

Targeting systemic inflammation in patients with obesity-related pain



How best to prevent acute pain from becoming chronic

One practice's success with platelet-rich plasma therapy

Would you recognize this pain syndrome?

September 2013

CONTENTS



S22



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FEATURE ARTICLES

S3 | How best to prevent acute pain from becoming chronic?

Michael R. Clark, MD, MPH, MBA

S10 | One practice's success with platelet-rich plasma therapy

Wendi Lundquist, DO, FAAPMR, DABPM
Ray Stanford, BS, MS-II

S16 | Neurogenic thoracic outlet syndrome: An often overlooked but treatable condition

Scott Pritzlaff, MD
Adam J. Carinci, MD
Paul J. Christo, MD, MBA

S22 | Obesity-related pain: Time for a new approach that targets systemic inflammation

Robert A. Bonakdar, MD

Cover illustration: Dave Cutler

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How best to prevent acute pain from becoming chronic?

The best approach is to find the individual risk factors and known predictors and manage them early on.

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Researchers struggle to understand the etiology, pathogenesis, and pathophysiology of chronic pain and continue to look for rational therapies that can alleviate this common problem. Perhaps the most important issue in chronic pain management is how to avoid having to treat it in the first place through prevention.

Where does chronic pain come from? The obvious answer is not very scientific: from acute pain. Yet acute pain is often defined as a separate entity from chronic pain, and treatment focuses on alleviating it to prevent suffering in the moment, with little discussion about how acute pain may affect the patient's future course.

Preventing chronic pain requires a more patient-centered approach. Clinicians need to formulate a plan for each patient taking into account individual risk factors and known pre-

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TABLE 1
Risk factors for developing chronic pain

Type of risk factor	Demographic variables	Acute pain characteristics	Psychological factors	Contextual details
Specific risk factors	Age	High pain intensity	Negative emotion	Injured at work
	Gender	Long pain duration	Depression	Work safety
	Education	Radiation of pain	Anxiety	Work satisfaction
	Employment	Prior episodes of pain	Anger	Compensation
	Health status	Multiple sites of pain Multiple somatic symptoms	Fear	Litigation
			Stress	Social support
			Distress	External attributions of responsibility
			Catastrophizing	
			Hypervigilance	
			Self-efficacy	
Neuroticism				
Pain sensitivity				
Somatization				
Critical risk factors	Poor health status	Severe pain intensity	Depression	Litigation

dictors for the development of chronic pain. These risk factors and predictors will help create a picture of a patient who may be on the path to chronic pain. Physicians can reduce the likelihood of the patient developing chronic pain if a rational recipe of therapies are prescribed and implemented in a coherent and coordinated fashion.

What is chronic pain and who develops it?

The existing definitions are unsatisfying. They usually include criteria that detail severity (>6-7 on a 10-point scale), duration (>3-6 months), and impairment (decreased function or quality of life). These definitions are arbitrary attempts to create a pathologic category distinct from normal functioning.¹

If the focus begins with acute pain, tissue injury has usually occurred. There is a cascade of physiologic events that begins with local inflammation, sensitization of peripheral nociceptors, alterations in transduction, increased conduction, and sensitization of dorsal horn nociceptors.² The overall system, which warns

and protects from noxious stimuli, is modulated by descending efferent pathways and mediated by a host of components and processes such as the *N*-methyl-D-aspartate (NMDA) receptor, neurotransmitters, neuromodulators, wind-up, decreased inhibition, and increased synaptic efficacy. This acute sensitization increases awareness of pain, limits damage, promotes healing, and is reversible.

In contrast, the pathophysiology of chronic pain suggests that in the presence of severe nociceptive activation, persistent inflammation, and neuronal damage, central sensitization emerges and causes nerve cell remodeling.³ In this situation, reversible modulation begins to deteriorate into irreversible modification.

The literature is extensive with studies describing risk factors for developing chronic pain.^{2,4-6} These factors are summarized in **TABLE 1**.

How should physicians estimate the risk of chronic pain?

