Pregnancy hormone holds promise for leapfrogging trauma, surgery recovery

Edward K. Rodriguez MD, PhD, Chief of Orthopaedic Trauma at BIDMC, introduces himself as “an orthopaedic trauma guy.” But he’s also a research guy, one of a team working collaboratively to develop a treatment that could both shorten and improve recovery from frozen shoulder and a host of other injuries and surgical repairs.

“About 12 years ago, I saw three young women over a period of six months who each had very severe, distal humerus fractures of the elbow,” said Rodriguez. This type of fracture, a break in the lower end of the upper arm bone, is “notorious for resulting in long-term lack of motion. You can lose more than 50 percent of your ability to extend and flex your arm fully, as well as to bend it in a way that you would to type on a keyboard.”

Rodriguez repaired the women’s fractures, and assumed they would go back to their lives with the expected range of motion limitations. A few years later, all three coincidentally returned to see the surgeon again within a six-month time-period.

“All three of them said to me ‘Look!’—and showed me that their full elbow motion had been restored,” recounted Rodriguez. When asked what they had done to achieve the recovery, he discovered a common thread: each had had baby.

“As most women who have been biological moms can attest, the last trimester of pregnancy is known for very floppy joints. All your joints get loose, you start walking with a wobbly gait. It’s all in preparation for your pelvis ligaments to soften up so you can deliver the baby safely,” Rodriguez said. What creates this effect is relaxin, a hormone produced during pregnancy.

“It occurred to me, wouldn’t it be great if we could just make a single joint pregnant anytime we have a stiffness problem?” said Rodriguez. “What if we could somehow harness relaxin, and then raise the concentration of it in the joints to pregnancy levels just for a few weeks after injury, trauma or surgery to loosen up the joint and prevent heavy scarring?”

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Letter from the Chairman

Dear Colleagues and Patients:

As we ramp up from the summer months and embark upon the New England autumn, I hope you took time off to enjoy the warm weather and family time. Despite the vacation schedules, we continued our mission of caring for patients and advancing clinical research. We greeted two surgeons and made inroads studying a type of injection that could drastically reduce the time and effort it takes for patients to recover from orthopaedic trauma.

One of the latest surgeons to join our diverse, accomplished team is Dr. Jacob Drew. A joint surgeon, Drew is returning to his native Massachusetts following three years at the Department of Orthopedics at the Medical University of South Carolina. Among his many qualifications is experience with the anterior approach to hip replacement and research on pre- and post-operative pain management for arthroplasty patients.

We are also pleased to welcome Dr. Sammy Dowlatshahi, who joins Dr. Matthew Iorio as one of the first surgeons at BIDMC to hold dual positions in orthopaedic hand surgery and plastic surgery. Dr. Dowlatshahi’s path has included extensive study in his native England, Germany and right here in Massachusetts: Dowlatshahi completed a fellowship at BIDMC in hand surgery and microsurgery, a residency at University of Massachusetts Medical Center, and biomechanical research work at Worcester Polytechnic Institute.

In this issue, you can also read about how BIDMC investigators are looking at a hormone produced by pregnant women to prevent the stiffening of joints following orthopaedic trauma or following surgical procedures. While further study and government approvals are needed, the research could have a relatively quick path to market.

With winter on the horizon, we offer an article on treatment for an issue common to cold climates such as in New England: Raynaud’s disease. You can learn about Dr. Carl Harper’s approaches to the temporary but sometimes severe discomfort and numbness of the fingers affected by this condition. Since coming on board a year ago, he’s been offering a range of options that can help Raynaud’s patients through the worst of their symptoms—which are especially aggravating in the winter.

Finally, we proudly present a sampling of the academic and career accomplishments of department members.

Sincerely,

Mark C. Gebhardt, MD
Chief, Carl J. Shapiro
Department of Orthopaedics
Raynaud’s symptom relief options include Botox injections

Anita was 37 when she noticed her fingertips turning white, feeling cold, turning blue, and then returning to normal. It was November, when the frost had just begun to appear on her Honda Civic’s windshield before heading off to work at a Boston financial company. Although the episodes continued, they only happened when she didn’t wear gloves and didn’t last long, so she shrugged them off. Over the next few years the bouts got more frequent and lasted longer. When they began affecting her job as a computer analyst, which required keyboarding, she visited her primary care physician who told Anita that she had Raynaud’s disease.

