NewYork-Presbyterian

2018 • Issue 1

ADVANCES IN RHEUMATOLOGY

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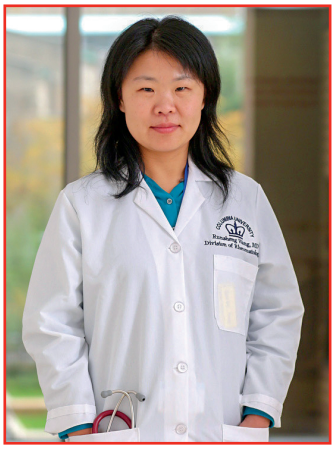
The rheumatology program at NewYork-Presbyterian Hospital is comprised of faculty affiliated with Weill Cornell Medicine and Hospital for Special Surgery, and Columbia University College of Physicians and Surgeons. The program provides state-of-the-art care to patients with the broad range of inflammatory and autoimmune diseases, pursues groundbreaking research at both the laboratory level and through clinical studies, and offers comprehensive training to medical residents and fellows.

BEST HOSPITALS U.S.News & WORLD REPORT NATIONAL RHEUMATOLOGY 2017-18

NewYork-Presbyterian Rheumatology ranks #3 in the nation.

Ankylosing Spondylitis: An Ongoing Diagnostic Challenge

Norman Cousins and Ed Sullivan were among the more prominent individuals to have had ankylosing spondylitis (AS). Less famous was Leonard Trask, who is reported to be the first case of AS described in the United States in 1858, although accounts of AS by the Greek physician Galen date back as early as the second century. While AS has a long history, diagnosis in its early stages has remained elusive.



Dr. Runsheng Wang

The delay in diagnosis is among the reasons that **Runsheng Wang, MD, MHS**, a rheumatologist in the Division of Rheumatology at NewYork-Presbyterian/Columbia University Irving Medical Center, developed a clinical and research interest in spondyloarthritis, with a particular focus on ankylosing spondylitis. Prior to joining Columbia, Dr. Wang was a Lawrence Shulman Scholar in Translational Research at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and she is a recipient of the Rheumatology Research Foundation Scientist Development Award.

"The main symptom of ankylosing spondylitis is inflammatory back pain caused by inflammation in the spine. It has many associated symptoms, such as peripheral arthritis, uveitis, and inflammatory

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Current Thinking on Bone Health

Osteoporosis has long been called a silent disease since there are no warning signs or symptoms until fractures occur. In the United States alone, an estimated 1.5 million fractures each year are attributed to low bone density. "And the risks of osteoporosis are not relegated exclusively to women – males represent 20 percent of all cases," says rheumatologist **Linda A. Russell, MD**, Director of the Osteoporosis and Metabolic Bone Health Center at Hospital for Special Surgery. For more than 30 years, the Center – which was the first program of its kind in the nation – has pursued its mission to prevent osteoporosis and to provide treatment options that promote bone health. Today, the Center is the only one in New York City that holds the International Society for Clinical Densitometry Facility Accreditation.

Dr. Linda A. Russell

In addition to evaluating and caring for patients with metabolic bone disease, Dr. Russell, who is also Director of Perioperative Medicine at Hospital for Special Surgery, has focused her attention on perioperative bone health, leading a team that includes specialists in rheumatology, endocrinology, and orthopedics. "We evaluate the bone health of a range of patients beyond those individuals whose age puts them at risk for osteopenia or osteoporosis," says Dr. Russell. "These include patients taking

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Ankylosing Spondylitis: An Ongoing Diagnostic Challenge *(continued from page 1)*

bowel diseases," says Dr. Wang. "The under-diagnosis of AS is partly due to under-recognition of its symptoms, resulting in a delay in referring patients to rheumatologists. But the delay is also due to the diagnostic method. We rely on the structural changes on pelvis X-rays to determine the diagnosis. However, it takes five to 10 years from symptom onset for the structural changes to become visible on pelvis radiographs, and by then the damage is already there. So how can we diagnose these patients earlier?"

To address this question, a new concept, axial spondyloarthritis, was proposed in 2009, and was intended to include the early phase of ankylosing spondylitis and ankylosing spondylitis itself. Developed by the Assessment of SpondyloArthritis International Society (ASAS), the classification criteria of axial spondyloarthritis includes patients who have classic presentation and radiographic findings of AS, and those who have symptoms of AS without structural changes on pelvis X-ray. The latter is called non-radiographic axial spondyloarthritis.

The ASAS criteria, however, raised several questions for Dr. Wang and others in the field. "Is non-radiographic axial spondyloarthritis truly a precursor stage of ankylosing spondylitis? Do all patients eventually evolve into the stage of ankylosing spondylitis? Will some patients stay in that stage and not progress? Or, in some patients, will their symptoms resolve over time?"

Some studies have examined similar questions in the past, but none provided sufficient answers due to duration of the studies. "Researchers examined these similar questions in prospective longitudinal studies," says Dr. Wang. "However, because five to 10 years of follow-up is required to definitively determine the outcomes of these patients, previous studies had significant loss of follow-up during such long duration, particularly loss of patients with milder symptoms."