In the vast majority of cases, the cause of acute pain will be obvious. The problem occurs,

however, when the acute pain cannot be alleviated and its cause remains elusive. When attempting to determine your patient's risk for developing chronic pain, 4 perspectives will help to group possible causes and separate them into classes with distinct mechanisms (see TABLE 2).⁷⁻⁹

- **The disease perspective.** Refractory acute pain may be caused by an *undiagnosed disease*.
- **The behavioral perspective.** The patient may be engaged in *unproductive behaviors* that contribute to the acute pain or interfere with its treatment.
- **The dimensional perspective.** *Intrinsic traits* may inhibit his or her response to therapies or evoke more severe pain.
- **The life story perspective.** *Life stressors* (eg, unemployment, marital strain) may be present that distract and demoralize the patient, such that the focus on treating acute pain is lost in a sea of other problems.

When a patient with persistent acute pain does not respond to treatment in a timely fashion, the physician should expand the evaluation to include these 4 domains.^{10,11}

For instance, when examining a patient's life story, expand the history to learn more details about the patient. Try to understand what suffering from pain means to the patient. As the relationship between you and the patient grows, help him or her find an answer to the question, "What good does life hold for me?"

In contrast, when exploring the behavioral perspective, focus on what the patient is doing.

Often, an individual is engaging in unproductive behaviors that make the acute pain worse. Point out these problematic behaviors when they occur. Then shift the patient's emphasis to thinking about his choices and what goals he is trying to accomplish. As more productive behaviors emerge, reinforce them with positive feedback. Gradually, the patient will become more capable and the distress and disability will be extinguished.

The other 2 perspectives emphasize aspects of the patient rather than the things he or she is doing and encountering. The dimensional perspective, for instance, concerns individual traits. If the patient's constitution is not capable of handling acute pain, his ability to cope will be overwhelmed. To determine if this is the case, you need to gain an understanding of who the patient is and quantify specific traits, including intelligence, introversion, and openness. Formal neuropsychiatric testing is not required, but informal descriptions provided by the patient and family members will illuminate relative strengths and weaknesses.

To help the patient, guide him toward his strengths and provide the education needed to meet the demands of the situation. For example, a patient who is shy and detail oriented will need help asking for more information about his pain and its treatment before feeling less anxious about a mysterious process that is causing his suffering. Lay out careful and specific treatment plans instead of simply offering reassurance that the situation will improve.

Finally, regarding the disease perspective:

TABLE 2
Perspectives of acute pain evaluation⁷⁻⁹

	Perspective			
	Disease	Dimensional	Behavioral	Life story
Distinction	What the patient has	Who the patient is	What the patient does	What the patient encounters
Logic	Categorical	Quantitative	Goal and purpose	Narrative
Concept	Cause and effect	Composition and context	Choice and outcome	Event and meaning
Treatable risk factors for chronic pain	Major depressive disorder	Somatosensory amplification	Fear and avoidance	Posttraumatic stress disorder
	Neuropathic pain	Multiple somatic symptoms	Substance abuse	Catastrophizing
Treatments	Antidepressants	Relaxation training	Physical therapy	Interpersonal psychotherapy
	Anticonvulsants	Cognitive-behavioral psychotherapy	Substance abuse counseling	Patient support groups

Using the 4 perspectives provides a patient-centered approach that will allow clinicians to make rational treatment decisions.

While the disease process causing acute pain is likely known and the “broken part” is being addressed, the patient may have another disease that’s interfering with pain treatment. You should always be thinking about comorbidities and their specific etiologies. Fixing these problems will minimize the total pathologic burden and improve the likelihood of being able to control acute pain.

Using these 4 perspectives to organize risk factors for the development of chronic pain provides a logical patient-centered approach that will allow clinicians to make rational treatment decisions.^{12,13} For example, new-onset chronic pain is more likely to occur in the presence of diseases such as pain sensitization and major depressive disorder. Individual variations in one’s propensity to experience distressing somatic symptoms or one’s ability to modulate nociceptive processes are dimensional traits linked to developing chronic pain.

Similarly, if a patient in acute pain abuses medications or avoids healthy behavior out of fear that it will cause more damage and increase pain, he or she may create a vicious cycle of continued pain and deteriorating function. And finally, the meaning a patient in pain attaches to this experience and how he or she links it to other life encounters may produce catastrophic interpretations and posttraumatic stress reactions, which in turn will undermine recovery.

Using the 4 perspectives to guide treatment

A closer look at the 4 perspectives will shed light on how each can inform treatment decisions.