Raynaud’s (pronounced ray-NOZ), sometimes called a disease, phenomenon or syndrome, is a rare disorder characterized by vasospasms. These brief episodes of narrowing of the arteries reduce blood flow to the fingers and sometime the toes.

Raynaud’s attacks like Anita’s can last less than a minute or as long as several hours, and can occur daily or weekly. During an attack, fingers and toes may go from white to blue to red. They may also feel cold and numb from lack of blood flow. As the blood flow returns, fingers or toes can throb and tingle.

“What causes the symptoms is poorly understood. What we do know is that it’s not just abnormal nerves or abnormal vessels, but the way the nerves and vessels interact with each other and send signals to the brain,” explained Carl Harper, MD, a hand and upper extremity surgeon at BIDMC.

There are two types of Raynaud’s disease—primary and secondary, both of which have symptoms that can be triggered by a cold climate like New England’s and stress. Primary Raynaud’s disease affects women more than men. People with a family history of Raynaud’s may also be more prone to the condition.

People with primary and secondary Raynaud’s have similar symptoms, explained Harper, but those with the secondary type often have an underlying vascular disease such as diabetes. “Although the types are different, you begin treatment in the same way.”

Avoiding cold and damp conditions is the best way to thwart a Raynaud’s attack, according to Harper. Keeping the hands and feet warm and dry, especially in winter, is crucial to preventing symptoms. Other ways to avoid attacks include turning down air conditioning, warming up your car in cold weather, and wearing gloves when taking food out of the refrigerator or freezer.

Lifestyle changes can also help people with Raynaud’s reduce the frequency, length and severity of attacks. Some of these are quitting smoking, exercising, managing stress and moving to a warmer climate.

Non-surgical treatment

When a patient is first diagnosed, a primary care physician or rheumatologist may recommend non-surgical treatments to help prevent Raynaud’s attacks. Occupational therapists can work with the patient to understand triggering conditions and suggest avoidance behaviors. Physical therapy and biofeedback are other options. “Biofeedback loops can be taught—it’s not dissimilar from meditation: you can actually stimulate your vessels to dilate and improve the blood flow to your hands,” said Harper.

Medications may be prescribed to control Raynaud’s. “Various drugs have varying levels of support in the literature, but in general calcium channel blockers such as nifedipine are first line agents in the prevention and treatment of Raynaud’s phenomenon,” he said.

A relatively new non-surgical treatment to help those with primary or secondary Raynaud’s is botulinum toxin (Botox) injections. In an office or clinic setting, a physician uses a special ultrasound machine to map out the arteries in the hand. Then the physician deposits a tiny amount of botulinum toxin using an extremely small needle into the area near those arteries where the affected nerves are located. “This allows the nerves to send signals to the vessels saying, ‘Why don’t you relax a little bit and allow the blood flow to return to the fingers?’” said Harper.

There are multiple possible injection sites: two in the wrist, and five to 10 in the hand depending on where the patient’s symptoms are located and their severity. A person

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Sammy Dowlatshahi, MD, is a man of duality: he hails from two continents, and practices two surgical specialties.

Dowlatshahi (pronounced doo-LAT-sha-be) was born in England and spent his first few years there before moving with his family to Canada. At the age of 10, he moved back to Europe—Germany this time. And when he joined BIDMC in September, Dowlatshahi accepted a dual appointment in orthopaedic surgery and plastic surgery.

While he wanted to be a surgeon from an early age and his passion propelled him through the first couple of years of medical school, Dowlatshahi had a change of heart about half way through. “I was going to give up medicine altogether. Medical school was so theoretical. I didn’t see a single patient the first few years, and I thought ‘This is not for me.’ I looked into studying music and physics.” Meanwhile his sister, also a medical student, made a pivotal introduction. “She had worked with Dr. Lowka, a very well-established and respected hand surgeon in our town of Freiburg,” said Dowlatshahi. “She told me I should spend time with him.”

