similar increase in BMD and reduction of fracture risk in patients with T2D as in patients without diabetes. Increase in the spine and total hip BMD did not differ between groups; interestingly, the increase in femoral neck BMD was significantly greater in T2D patients than controls [41]. An integrated analysis of 4 prospective observational studies assessing the antifracture efficacy of teriparatide in 8828 patients with osteoporosis and comorbidities showed that the relative reduction in clinical fracture rate was greater in diabetic than in nondiabetic subgroups [42].

Abaloparatide, a PTH-rp analog, is a selective activator of the PTH-1 receptor signaling pathway that preferentially stimulates bone formation in a short period with a concurrent lesser increase in bone resorption [33,43]. For this reason, abaloparatide is appealing for the treatment of bone fragility in patients with diabetes. Post hoc analysis of postmenopausal women with T2D from the Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE), a phase 3, double-blind, randomized, placebo- and active-controlled trial [44], demonstrated a significant increase in BMD at all skeletal sites, improvement in trabecular parameters, and fewer nonvertebral fractures in treated participants than in the placebo arm [45].

### **Newer anabolic therapies: anti-sclerostin antibodies**

The anabolic Wnt signaling pathway stimulates osteoblast-mediated bone formation and prevents osteoclast differentiation and function. Sclerostin, a physiological Wnt inhibitor, is secreted by mature osteoblasts and osteocytes. An antisclerostin monoclonal antibody has been developed as an osteoanabolic therapy. In diabetic animal models, sclerostin antibody treatment has been shown to enhance bone formation and quality by facilitating osteoblast differentiation and bone mineralization in insulin-deficient mice, and enhance bone mass at the spine and femur with a final BV/TV higher in the T2D mice compared to controls [46,47]. Treatment

with sclerostin antibody also resulted in improvement in bone strength of similar magnitude in diabetic and nondiabetic animals. In the Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH), romosozumab, an antisclerostin monoclonal antibody, increased bone formation and significantly reduced vertebral and nonvertebral fractures compared to alendronate [48]. Romosozumab was approved in 2019 for use in postmenopausal women at high risk for fractures. Clinical data on the efficacy of romosozumab in patients with diabetes are lacking. Considering the concern about increased cardiovascular risk as observed in phase 3 studies comparing romosozumab to alendronate [49], a post hoc analysis of diabetes subgroup may be informative before prospective studies of romosozumab can be considered in this high-risk population.

Overall, pivotal anabolic trials and comparative studies have demonstrated greater and faster antifracture efficacy with anabolic therapies than with antiresorptive therapies, providing a clear rationale for the use of these medications in individuals at high risk for fracture. In theory, osteoanabolic treatments should be superior to antiresorptive therapies in patients with diabetes, as treatment with anabolic therapy addresses the underlying pathophysiology of reduced bone formation. Available evidence suggests favorable outcomes in patients with diabetes with the use of osteoanabolic therapies (Table 1). Prospective studies are required to further validate these findings, specifically in patients with diabetes, both T1D and T2D.

### **General principles of bone health management**

General principles for the preservation of bone health and prevention of fragility fractures in patients with diabetes should include universal recommendations on bone health while simultaneously addressing diabetes-specific factors that contribute to increased fracture risk. Lifestyle interventions are recommended for both osteoporosis and diabetes. Regular physical activity (weight bearing exercises) helps prevent bone loss and aids in glycemic control. Vitamin D deficiency is prevalent in patients with T1D and T2D; therefore, adequate replacement with vitamin D supplements is often required [50,51]. Patients should ensure adequate calcium intake as well. Maintaining mineral homeostasis is particularly important in the presence of diabetic nephropathy, as disruptions in mineral metabolism can lead to secondary hyperparathyroidism that can further weaken bone integrity. Microvascular complications in patients with diabetes are associated with reduced BMD, inferior bone



**Table 1.** Effects of osteoporosis medications on BMD and fracture risk in type 1 and type 2 diabetes<sup>a</sup>

Medications	Type 1 diabetes		Type 2 diabetes	
	BMD	Risk of fracture	BMD	Risk of fracture
Alendronate [24,26]	↑	↓	↑	↓
Risedronate [23,25]	↑	NA	↑	NA
Zoledronate [28]	NA	NA	NA	↓
Denosumab [29]	NA	NA	↑	↓
Abaloparatide [44,45]	NA	NA	↑	↓
Teriparatide [40–42]	NA	NA	↑	↓
Romosozumab [48]	NA	NA	NA	NA

<sup>a</sup>Only available evidence is from observational studies and posthoc analyses.

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

quality, and increased fracture risk [12]. Adequate glycemic control is recommended to reduce all complications in diabetes [52]. Importantly, patients should be counseled about fall prevention, as patients with diabetes are at high risk for falls [53]. This increased risk is multifactorial in etiology. In addition to diabetic complications such as neuropathy and retinopathy, both hyperglycemia and hypoglycemia are associated with an increased risk of fracture and falls [53,54]. Therefore, in older adults or those with a high risk of hypoglycemia, avoidance of sulfonylureas (which can cause drastic hypoglycemia) and a less stringent glycemic target are encouraged, as recommended by the American Diabetes Association guidelines [52]. Finally, anti-hyperglycemic medications such as thiazolidinediones and canagliflozin (an SGLT2 inhibitor) with an unfavorable effect on bone metabolism, should be avoided in patients with diabetes and bone fragility [30].

## CONCLUSION

Current gaps in our knowledge of the mechanisms causing bone fragility in diabetes and the lack of prospective studies evaluating efficacy of antifracture therapies in patients with diabetes are barriers to effective treatment of compromised bone health in this population. Studies suggest similar efficacy of bisphosphonates in patients with and without diabetes, and there is no concrete evidence against the use of bisphosphonates in patients with diabetes. The majority of patients with diabetes included in the studies have been those with T2D. The efficacy of antiresorptive therapy in T1D is lacking. Limited evidence suggests that denosumab may be a preferred option for older patients with diabetes or for those with compromised kidney function. In the absence of randomized trials, the role of antiresorptive treatment in diabetes remains unproven.

Anabolic therapies increase bone formation and, consequently, are more appealing in the setting of a low bone turnover state observed in patients with diabetes. The findings from mouse models, observational studies, and post hoc analyses of osteoanabolic therapies in patients with diabetes are promising. Randomized controlled trials exploring how different therapeutic approaches affect bone structure, bone remodeling, and fracture outcomes are needed to fully elucidate and validate the benefit of anabolic therapies in diabetes.

## Acknowledgements

*M.S., A.A. and R.D. wrote the manuscript. D.S.R. and R.D. edited and reviewed the manuscript. All authors approved the final version. The authors thank Dr Karla D Passalacqua, Senior Medical Writer, Henry Ford Hospital for assistance with manuscript preparation.*

## Financial support and sponsorship

*This work was partly supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) of the National Institutes of Health (NIH) under Award Number AR062103.*

## Conflicts of interest

*There are no conflicts of interest.*

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