

Side effects explained: Why common drugs can lead to broken bones

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New research helps to explain why some commonly used drugs come with a serious downside: They up your odds of breaking a bone. The drugs in question, glucocorticoids (e.g. cortisone and prednisone) and the insulin sensitizer rosiglitazone work through entirely different mechanisms as therapies for inflammatory diseases and diabetes respectively, and two studies in the June issue of *Cell Metabolism* now show that they lead to bone loss in different ways too.

Both research teams, one at the University of Texas Southwestern Medical Center and the other at the Fritz-Lipmann Institute in Germany, say that this new molecular understanding of what happens to bone could lead to the design of drugs with fewer side effects. They also provide new insight into the basic biology of bone.

"People taking a high dose of glucocorticoids can be pretty sick with [rheumatoid arthritis](#) or severe asthma, for example, and in that case their systemic fracture risk doubles," said Jan Tuckermann of the Fritz-Lipmann Institute. "For a young person, that might be OK because their risk is very low to start, but, as you become older, it's a real problem."

In fact, osteoporosis is just one of a range of glucocorticoid's side effects, all of which look something like normal symptoms of aging, he added. Glucocorticoids are still used because they remain one of the most potent anti-inflammatories around. "Our goal is to find a way to reduce the side effects," Tuckermann said.

It should come as no surprise that glucocorticoids have unwanted effects. They represent a class of steroid hormone and glucocorticoid receptors are found in cells all over the body, including in the bones. But scientists didn't know which bone cells were important in producing the side effects on [bone loss](#).

Bone is a rather dynamic tissue, explained Yihong Wan of UT Southwestern, the senior author of the other study. It is constantly being remodeled through a careful balance between the activities of bone-building osteoblasts and bone-resorbing osteoclasts.

Tuckermann's team now finds that glucocorticoids act on the osteoblast side of that equation. Studies in mice showed that animals lacking glucocorticoid receptors in their osteoblasts didn't show the same bone loss that glucocorticoids normally bring.

They were able to drill down further into the details of that interaction, and the results come as somewhat bad news. In fact, Tuckermann explained, activated glucocorticoid receptors are known to function in two different ways. Once the activated receptors enter a cell nucleus, they either find another receptor and partner up (to form a dimer) or they act indirectly, via other transcription factors (proteins that influence other genes). When glucocorticoid receptors form dimers, they go on to influence glucose metabolism. It is when they remain in their lone, monomer form that they play a role in inflammation.

Many had suspected that the beneficial effects of glucocorticoids stemmed from that inflammatory pathway while the side effects resulted when the receptor formed dimers to influence glucose. Tuckermann's team now finds that it isn't really that clear cut. In fact, mice whose glucocorticoid receptors couldn't partner up with one another to influence glucose still developed bone loss on the drug.

But there is some good news too. The ill effects in bone all stem from one particular transcription factor, known as AP-1, their evidence shows. Tuckermann says it may now be possible to fine-tune glucocorticoid drugs such that they don't lead to that AP-1 interaction.

In the second study, Wan's team wanted to understand why long-term use of rosiglitazone in patients with diabetes make bones more fragile in diabetic patients, who are already at increased risk of bone fractures as it is. The insulin-sensitizing drug is known to act through the so-called peroxisome proliferator-activated receptor g (PPARg), a receptor that plays diverse roles in fat cell development, lipid metabolism and insulin sensitivity.

Emerging evidence suggested that PPARg also has an important job in bones. Earlier studies found that it suppresses the bone-building activities of osteoblasts. At the same time, an earlier study by Wan's team showed that PPARg speeds up the differentiation and activity of osteoclasts, to break down more bone.

Further experiments by Wan and her colleagues reveal some of the other players involved. They find that rosiglitazone's side effects on bone involve a transcriptional coactivator known as PGC1b, which coordinates with another molecular actor known as ERR α . Strikingly, they report, animals lacking PGC1b in their osteoclasts grow completely resistant to rosiglitazone-induced bone loss.

Wan notes that the effects of the drug on osteoblasts seem to occur through a different intermediary. This new understanding of how PPARg action in different types of cells will facilitate the design of improved diabetic drugs, such as selective PPARg modulators that retain the insulin-sensitizing benefits but dampen the detrimental bone loss effects, the researchers say.

The bottomline for Wan is this: "There is an explanation for why this diabetes drug causes bone loss," she said. "Based on this knowledge, better drugs can be developed."

More information:

- Wei et al.: "PGC1 β Mediates PPAR γ Activation of Osteoclastogenesis and Rosiglitazone-Induced Bone Loss." Publishing in Cell Metabolism 11, 503-516, June 9, 2010. [DOI:10.1016/j.cmet.2010.04.01](https://doi.org/10.1016/j.cmet.2010.04.01)
- Rauch et al.: "Glucocorticoids Suppress Bone Formation by Attenuating Osteoblast Differentiation via the Monomeric Glucocorticoid Receptor." Publishing in Cell Metabolism 11, 517-531, June 9, 2010. [DOI:10.1016/j.cmet.2010.05.005](https://doi.org/10.1016/j.cmet.2010.05.005)

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