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Diabetes and Bone: What is the Relationship?

The increase in the prevalence of diabetes, particularly type 2 diabetes mellitus (T2DM), is alarming. Generally, more attention is given to well-recognized complications associated with diabetes, including retinopathy, nephropathy, neuropathy, and cardiovascular disease.

Currently, more data is emerging linking diabetes to bone fragility, leading to its recognition as another complication of diabetes: diabetic bone disease.

The pathophysiology of both disorders (diabetes and bone fragility) and related complications is multifactorial, and various mechanisms may be involved.

Hyperglycemia per se has a toxic effect on osteoblast precursor cells, favoring their transformation into adipose cells and thereby causing an imbalance in bone remodeling.

Moreover, hyperglycemia leads to the production of a series of metabolites known as "advanced glycation end products" (AGEs), which have a deleterious effect on the skeleton. The accumulation of these AGEs affects both the structure and the strength of the bone. Additionally, there is a low remodeling state that in turn leads to a higher risk of fracture.

Obesity and insulin resistance, particularly associated with T2DM, also have a negative effect on bone metabolism. Finally, sarcopenia, understood as the loss of muscle mass, strength, and function in older adults, is more prevalent with age, leading to poorer muscle function and a higher risk of falls and consequently fractures. The greater loss of muscle mass, along with increased adipose tissue, leads to the production of larger quantities of molecules known as adipokines, which have deleterious effects on bone.

From the perspective of bone tissue, a series of molecules are also produced that seem to have different effects on glucose metabolism. Noteworthy among them is osteocalcin, which in some studies is related to increased insulin sensitivity, or on the opposite side, osteoprotegerin, or RANK ligand (RANKL), which has been associated with insulin resistance and a higher risk of diabetes.

Among the known factors that influence an increased risk of fracture in people with diabetes are the course of the disease and the degree of glycemic control. Other systemic mechanisms that influence diabetes-related bone fragility include chronic kidney disease—very common in people with long-standing diabetes—and dysregulation of the calcium-vitamin D-parathyroid hormone (PTH) axis, as poor glycemic control results in greater calcium loss through urine, stimulating PTH secretion and thereby favoring bone resorption.

To assess bone resistance, we measure bone mineral density (BMD); the reference test for this is bone densitometry using dual-energy X-ray absorptiometry (DXA), but this technique has its limitations in the assessment of people with diabetes.

In T2DM, an increased BMD has been observed vs subjects of the same age and sex without diabetes, which could lead to an underdiagnosis of fracture risk, which is known to be increased if only DXA data is considered. This paradoxical phenomenon of greater bone mass in subjects with T2DM seems to be related, as previously mentioned, to the high prevalence of obesity and the known association of higher BMD in people with a higher body mass index.

In this context, the use of other techniques, such as the trabecular bone score (TBS), an imaging modality that assesses the state of trabecular bone microarchitecture, or high-resolution peripheral quantitative computed tomography (HR-pQCT), could help improve the estimation of osteoporotic fracture risk in diabetic patients. However, of note that these techniques may not be available in all centers.

Another tool frequently used to estimate the 10-year fracture risk is the **FRAX scale,** which includes risk factors such as age, sex, weight and height, personal or family history of fractures, corticosteroid use, smoking, and alcohol consumption, among other data, but also tends to underestimate the fracture risk in diabetic patients.

In summary, epidemiological studies indicate a clear increase in the risk of hip fracture and, to a lesser extent, vertebral fractures.

But not only is T2DM associated with altered bone metabolism, type 1 diabetes mellitus (T1DM) has also been linked to a higher prevalence of fractures. In T1DM, the increased fracture risk is observed even in the early stages of the disease, suggesting that there are factors beyond the duration and degree of control that lead to the development of poorer quality bone, resulting in a lower »

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» peak bone mass and consequently a higher future predisposition to fractures.