He took his sister’s advice, and fell in love with hand surgery. “Dr. Lowka told me I could get into hand surgery via orthopaedic surgery or plastic surgery. I set up several rotations and worked with three well known Boston hand surgeons, when I was still living in Germany. So hand surgery was my saving grace—it kept me in medicine and got me interested in plastic surgery.”

After a residency in plastic surgery and reconstructive surgery, Dowlatshahi completed a fellowship at BIDMC in hand surgery and microsurgery.

It was yet another duality that drew Dowlatshahi to a staff position at BIDMC. The role enables him to be part of an academic group that provides advanced reconstructive microsurgery and hand surgery, and at the same time practice in a community setting. “The option was offered to me to work in Dedham as well as with the BIDMC team in Boston. It’s the best of both worlds.”

He sees patients at the New England Baptist Hospital site in Dedham. “I’m excited to be providing health care right in the community so patients can avoid a trip downtown,” he said. “You can establish meaningful and lasting relationships with local physicians and patients in the community setting.”

In the research arena, Dowlatshahi’s accomplishments include being a principal investigator of several bioengineering projects involving the upper extremities as well as microsurgery at Worcester Polytechnic Institute. Some of the resulting medical devices have been patented for their novelty. Also, his team established the first small joint finite element analysis model described in literature. Dowlatshahi used this method, pioneered in aeronautical engineering to solve complex elasticity and structural problems, to study wear and tear in small joints of the hand.

Another major research interest of Dowlatshahi’s is anatomy. “Anatomy has been studied since ancient times, but there are parts of the body that haven’t been looked at yet,” he said. He has discovered structures in the human web spaces between the fingers and within the nasal ala (wing of the nose) that hadn’t previously been described.

In his clinical practice, Dowlatshahi addresses all upper extremity problems including arthritis, fractures and nerve issues. He views his patients as partners, and treats each patient with care and respect. “I try to provide personalized care: it’s customized to each individual patient,” said Dowlatshahi. “One patient may benefit from a specific procedure for a particular problem, while another patient with the same problem may require a

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Jacob M. Drew, MD, Joint Surgeon

Jacob Drew, MD, grew up near the ocean in Dennis, Massachusetts, and had a passion for sports. “I played baseball in high school and college, and for a while I wanted to spend the rest of my life playing or being involved with baseball,” Drew said. While he still opts for seaside habitats, Drew’s affinity for sports has evolved into a different dream: helping people—including athletes—to live their lives fully by practicing orthopaedic surgery.

Drew ultimately decided on a hip and knee replacement specialty because of its mechanical nature, but more importantly, he was drawn to the positive outcomes that patients typically experience. “Sometimes joint problems are complicated, other times they’re more straightforward. But we are generally able to offer predictable solutions that get patients back on their feet, give them back mobility, and restore independence.”

Drew joined the BIDMC orthopaedic team this summer following a three-year stint as assistant professor in the Department of Orthopedics at the Medical University of South Carolina in Charleston.

The opportunity to remain engaged in academic medicine was a key factor in Drew’s decision to join BIDMC, but not the only one. “There are a lot of academic institutions in Boston,” he noted, “but Beth Israel is on the cutting edge in orthopaedics—very forward thinking—and so I’m excited to join this practice.”

Drew’s research interests revolve around improving the outcome of joint replacement surgery. One area of focus is pain control prior to and after surgery. His work on pain control for total knee replacement patients seeks to identify the optimal balance between pain control and maintenance of functional capacity.

“We have the ability make the entire leg numb for many days after surgery, but then patients can’t get out of bed or walk around. The flip side is we have the ability to allow them full function, but sometimes that falls short of appropriate and adequate pain control,” said Drew. “We’re trying to find the happy medium through sophisticated, patient-centered studies.”

Another research area Drew has been exploring is the molecular and genetic basis for range of motion following knee replacement surgery. “We’re working to identify those outlier patients who tend towards one extreme or the other in terms of post-operative motion—either too much or too little—so that we might adapt the surgery and optimize the ultimate function of their total knee replacement.”