A Novel Longitudinal Study

To address this challenge, Dr. Wang and her colleagues decided instead to conduct a retrospective population-based cohort study using a resource available through the Mayo Clinic called the Rochester Epidemiology Project, a medical linkage system with detailed medical records of the entire population of Olmstead County, Minnesota, including diagnostic and procedural codes since 1966.

"The diagnostic code for axial spondyloarthritis did not exist until the recent adoption of ICD-10. However, the Rochester Epidemiology Project includes detailed medical information of all Olmstead County residents and provides the opportunity to identify these patients based on their symptoms," explains Dr. Wang. "In order to apply the ASAS classification criteria, we had to pin down the symptoms of each patient in combination with diagnostic and procedural codes for back pain, test results for HLA-B27, and MRIs of the pelvis."

The researchers culled data on patients between 1985 and 2010 and, after screening 2,151 patients, they identified 83 subjects – 18 in the imaging arm, 65 in the clinical arm – with new-onset non-radiographic axial spondyloarthritis. They then followed these subjects from disease onset through March 15, 2015, using survival analysis to measure the time to progression to AS.

"We found that about one-third of patients with non-radiographic axial spondyloarthritis eventually progressed to ankylosing spondylitis," adds Dr. Wang. "The next step was to stratify the risk for progression to AS in these patients." The study found that subjects in the imaging arm were 3.5 times more likely to progress to AS than those in the clinical arm. In their paper, published in the June 2016 issue of *Arthritis & Rheumatology*, the researchers conclude, "This finding suggests an important difference among the entities included in the non-radiographic axial spondyloarthritis umbrella, one of which is much closer to 'preradiographic' AS, while the other represents a condition with a different prognosis."

Building on their original research, Dr. Wang and her colleagues undertook a subsequent study to examine the long-term prognosis of patients with new-onset inflammatory back pain, the earliest and most common symptoms in patients with axial spondyloarthritis. They used the resources of the Rochester Epidemiology Project,

> **"There is a delay of five to 10 years in diagnosing ankylosing spondylitis from the onset of symptoms. How to timely and accurately diagnose these patients becomes one of the most important questions because we have highly effective drugs that can relieve symptoms of these patients. Understanding its natural history and identifying risk factors that predict disease progression will help us answer this question."**
>
> **— Dr. Runsheng Wang**

examining the records of patients, 16 to 35 years old, with clinical visits for back pain from 1999 to 2003 to identify those with new-onset inflammatory back pain. Of the 5,304 patients screened, 124 were identified with this condition. The researchers followed these patients for a median of 13.2 years, examining their progression either to spondyloarthritis, a non-spondyloarthritis diagnosis, or resolution of back pain. "At 10 years, we found that the probability of having spondyloarthritis was 30 percent, while the probability of resolution of inflammatory back pain was 43 percent," notes Dr. Wang. "The most important predictors for progression included uveitis, male sex, and family history of spondyloarthritis."

Moving forward, Dr. Wang will collaborate with other investigators in North America to validate and improve the classification criteria of axial spondyloarthritis. Her long-term goal is to identify predictors for disease progression and to develop an effective treatment strategy to prevent structural damage and disease progression in these patients.

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Current Thinking on Bone Health

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medications that cause bone loss, such as glucocorticoids to treat chronic obstructive pulmonary disease, asthma, colitis, and rheumatoid arthritis, and aromatase inhibitors that are used to treat breast cancer. These two, in particular, are very common medications that contribute to bone loss and would warrant a patient's evaluation for metabolic bone health. In addition, certain conditions, such as celiac disease and multiple myeloma, predispose someone to bone loss, so we also screen for those when individuals present with osteoporosis or fracture."

Dr. Russell and her colleagues will also evaluate adults who have suffered low-impact fractures and those who are preparing to have major orthopedic procedures, such as a spine fusion or a revision total hip replacement. "We will test these patients preoperatively and, if indicated, put them on a treatment plan so that their bone is as strong as possible for surgery," she says.

Measuring Bone Loss Today

In addition to the standard bone densitometry test (DEXA) to measure bone loss, Center physicians also obtain a trabecular bone score (TBS), which indicates the porosity of a vertebral body as a measure of the strength and quality of the bone. "TBS is related to bone microarchitecture and provides skeletal information that is not captured by the standard bone mineral density measurement," says Dr. Russell. "In a current study, we are also using TBS for patients with ankylosing spondylitis because of its possible greater accuracy as a fracture risk assessment tool."

At the time the DEXA is obtained, a patient can also have a femur fracture assessment. This test gives a pictoral view of both femurs. Cortical thickness can be assessed; when increased, it may be a sign of an impending atypical femur fracture.