The disease perspective rests on a logic in which an etiology induces pathology, which in turn produces signs and symptoms that characterize a clinical syndrome. One example of a disease increasing the risk of acute pain becoming refractory to treatment and becoming chronic pain is the sensitization that occurs in the nociceptive system.¹⁴ Multiple mechanisms, such as peripheral sensitization, ectopic hyperactivity, and altered response mechanics of nociceptive neurons, intensify acute pain and its resistance to traditional analgesics. However, these pathophysiologic mechanisms define pharmacologic targets, such as sodium channel blockers and serotonin-norepinephrine reuptake inhibitors (SNRIs), to desensitize nociceptive processing.

Another disease to consider in this context is major depressive disorder.¹⁵ While patients

in pain become demoralized and depleted over time spent suffering, major depression is a bodily disorder of neurotransmitter function. Longitudinal studies demonstrate how the presence of a major depressive disorder increases the risk of new-onset chronic pain.¹⁶

The behavioral perspective incorporates a logic in which drive leads to choice and learning results from the outcome. The fear and avoidance model of pain shows how injury and pain can be confronted and result in recovery and return to function.^{17,18} The problem occurs when pain is met with fear and avoidance behaviors that result in disuse, disability, and more pain. This vicious cycle prevents the patient from responding to pain treatment, which increases the probability of a chronic pain syndrome taking hold.

Addiction is another example of a behavioral disorder that increases the risk for chronic pain. If medication abuse precedes or occurs in conjunction with acute pain, achieving intoxication replaces the goal of pain relief.¹⁹ Pain now drives the patient to consume the addictive substance in excess. Disorder ensues and the behavior spirals out of control. The prevention of chronic pain is more likely if these forms of behavior are stopped and the goals of a patient’s choices are aligned with the practitioner’s desire for alleviating pain and restoring health.

The dimensional perspective contributes to persistent acute pain by presenting a situation to the patient that provokes a vulnerability rather than providing an opportunity to meet the demand. In other words, the patient is not equipped to deal with acute pain because of who he is and the capabilities at his disposal. For example, every individual has an endogenous analgesic system. This system has the capability of modulating pain so that, when confronted with acute pain, the system can potentially decrease nociceptive processing in such a way that the person experiences less pain with the same stimulus.^{20,21} Individuals with a less efficient system are not able to suppress nociception when exposed to painful stimuli and are at increased risk for the development of chronic pain.²²

Similarly, all individuals have the ability to detect somatic sensations. Some are more aware of these sensations than others. People with greater somatization or somatosensory amplification are more likely to seek health care and experience distress about their symptoms.²³⁻²⁶

The life story perspective acknowledges

that patients are living a narrative, one that includes a setting, a sequence of encounters, and an outcome. Some life events are interpreted as traumatic by the individual and can progress to reexperiencing that event, avoiding reminders, and being hyperaroused by potential threats. Studies that look at the outcome of motor vehicle accidents and whiplash have found great variation across countries and a decrease in claims if victims receive fewer financial benefits for the condition. More sophisticated research finds no dose effect between the intensity of trauma and the probability of developing chronic whiplash pain. The meaningful elements, not the physical ones, of the context of the accident are the major predictors.

Catastrophizing is a more multifaceted condition that refers to an exaggerated response to a painful experience.²⁷ Magnification, rumination, and helplessness cause the patient to worry about or expect major negative consequences from his acute pain. Catastrophizing is predictive of the development of chronic pain, disability, and poor quality of life. But this problem can be modified with a variety of psychological therapies ranging from illness education to cognitive-behavioral therapy.^{28,29}

A case report illustrates the value of preventive therapy

Mr. H, age 44, presented to his family physician with acute low back pain after playing softball with his friends. He has had intermittent mild low back pain for the past 15 years but never sought treatment before. His medical history includes hypertension, hyperlipidemia, and being overweight. He takes a statin and low-dose beta-blocker, has had no surgeries, and does not use illicit drugs or abuse alcohol. He works as an accountant and is under tremendous pressure at work to be more productive and less obsessed about making mistakes. He is married and worries about the health of his 2 children, although neither has had any serious medical problems.

Mr. H's physical examination was normal except for some bilateral tenderness in the paraspinal and oblique muscles. His pain increased with movement, but his straight leg raising test was negative. His gait was mildly antalgic, and he sat in a chair with discomfort but exhibited full range of motion. He was initially treated with anti-inflammatory medications and muscle relaxants and was given instructions to

gradually increase his physical activity and avoid strenuous exercise, but not to spend daytime hours in bed.