At BIDMC, Drew evaluates patients for any problems affecting the hip or knee. These include degenerative diseases such as osteoarthritis and rheumatoid arthritis as well as acute injuries and trauma. He also evaluates patients who have had a prior surgery or joint replacement that is not working out as well as expected—for example, joint replacements that are painful, dysfunctional or infected.

“My goal is to try to improve upon each problem in a way the patient is comfortable with. We’re going to try the least invasive strategy first and consider surgery only when there are no other reasonable options remaining,” he said.

Drew’s approach to care involves listening to, educating and sharing decision making with patients. “It’s important to understand the patient’s goals as well as their concerns.”

Many patients ask when the best time to get a total joint replacement is. “Once they understand the options, the timing is typically their call. The patient tells me when the time is right, not the other way around, and then we move forward together,” said Drew.

Among the range of non-surgical and surgical treatment options Drew offers, one area of special expertise is performing the anterior approach to total hip replacement. This technique uses a small incision, does not require cutting any muscles, and can lead to faster return to work and daily activities than other surgical approaches.

One of the most satisfying aspects of his job is seeing positive results, Drew explained. “After we’ve agreed upon a treatment plan and applied it, I see patients in the office and hear how pleased they are to be back to independent living, recreational activities and sometimes even athletics. That’s really the best part of it for me.”

Drew is responsive to whatever level of involvement a PCP wants along a patient’s path to joint health. “I like to be flexible, available and accommodating to the PCP’s needs.”

Drew, his wife and three children live in Duxbury. He likes to spend his spare time with them by enjoying activities near the water including fishing and boating.

Dr. Drew sees patients at BIDMC, BID-Needham and BIDHC-Chestnut Hill. For an appointment, call 617-667-3940 or email orthojoints@bidmc.harvard.edu.
Rodriguez learned that drug companies produce recombinant relaxin. However, it is not FDA approved for any use—yet. “One large pharmaceutical company tried to get it FDA approved for the treatment of cardiomyopathy and liver cirrhosis, which are very fibrotic conditions, but relaxin hasn’t been addressed as a potential therapeutic modality to treat stiff joints.”

Rodriguez turned to Ara Nazarian, PhD, principal investigator at BIDMC’s Center for Advanced Orthopaedic Studies, for help developing and testing out his idea. Together with other BIDMC researchers in the lab, they developed an animal model of shoulder joint stiffness or frozen shoulder that could be readily replicated in the laboratory and involves a site that would be easy to inject. (Frozen shoulder occurs when the shoulder gradually becomes painful and stiff spontaneously or after injury.)

Next, the research team studied the evolution of the injury without treatment and with frequent injections of relaxin. They also tried different dosing amounts and timing to determine the optimal combination. The results showed relaxin works to significantly speed recovery and quickly loosened up the joint, returning 98 percent of normal motion within days.

**Sustained release**

With the initial success of relaxin injections in animals, the BIDMC team began to think about how it might be delivered to people. Relaxin has a short half-life—only two and half hours—so the hormone must be delivered constantly to the joint. A continuous infusion isn’t practical for humans; they needed a sustained release delivery system. “Our goal is to harness relaxin into a polymer gel we can inject into a joint and deliver an appropriate dose for several weeks to loosen up the fibrotic condition of any joint,” said Rodriguez.

To accomplish this, Nazarian reached out to polymer scientist Mark Grinstaff, PhD, Professor of Biomedical Engineering, Chemistry, Materials Science and Engineering at Boston University. Grinstaff identified a hydrogel that could continually release relaxin when injected.

Now in the final stages of animal research, the BIDMC investigators are seeking to demonstrate the efficacy of the relaxin hydrogel. The work involves injecting the gel into the shoulder to show it releases over time and has the same effect as multiple injections of relaxin.

**From practice to theory to practice**

Recently the BIDMC relaxin investigators applied to the National Institutes of Health for a series of grants that will enable them to continue to pave the way for testing relaxin in humans. Such funding would support examination of relaxin’s systemic effects and pharmacokinetics, and fine tuning of the hydrogel. “We’ll look at dosing: how much and how fast the gel needs to be delivered to be effective,” said Nazarian. The safety of relaxin for humans has already been established because it’s a hormone produced by the body.

