High-tech imaging could reveal mysteries of bone damage in kids with chronic disease

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Linnea Holm used a dynamometer in Mary Leonard's lab to test the strength of muscles in her lower leg and ankle region. Data from the machine helps researchers determine how muscles may affect the strength and quality of bones. Credit: Leonard lab

Kyla Kent had just finished conducting CT scans of bones in a 10-year-old boy's forearm and lower leg. Walking him back to the waiting room, she asked how he wanted to explain the images to his mom.

The detailed view provided by the CT machine, a high-resolution peripheral quantitative computed tomography scanner called XtremeCT II, is giving Stanford scientists unusually precise information about the toll of chronic diseases on children's bones. But young research participants are often more excited about the images' gee-whiz factor. Kent could sense the boy's mental wheels turning.

"Mom, here's what happened," the boy said. "From a single cell, a very small wizard was born. And he goes inside my arm—it doesn't hurt, I just felt a little pinch—and while he's in there, he takes a picture of the inside of my bone with his iPhone 6s camera!"

Kent, telling the story, stopped and chuckled. "I could not have come up with that explanation on my own," she said. Kent is the technical director of the Stanford Assessment of Bone and Muscle Across the Ages Center, or SAMBA Center, a multidisciplinary research effort to document and find ways to improve bone health over the life span.

The work, much of which focuses on kids, is led by Mary Leonard, MD, professor of pediatrics and of medicine and the center's founding director. Many chronic childhood diseases, including diabetes, chronic kidney disease, inflammatory bowel disease, congenital heart defects and childhood cancer, take a silent toll on patients' bones. Leonard and her team want to help patients maximize their bone health in childhood and reduce their risk for osteoporosis later on.

'A critical period'

"Childhood and adolescence is a critical period for building a big, strong,

healthy skeleton," said Leonard, who holds the Arline and Pete Harman Professorship for the Chair of the Department of Pediatrics.

Healthy children and teens have a unique opportunity to build a bulwark of bone mass to prevent osteoporosis later in life, she said. Throughout childhood, and especially during the growth spurt of puberty, the bones are constantly being reshaped by the interplay of two types of bone cells: osteoclasts, which chew up existing bone, and osteoblasts, which build new bone and mineralize it with plenty of calcium and phosphorus. In healthy kids, many different physiological factors—including diet, weight-bearing exercise and the activity of various hormones—affect the bone-modeling process, shaping how big and heavy the bones become.

"The flip side is that in chronic disease, we think there's a window during development when kids' bones are especially vulnerable," Leonard said. Chronic disease can hurt adults' bones, too, but for children who are supposed to be building enough bone to last a lifetime, the effects can be especially severe. "And once you stop growing, there's little opportunity to make the bones thicker," she added. "That ship has sailed."

As experts at Lucile Packard Children's Hospital Stanford and other institutions develop new ways to help children survive previously life-shortening illnesses, long-term damage to kids' bones becomes more important to address. "We need to shift focus to health across the life span," Leonard said.

A powerful scanner

One key tool in Leonard's efforts to do that is the SAMBA Center's high-resolution CT scanner, the only such machine west of Missouri. It is designed to provide an extremely detailed view of the bone structure inside the arms and legs, and it uses much less radiation than a typical

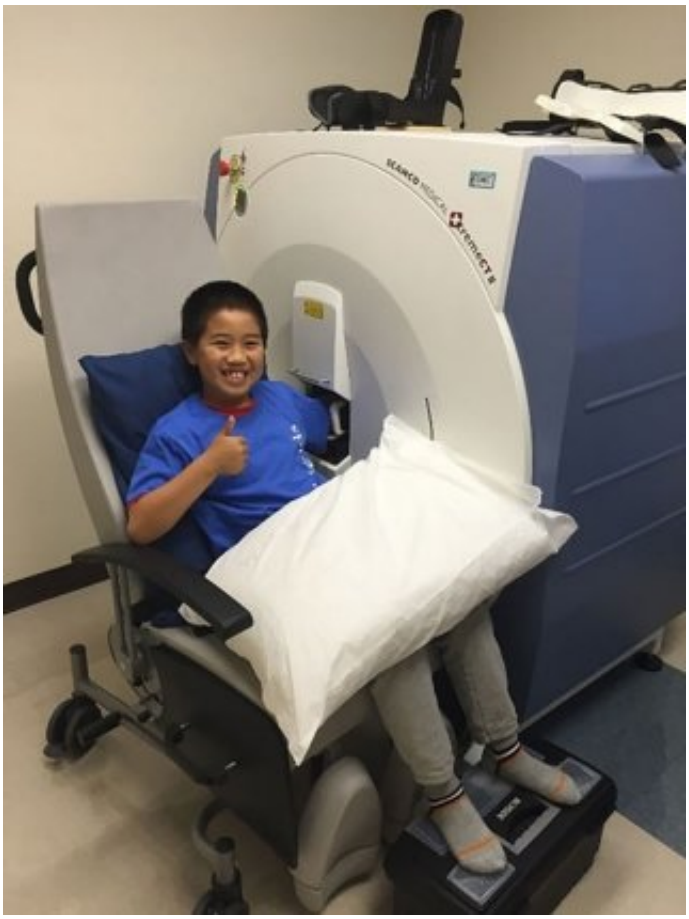
medical CT scanner.