On follow-up over the next 6 months, the patient had not returned to his baseline level of function, and he said the medications provided only partial relief. He continued to complain of low back pain, rated as a 5 on a 10-point scale. He was becoming increasingly worried about his symptoms and was concerned that he might need more detailed examinations; he feared he might need surgery. He said his performance at work deteriorated and he was not socializing with his family at night or on the weekends.

Mr. H had been referred for supervised physical therapy, but that seemed to have done little good. After 6 months of persistent pain and accompanying symptoms, the physician made the diagnosis of a major depressive disorder in the context of anxious, obsessional, and introverted traits. The patient was overwhelmed by his pain and demands at work with resultant loss of functioning, including avoidance behaviors leading to further physical deactivation and weakness.

A new treatment approach. The patient was started on an SNRI and encouraged to remain in physical therapy and to increase the frequency of sessions to 3 times per week. In addition, he was referred to a behavioral psychologist for training in relaxation therapy and coping skills training for stress management.

Within a month, Mr. H reported an improved mood, decreased anxiety, and a sense that he was making progress. He was more engaged with physical therapy and was practicing self-directed relaxation techniques. His pain was improved and he had decreased his use of analgesics and muscle relaxants. The patient was back at work full-time and had negotiated a decreased workload for several weeks so he could catch up on his backlog of accounts.

Mr. H's case illustrates the value of early intervention to prevent chronic pain in patients with acute pain. As mentioned earlier, such interventions rely on evaluation for any potentially dangerous outcomes related to acute pain, screening for risk factors for chronic pain, providing guidance and advice for returning to previous levels of function, using medication conservatively, and having frequent follow-up visits to assess progress. However, if the patient is at higher risk for the development of chronic pain, a more comprehensive and evidence-based approach should be instituted. Consultants who can play an integral role on the pain

Catastrophizing is predictive of the development of chronic pain, disability, and poor quality of life.

The best way to treat chronic pain is to prevent it.

management team include a physical therapist, psychologist, psychiatrist, substance abuse counselor, and physiatrist.

This case highlights several risk factors for developing chronic pain if acute pain is not addressed early and aggressively. It shows how several potential etiologies of chronic pain can be assessed and managed before chronic pain becomes an independent problem. This patient had persistent acute pain that was poorly controlled with traditional analgesics, and his situation was notable for temperamental vulnerabilities, fear and avoidance behaviors, and significant life stressors.

Ultimately, coexisting major depressive disorder had amplified the patient's symptoms and further overwhelmed his ability to manage his acute pain. Targeted treatment for reducing his pain—but also increasing his function and alleviating his depression—allowed him to feel capable of being successful and returning to healthy activities. This potentially overwhelming case for the physician was successfully organized around the 4 perspectives of disease, behavioral, dimensional, and life story described earlier.

Applying basic principles

In summary, the best way to treat chronic pain is to prevent it. The perspectives outlined in this article provide a framework for targeting modifiable risk factors that can decrease the likelihood of acute pain becoming chronic.

The basic principles are sound: Repair and cure a disease; guide and strengthen an inherent vulnerability; extinguish unproductive behaviors and expose the patient to productive habits; and rescript the patient's interpretations of failure to remoralize and instill a sense of mastery of life's burdens.

Rational treatment includes:

- pharmacologic agents for common diseases that predispose to chronic pain
- the use of body awareness techniques and biofeedback to reduce somatosensory amplification
- confrontation of abnormal illness behaviors with group-based psychotherapies and active physical therapies
- patient support groups and interpersonal psychotherapies to show the patient how others have overcome stressful life events, as well as to keep him or her engaged with life in general.

The risk factors for chronic pain in the

patient with acute pain are recognizable. Identifying them will help you prevent this unwelcome transition and address the barriers to restoring health and function.

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One practice's success with platelet-rich plasma therapy

The 3 cases presented here represent the kind of success that one pain center is having with platelet-rich plasma therapy for the treatment of musculoskeletal pain.