If approved for use in humans, relaxin has the potential to deliver substantial benefits.

The problem of frozen shoulder provides an example of these hoped-for benefits. This condition is commonly treated with long-term physical therapy that can be time consuming and costly. Even with therapy, range of motion may not return 100 percent. “If relaxin therapy meant your shoulder motion could come back in six or eight weeks, it would be a huge improvement over the current standard of care,” Rodriguez said.

Relaxin would be administered locally like steroid shots. “When the gel is placed into the joint capsule, it doesn’t reach the rest of the body,” said Rodriguez. “We designed the delivery method so your shoulder or your knee is never exposed to more than what a pregnant person would generate in a few weeks.”

The greatest potential of relaxin would be its ability to prevent joint stiffness after trauma and joint replacement surgery. “A surgeon closing the knee joint could drop in a pellet of relaxin, which releases over the postoperative period so the scar doesn’t form to stiffen the knee,” envisioned Rodriguez.

The BIDMC relaxin project represents a rare instance: a physician making a clinical observation, taking it to a laboratory and seeing a team of animal research, biomechanical and biochemical experts develop it into a therapy in short period of time.

“I observed a real need in my daily clinical practice. It has high translational potential and could be in the clinic in just a couple of years. That’s a remarkably short period of time relative to traditional pharmaceutical development, which can take decades,” said Rodriguez.
RAYNAUD’S SYMPTOM RELIEF continued from page 3

might receive from two to 12 injections total, which can be performed under a local anesthetic. Some patients feel soreness at the injection sites for a day or so afterward.

“It has only been in the last five or 10 years that the Botox method has been studied with any degree of good science,” Harper explained. “But what we’re understanding, especially in primary Raynaud’s patients, is that you get a tremendous benefit from Botox injection into the hands. It causes a sympathetic blockade—it blocks the fight or flight response in your hands—causing your vessels to dilate.”

The procedure can help patients live symptom-free for three to six months. “It can be very efficacious to undergo Botox injection in the early fall when temperatures start to fall off. It can spare you a winter of misery,” said Harper.

LOWER RISK TREATMENT OPTION

Patients with primary Raynaud’s tend to respond more readily to non-operative treatments while secondary Raynaud’s patients often require a surgical intervention.

But there is some cross over, according to Harper. “Some primary Raynaud’s patients are so severe that they require surgical reconstruction. And there are some patients with secondary Raynaud’s that respond very well to non-operative treatment.” Botox injections offer a low risk, lower cost treatment option for those with primary Raynaud’s.

Harper became interested in building on his knowledge of Raynaud’s last fall, when he saw several patients in a row with Raynaud’s phenomenon complaining of significant discomfort. “I read everything I could about Raynaud’s in the hand surgery literature and found it fascinating. There are a lot of questions for which we still don’t have answers. It spoke to me as problem that could benefit tremendously from good science.”

He also began an ongoing study at BIDMC with the goal of identifying which Raynaud’s patients will benefit most from Botox. His hypothesis: most people with primary Raynaud’s phenomenon respond favorably to a Botox injection for three to six months with minimal side effects, and patients with secondary Raynaud’s or primary Raynaud’s phenomenon who have failed medical management are best treated with a surgical procedure to rebuild the arteries.

Harper’s team collects patient demographic information, and symptoms and outcomes at six weeks, three months and a year following treatment.

MICROSURGERY

Patients with primary or secondary Raynaud’s who continue to have problems and develop digital ischemia can experience severe pain and significant infections in their fingers. If non-surgical options haven’t worked, surgery offers the next line of treatment to restore blood flow in the hand.

The goal of surgery is the same as that of Botox injection: relieving the constricting forces on the vein nerves and vessels in the hand. “Botox targets the nerves, telling them to tell the arteries to relax. If that doesn’t work, we go directly to the source, the arteries, and remove the microscopic nerves that are mediating the excessive constriction,” Harper said.

Surgery (sympathectomy) requires operating with 40x magnification and intricate dissection of the sympathetic nerves. After removing the microscopic nerves around the blood vessels, the surgeon takes a vein from the arm or foot and rebuilds the arteries in the hand.

