Contrary to what many think, bone is a dynamic tissue that responds to many cues from other organs: progesterone, estrogen, vitamins, phosphorus, calcium, metabolic products, and other substances. Research on bone health has shown that osteoporosis—the loss of bone mass leading to thin and fragile bones—is related to a number of conditions such as aging, renal disease, inflammation, estrogen deficiency, and diabetes.

Diabetes, a condition in which the body’s energy metabolism is impaired, has major consequences for bone health and is of particular interest to Beata Lecka-Czernik. Cells use glucose as their energy source, but first that glucose must enter the cell, a process
The anti-diabetic drug rosiglitazone delays bone regeneration (healing) and causes accumulation of fat at the site of healing (bottom panel – white areas represent fat cells).

3D images of bone generated with micro computed tomography

Histological visualization of adipocytes (fat cells) within bone defect

orchestrated by the hormone insulin. Glucose is toxic when outside the cell. Lecka-Czernik explains that individuals with Type 1 diabetes, in whom the pancreas does not produce insulin, break bone sevenfold more often non-diabetics, while individuals with Type 2 diabetes, whose cells do not respond to insulin and thus cannot metabolize glucose, have a twofold higher fracture rate than non-diabetes. "The bone quality is less in diabetes. The bone is less hydrated and more fragile, like a dry stick," she says.

There are some powerful drugs, called TZDs, available to treat Type 2 diabetes, Lecka-Czernik says. They are very efficient at controlling high blood glucose levels but have a deleterious effect on stem cell differentiation in the bone marrow. These drugs allow cells to "see" insulin and so admit the passage of glucose molecules. Unfortunately, they have a negative side effect: they hijack stem cells into becoming fat instead of bone. The result is accentuation of the aging process as bone mass decreases and fat in bone increases. "We don't know to what extent this process affects functional bone marrow," Lecka-Czernik notes, "but fat releases different factors that may also affect bone formation. It is a cascading effect."

Working with structural chemists at Scripps Research Institute, Lecka-Czernik is testing some new compounds. The goal is to develop anti-diabetic drugs that have the same advantageous biological activity as existing drugs but without the adverse effect on bone. In lab tests of these new compounds, both in vitro and in mice, she has seen either no effect on bone mass or even improved bone mass. "It is possible to develop new drugs that are both efficient for treatment of diabetes and safe for bone," she remarks.

In the course of testing these new compounds, Lecka-Czernik confirmed a surprising—and exciting—discovery. "Some of these compounds are able to convert white fat into brown fat," she states. White fat is for energy storage; it is the fat responsible for obesity and, by extension, diabetes. Brown fat is so named because it contains a lot of mitochondria—the organelles that produce energy in the cell. It is metabolically active and capable of rapidly producing energy. Even though it is fat, brown fat acts as a power plant and actually burns white fat by using the energy stored there.

Some of the new anti-diabetic compounds enable fat cells to convert the white fat into brown, says Lecka-Czernik. In experiments with an animal model in which white fat cells converted to brown fat, the animals were lean and had higher bone mass than controls. The brown fat is releasing into the bloodstream proteins that act as hormones and stimulate bone formation, she comments. "We believe that these new compounds have beneficial effects on bone by acting on fat," she adds.

This discovery opens the door to a unique possibility—targeting fat to treat obesity, diabetes and osteoporosis simultaneously. With eyes sparkling, Lecka-Czernik says, "Our hypothesis is to target fat instead of bone to produce factors strengthening bone. It can only be more efficient to have an all-in-one treatment for multiple diseases." Her excitement of such potentially effective treatment is palpable when she talks about these new discoveries.

Lecka-Czernik comments that she owes much of her research discoveries to her association with other researchers. "We have to recognize that body physiology is integrated and that we must approach it as a complex whole. A single, focused approach can lead to adverse effects elsewhere, which says a lot for an interdisciplinary approach."

She adds that the Center for Diabetes and Endocrine Research (CeDER) involves a number of researchers who learn from each other. "We are tracking diabetes from different directions and perspectives. Diabetes is not caused by just one thing, and the consequences are so general."

Lecka-Czernik says that the kind of interdisciplinary cross-fertilization she can find with her colleagues in CeDER is just what is needed to crack some of the mysteries associated with the effects of diabetes.