"High-resolution CT scans help us understand why the bones are weak," Leonard said. "Is it because the shell of the bone is thin? Is it not dense enough? Does it have pores or holes it shouldn't have?" These details are telling: Inflammation leaves one type of damage traced on the bone, steroid medications leave another. Vitamin D deficiency looks different, too. "If we understand the underpinnings of the fragility, it gives us insight into the mechanism of bone damage," she said.

The high-resolution CT is such a new tool that the Stanford team had to begin by creating a normative database of bone scans from healthy children, a process that is still underway. They are also collaborating with other scientists around the world to agree on standardized methods for running the scans.

Once the high-resolution CT data is collected, it's studied using finite element analysis, a technique borrowed from engineering physics. "We treat the bone like it's a bridge or airplane wing and see: What is the failure load?" Kent said. Two children with the same bone density may not have the same functional level of weakness in their bones; high-resolution CT can distinguish between them.

"We don't do these scans to predict fractures in children; we do it because we want to understand what their disease is doing. It helps us think more about different treatment options," Leonard said.



Ryan Shih underwent a high-tech CT scan. This particular machine provides an extremely detailed view of the bone structure inside the arms and legs, and it uses much less radiation than a typical CT scanner. Credit: Leonard lab

The team's work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

The team is also using more traditional methods of assessing bone health , including dual X-ray absorptiometry, or DXA, scans, which provide information about children's overall bone mass, lean body mass and body composition, as well as hand-grip testing, leg-endurance testing and maximum force generation tests, which measure different elements of

limb strength to allow the team to assess how bones and muscles function as a unit.

In healthy kids, bones and muscles work together to prompt the bone to grow, Leonard explained. "Your bone is listening: 'You're putting me under stress; I can sense the forces and I'll respond by getting stronger,'" she said. "When children are bedridden, they can lose a lot of bone mass because the signaling process isn't occurring. And in many chronic diseases, the patients who have the worst muscle mass also have smaller bones—not just less dense, actually smaller."

Putting bone discoveries to use

Bone health discoveries are already strengthening some patients' bones.

For instance, new medications for inflammatory bowel disease, which includes Crohn's disease and ulcerative colitis, now allow doctors to avoid treating kids with drugs that damage their bones. "These kids used to get treated with high doses of prednisone," Leonard said. "They had terrible skeletal fragility." The steroids led to vertebral compression fractures, injuries more typically seen in elderly osteoporosis patients. Now, doctors can instead prescribe biologics that selectively suppress gut inflammation and directly block the inflammatory molecules that damage bone.

Not only are the patients better off, the new treatments are helping researchers tease apart how much bone damage is caused by steroids and how much by the disease itself, since inflammation also damages bone. Leonard co-authored a recent series of studies demonstrating that children and adolescents with Crohn's disease have remarkable improvements in growth, muscle mass and bone density and size after treatment with biologics. "These patients have made the most progress because treatments for the disease have improved so much," Leonard

said.

For other chronic diseases, there's farther to go. In the 25 years Leonard spent at the Children's Hospital of Philadelphia before moving to Stanford in 2014, much of her research was devoted to understanding bone damage in children with chronic kidney disease. Metabolism of the bone-building hormone vitamin D is regulated by the kidney: When the kidneys don't work, a complex cascade of calcium and phosphorus regulation gets thrown off and damages the bones. Leonard and her colleagues have shown that children with kidney disease have thin bones with low density and increased risk of fracture.

Today, Leonard's team is using both DXA scanning and their high-resolution CT scanner to get a more detailed view of these patients' bones.

"I think it will be really interesting to see how different their bone microarchitecture will be compared with the healthy controls we're also scanning," said Candice Sheldon, MD, a clinical fellow in pediatric nephrology whom Leonard is mentoring.

Looking ahead

Chronic kidney disease patients tend to be shorter than average, Sheldon said. Although growth-hormone and vitamin D supplementation are already used to help promote growth and protect these patients' bones, they are still more likely to break bones than healthy kids. "We still haven't figured out how to optimize therapy so these kids are as close to their healthy counterparts as possible," Sheldon said. She hopes the CT scans will give clues as to the exact mechanism of bone damage that will put the team on the trail of better therapies.

The team also hopes to understand how receiving a kidney transplant

affects children's bones. After transplant, how much do the bones recover? Packard Children's has the largest kidney transplantation program in the country and spearheaded the development of steroid-free immunosuppression regimens in children. This is the ideal place to determine if bone density, structure and strength can recover following kidney transplant in children and adolescents.

In the future, Leonard hopes to investigate the long-term impact on bones of a new form of bone-marrow transplantation being developed at Stanford for certain cancer patients. Radiation therapy that is traditionally used to prepare patients for bone-marrow transplant also damages their bones, leaving childhood cancer survivors who have received the transplants with low bone density, low muscle mass and high body fat over the long run.

But a Stanford team led by Judith Shizuru, MD, Ph.D., professor of medicine and of pediatrics, and Maria Grazia Roncarolo, MD, professor of pediatrics and of medicine, is developing an antibody-based method of preparing patients for bone-marrow transplant that is intended to allow them to skip radiation.

"They're the first to do a stem cell transplant that doesn't require radiation, and we'll have an opportunity to see if this incredible new therapy prevents fractures in these patients," Leonard said.

Her team hopes their discoveries will translate into better ways to keep kids' bones strong for decades to come. "Bone fractures are painful, and the young patients we're studying are already dealing with so many other medical problems," said Sheldon. "Ultimately, we want to strengthen their bones so they can be happier and more active in childhood and throughout their adult lives as well."