Harper works closely with rheumatologists at BIDMC to help treat patients with Raynaud’s. When primary care physicians refer patients for the disorder, BIDMC can provide a full range of diagnostic and treatment services.

Dr. Harper sees patients at BIDMC and BID-Needham. To make an appointment, call 617-667-3940 or email orthohand@bidmc.harvard.edu.

SAMMY DOWLATSHAHI, MD continued from page 4

different approach because of their profession, hobbies, medical history or sheer preference.”

His greatest gratification comes from helping patients and improving their quality of life. “When you are referred a patient, or a patient chooses you, it’s the highest honor and privilege. You give all you’ve got. You draw so much energy from it.”

Dowlatshahi has an open style with PCPs and referring clinicians and is always available to them. “You have to realize that the referring doc often knows the patient and his or her overall clinical and social situation better than you do. Only with a direct line of communication and respect for one another can you ensure the best outcome for your mutual patient. Our patients deserve this high standard of care.”

Dowlatshahi lives locally and is active in community service. When not working, he enjoys drawing and painting, philosophy and practicing traditional Japanese martial arts.

Dr. Dowlatshahi sees patients at BIDMC and the New England Baptist Hospital in Dedham. For an appointment, call 617-667-3940 or email orthohand@bidmc.harvard.edu.
Appointments and Grants

Arun Ramappa, MD, Chief of Sports Medicine and Shoulder Surgery, been named the Chief of Orthopedics for the Harvard University Health System. In this additional role, he will lead the development of orthopedic and musculoskeletal services for the healthcare system, which offers primary and specialty care to students, faculty and staff in the Harvard community.

Tamara Rozental, MD, Chief of Hand Surgery, recently received a grant from the Ruth Jackson Orthopedic Society to complete a prospective study to evaluate bone turnover markers and reference point indentation in premenopausal women with distal radius fractures.

Publications

Ara Nazarian, PhD, Center for Advanced Orthopedic Studies and Edward Rodriguez, MD, Orthopaedic Trauma, were co-authors of “Adhesive capsulitis of the shoulder: review of pathophysioloogy and current clinical treatments,” which appeared in the April 2017 edition of Shoulder & Elbow.

Rodriguez was also an author along with Paul Appleton, MD, Orthopaedic Trauma, and others of “Revisiting tension band fixation for difficult patellar fractures” in Journal of Orthopaedic Trauma, published in February 2017.

Christopher Miller, MD, was lead author and John Kwon, MD, co-author on “High variability of observed weight bearing during standing foot and ankle radiographs” in the June 2017 Foot & Ankle International. Both are foot and ankle surgeons.

Kwon and Nazarian were co-authors on “Proximity of the lateral calcaneal artery with a modified extensile lateral approach compared to standard extensile approach,” which appeared in the Foot & Ankle International March 2017 edition.

Rodriguez and Kempland Wallay, then a clinical research fellow at BIDMC, authored “Comparison of outcomes of operative vs. non-operative treatment of acetabular fractures in the elderly and severely comorbid patient.” The article appeared in the July 2017 European Journal of Orthopaedic Surgery & Traumatology.


Megan Anderson, MD, Chief of Orthopaedic Oncology, Santiago Lozano-Calderon, MD, PhD, Orthopaedic Oncology, and Mathew Iorio, MD, Hand Surgery, were co-authors on “Reconstruction of quadriceps function with composite free tissue transfers following sarcoma resection” in the June 2017 Journal of Surgical Oncology.

Spine Center surgeon Andrew White, MD, was one of the co-authors on “Invasiveness index as a predictor of surgical site infection after spinal fusion, revision fusion, or laminectomy” in Infection Control & Hospital Epidemiology published in January 2017.

Book Chapters

Megan Anderson, MD, Chief of Orthopaedic Oncology, and Brian Snyder, MD, PhD, Center for Advanced Orthopaedic Studies were authors on the chapter titled “Evaluation and management of pathologic femur fractures in children” in Pediatric Femur Fractures published by Springer in 2016.


Presentations