Regarding **assessment by DXA in T1DM, lower BMD has been described vs other subjects of the same age and sex.** The decline in BMD seems to occur at a young age and remains stable during subsequent follow-ups, suggesting that changes occur early in the disease progression. Lower BMD is not the only factor determining the higher fracture risk in T1DM. **Microarchitectural changes** detected by HR-pQCT and magnetic resonance imaging (MRI) show defects in bone tissue, both in the cortical and trabecular compartments, with lower trabecular density and volume.

The drugs used to treat diabetes also have effects on the bone and should be considered when selecting the most appropriate antidiabetic therapy.

Firstly, although metformin, the most widely used drug to treat T2DM, has not shown any effect on bone fragility in humans, preclinical trials suggest that it may promote osteoblast-induced bone formation. Regarding fracture risk, clinical study results are inconsistent: some retrospective studies and meta-analyses suggested a reduced fracture risk in patients treated with metformin, which has not been validated in other studies.

Secondly, sulfonylureas; although preclinical trials pointed to a positive effect on bone formation, studies in humans have not demonstrated this effect and are generally considered to have a "neutral" effect on BMD or fracture risk, although it is true that the higher incidence of hypoglycemia in patients taking this drug class may be associated with a higher risk of fractures, particularly in older or frail individuals, which should be taken into account when prescribing. »

THE ASSESSMENT BY DXA IN T1DM HAS SHOWN LOWER BMD VS OTHER SUBJECTS OF THE SAME AGE AND SEX

» As with sulfonylureas, the effect of insulin on fracture risk is related to the higher rate of hypoglycemia among users. Despite the anabolic effect of insulin in experimental trials, this positive effect has not been confirmed in human studies.

The most consistent data are related to thiazolidinediones. This drug class has a negative effect on bone, reducing BMD and increasing fracture incidence, particularly in postmenopausal women. The effect of GLP-1 analog treatment is still little known and data are preliminary. However, preclinical trials suggest a favorable effect on bone remodeling with a predominance of formation.

Regarding DPP-4 inhibitors, the latest meta-analyses show a neutral effect on bone metabolism, with no impact on fracture risk.

The current controversy lies with the therapeutic group of SGLT2 inhibitors. In early studies, particularly with the molecule canagliflozin, they were associated with an increased risk of fractures. However, after a more rigorous retrospective analysis of other studies that included all molecules in this group, that negative effect was not confirmed. Despite the relationship between diabetes and bone fragility/osteoporosis, there are no specific studies that have evaluated the effect of osteoporosis drugs in T1DM or T2DM. In general, analyses from different studies confirm similar efficacy in T2DM for the various therapies evaluated. The drugs used to treat osteoporosis also appear to have effects on glucose metabolism. Drugs used to treat osteoporosis also seem to have effects on glucose metabolism.

The most widely used antiresorptives—bisphosphonates—have not reported negative effects associated with a higher incidence of diabetes.

Recently, a study discussed the potential beneficial effect of denosumab, another drug in the antiresorptive group, where a benefit was observed in terms of lower fasting blood glucose.

No effect of bone-forming drugs—teriparatide—on glucose levels has ever been demonstrated.

Finally, studies including calcium and vitamin D supplementation have shown a reduction in fasting glucose levels as well as lower insulin resistance, measured by HOMA-IR index.

As a final recommendation, in young patients with diabetes and low bone mass, the promotion of healthy lifestyle habits and the achievement of adequate vitamin D concentrations, > 30 ng/mL, should be prioritized. Occasionally, to achieve this, supplementation with 25-OH vitamin D (calcifediol) or cholecalciferol will be necessary.

Additionally, in general, a proper calcium intake (800-1000 mg/day) should be ensured, as absorption and tolerance are better when calcium intake comes from the diet, with supplements initiated if requirements are not met.

In conclusion, **bone and glucose metabolism are strongly related. The assessment of osteoporosis risk in a person with diabetes should begin with a proper evaluation of fracture risk in the medical history, adding imaging tests to guide diagnosis in some cases, and, in general, adapting treatment to recommendations similar to those for the non-diabetic population.** D

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