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In primary care and orthopedic clinic settings in the United States, common musculoskeletal injuries account for nearly 100 million office visits annually.¹ Many orthopedic, primary care, and sports medicine physicians view platelet-rich plasma (PRP) therapy as an emerging treatment option for tendon, muscle, and bone injuries. PRP therapy appears to accelerate the healing process, reducing patients' pain and improving function. And our experience at Active Life Physical Medicine & Pain Center bears that out. We have administered PRP therapy to more than 400 patients for various tendinopathies, ligament strains, meniscal tears, degenerative joint disease, and other nonhealing painful areas with favorable results.

Disclosure

Dr. Lundquist reported that in October 2012, she was paid to speak on behalf of RS Medical, a distributor of a platelet concentrate system. Mr. Stanford reported no potential conflict of interest relevant to this article.

Photo: Paul Rapson / Science Source

In this article, we share what is known about this emerging therapy, and we describe 3 cases in which patients were successfully treated with PRP therapy.

How PRP therapy boosts the healing process

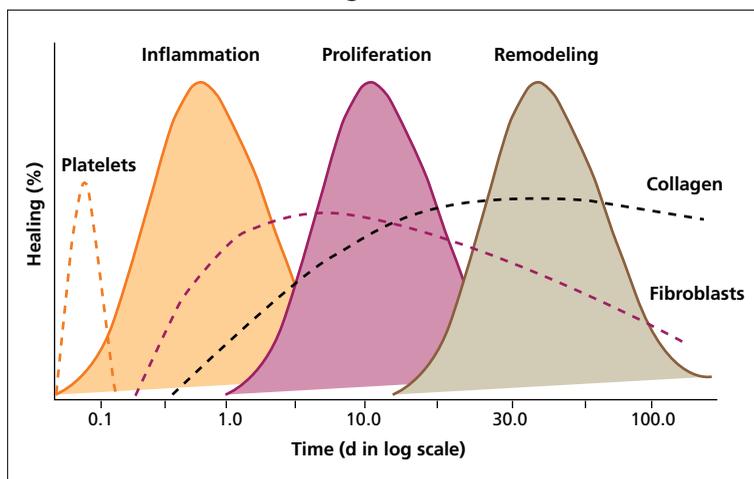
Platelets, the tiny cell fragments almost exclusively associated with blood clots, conjointly perform a fundamental role in tissue repair. Their foremost function, clotting, is the first step in the healing process. Once activated, platelets release a host of factors that include additional adjuncts in clot formation and several growth factors.¹ These growth factors significantly increase the proliferation of tenocytes, fibroblasts, chondrocytes, osteoblasts, and mesenchymal stem cells.²⁻⁴ The tissue-healing process takes place over 3 intricate and overlapping phases: inflammation, proliferation, and remodeling (FIGURE).⁵

Injecting platelets into the area of pathology is thought to kick-start and accelerate the healing cascade, enabling the body's healing mechanism to regenerate a new matrix of tissue. In a study to assess the effects of different PRP separation methods on human muscle, bone, and tendon cells, researchers compared PRP preparations produced by 3 different methods (2 single-spin and one double-spin process) from blood collected from 8 subjects.⁶ Human cells (osteocytes, myocytes, and tenocytes) from discarded tissue samples were treated with the 3 PRP preparations. All 3 PRP preparations produced increases in platelet concentration compared with native blood, but wide variation occurred within the same individual's blood draws, depending on the target cells studied.⁶

Clinical applications. In a randomized controlled clinical trial of 28 patients with chronic lateral epicondylitis, patients received either autologous whole blood or a PRP preparation under ultrasound guidance. PRP therapy was superior to autologous whole blood in the short term (6 weeks), based on an evaluation using a pain visual analog scale (VAS) score.⁷

PRP injections have also produced superior therapeutic results compared with injections of hyaluronic acid and corticosteroids.^{8,9} In a prospective cohort study with a control group, Spakova and colleagues treated 120 patients with grade 1, 2, or 3 knee osteoarthritis with either 3 intra-articular injections of a PRP preparation or 3 injections of hyaluronic acid.⁸ At the

■ FIGURE: The wound-healing cascade



This graph depicts the 3 overlapping phases of wound healing: inflammation (platelets create a clot, and platelet activation results in release of growth, hemostatic, and other factors); proliferation (characterized by angiogenesis, collagen deposition, granulation tissue formation, epithelialization, and wound contraction); and remodeling (collagen maturation and apoptosis of excess cells).