FRAX® is a fracture risk assessment tool that can evaluate the 10-year probability of a person's risk of fracture. This tool can be used to determine if a patient is at high risk for fracture when the DEXA scan indicates low bone mass. FRAX is based on risk factors such as age, weight, family or personal history of fracture, glucocorticoid use, diagnosis of rheumatoid arthritis, as well as bone density of the femoral neck. According to World Health Organization guidelines, treatment is recommended if the FRAX analysis shows a risk of any fragility fracture >20 percent in 10 years or a risk of hip fracture >3 percent.

Making Sense of Medications

Initially, the mainstay of treatment for osteoporosis was hormone replacement therapy, followed by bisphosphonates, which over the last few years has been the subject of controversy. "The first class of medications that we were using for the treatment of osteoporosis was the bisphosphonates," explains Dr. Russell. "We learned that if you take these medications for a prolonged period of time, more than 5 or 10 years without a holiday, there is an increased risk of

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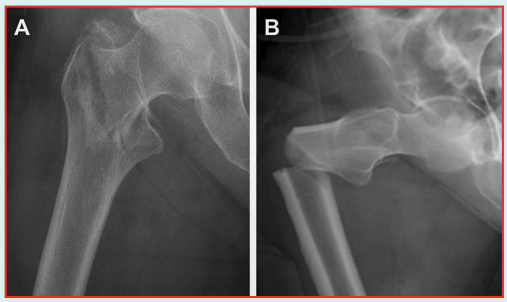
Contributing Factors to Atypical Femoral Fracture

A study conducted by faculty in the Department of Materials Science and Engineering at Cornell University in collaboration with researchers from Hospital for Special Surgery and Weill Cornell Medicine has shed light on why prolonged use of bisphosphonates can alter the composition of bone, making it more brittle and susceptible to atypical femoral fracture (AFF). The researchers examined biopsies of cortical bone from the shaft of the femur obtained from postmenopausal women during fracture repair surgery. The participants were placed in five groups, based on fracture type and bisphosphonate use.



Radiograph imaging showing morphology of a typical fragility fracture of the hip (A), compared with an atypical femoral fracture, or AFF (B). The nature of the AFF indicates a brittle fracture process, possibly due to excess mineralization of the bone. (Courtesy of Donnelly Research Lab)

Their findings indicated that the bone of women treated with bisphosphonates who had AFF was harder and more mineralized than bisphosphonate-treated women with typical osteoporotic fractures. The main function of bisphosphonates is to slow down the resorption of old bone, which is generally followed by remodeling. In healthy adults, cortical bone is constantly being resurfaced, but if that resurfacing process begins with resorption, and if resorption is slowed by bisphosphonates, the remodeling process is also affected. The result is that existing bone ages and becomes brittle over time.

Long-term bisphosphonate use also involves crack-deflection – the ability of the resurfaced bone to stop a microscopic crack from propagating, which can lead to a break. New layers of bone can act as a "firewall" of sorts, stopping a crack from spreading, but mineralized, older bone loses that function.

The FDA is now recommending patients use bisphosphonates for three to five years, followed by reassessment of their risk. "What we have observed is really the result of long-term treatment, well beyond what the FDA is recommending for these drugs now," says **Eve Donnelly, PhD**, Assistant Professor in the Department of Materials Science and Engineering at Cornell University. "Our work explains some of the underlying mechanisms of AFFs and can inform the refinement of dosing schedules for patients at risk of fragility fractures."

Reference Article

Lloyd AA, Gludovatz B, Riedel C, Luengo EA, Saiyed R, Marty E, Lorich DG, Lane JM, Ritchie RO, Busse B, Donnelly E. Atypical fracture with long-term bisphosphonate therapy is associated with altered cortical composition and reduced fracture resistance. *Proceedings of the National Academy of Sciences USA*. 2017 Aug 15;114(33):8722-27.

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Current Thinking on Bone Health *(continued from page 3)*

osteonecrosis of the jaw and atypical femoral fracture. Though these are unusual and rare occurrences, many patients worry about them tremendously. Then about five years ago, an article came out saying the bisphosphonates were harmful and then everyone stopped taking them."

When the number of hip fractures started to increase again, notes Dr. Russell, the medical world reconsidered their use. "Our current thinking is that we do want to use these medications when people are at high risk for fracture," says Dr. Russell. "But now, after patients have been on them for a while, we give periodic holidays from this therapy."

Denosumab, a human anti-RANK ligand antibody, has shown to induce sustained inhibition of bone resorption lasting for months after a single subcutaneous injection. "Denosumab is also an anti-resorptive agent," says Dr. Russell. "Denosumab is FDA approved for the treatment of osteoporosis in postmenopausal women at high risk of fracture, male osteoporosis, and for patients with cancer-induced bone loss. Teriparatide and abaloparatide are both anabolic agents; these agents promote bone formation. They can help reduce the risk of fractures and can aid in fracture healing."

Dr. Russell emphasizes that adults who have had a low impact fracture are at great risk for another fracture if left untreated and should be referred for testing and evaluation. "At our Center, patients are tested and then their case is presented to an interdisciplinary team," she says. "The final recommendations are given to the patient and their primary care physician."

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