Understanding the fundamentals of healing is essential to understanding the rationale behind platelet-rich plasma (PRP) therapy: It takes an average of 100 days for complete healing to occur. Collagen activity and fibroblast healing activity peak between Days 5 and 30, on average. At the platelets' peak in the initial hours after injury, signals are occurring to recruit the necessary healing factors. Injecting PRP into the injured area is thought to kick-start this healing cascade and accelerate tissue repair.

Source: Reprinted, with permission from the *American Journal of Roentgenology*, from Lee KS, Wilson JJ, Rabago DP, et al. Musculoskeletal applications of platelet-rich plasma: fad or future? *AJR Am J Roentgenol*. 2011;196:628-636.⁵

3- and 6-month follow-up, the PRP-treated group had significantly better results as measured by the Western Ontario and McMaster Universities Osteoarthritis Index and Numeric Rating Scale score.⁸

Similarly, Peerbooms et al compared injection treatment with a corticosteroid to a PRP preparation in a randomized controlled trial of 100 patients with lateral epicondylitis.⁹ The researchers defined treatment success as more than a 25% reduction a VAS pain score or DASH (Disabilities of the Arm, Shoulder and Hand) Outcome Measure score at one year. Study results showed that PRP injections were superior to cortisone injections, with 73% of the PRP group treated successfully compared with 49% of the corticosteroid group. While the corticosteroid-treated group showed improvement initially and then declined, the PRP-treated group improved progressively.⁹

A controversial therapy

PRP therapy is considered controversial because high-level clinical evidence is lacking for many indications. A 2009 systematic review of the orthopedic surgery and sports medicine

The most widely used application for PRP therapy is in treating lateral epicondylitis.

literature, for instance, noted that few controlled clinical trials had adequately evaluated the safety and efficacy of PRP treatments; the authors concluded that PRP is a promising but not proven therapeutic option for patients with joint, tendon, ligament, and muscle injuries.¹⁰

That said, smaller studies have found support for its use. Specifically, PRP therapy has been found efficacious in knee joint osteoarthritis, patellar tendon healing, and plantar fasciitis.^{8,9,11-13} The treatment is also helpful as an adjunct in arthroscopic rotator cuff repair with mesenchymal stem cells and dermal allografts.¹⁴

The most widely used application for PRP, however, is in treating lateral epicondylitis. One study of 140 patients with elbow epicondylar pain showed a 60% improvement of pain 8 weeks after PRP injection, compared with a 16% improvement in control patients; the PRP-treated patients reported an 81% improvement at 6-month follow-up.¹¹

The FDA weighs in. Although there is some debate as to whether the actual product (the patient's own blood) for PRP injection requires approval by the Food and Drug Administration (FDA), centrifuge devices involved in processing the blood must be FDA approved. Several of the PRP preparation systems available have been FDA 510(k) approved for point-of-care preparation since 1999, with the caveat that the device's labeling must indicate that "The safety and effectiveness of this device for in vivo indications for use has not been established."¹⁵

When to consider PRP therapy

Given that many patients with musculoskeletal injuries respond well to conservative treatments, such as physical therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or corticosteroid injections, the Active Life Physical Medicine & Pain Center where I [WL] work generally offers the option of PRP injection to those who have an isolated injury and for whom the risk of cortisone therapy or no treatment outweighs the risk of PRP therapy. Treatment-related complications of PRP therapy include soreness at the injection site, short-term stiffness, and increase in usual pain, which varies in length from one day to one month. Practice physicians also encourage patients to speak with their insurance carriers to determine coverage; most do not cover the procedure because it is considered investigational. The approximate cost for one PRP treatment is \$600 to \$800 per

body region, including the materials and labor for preparing the platelets.

When not to use PRP therapy. The International Cellular Medicine Society (ICMS) has published guidelines on the use of PRP therapy and lists the following as absolute contraindications to its use: platelet dysfunction syndrome, critical thrombocytopenia, hemodynamic instability, septicemia, local infection at the procedure site, and patient unwillingness to accept risks.¹⁶

In addition, relative contraindications include use of NSAIDs within 48 hours of the procedure, corticosteroid injection at the treatment site within one month, systemic use of corticosteroids within 2 weeks, tobacco use, recent fever or illness, cancer (especially hematopoietic or bone), hemoglobin <10 g/dL, or a platelet count <105/ μ L.¹⁶

How the PRP solution is prepared and administered

Although different concentrations of PRP are commonly used, a preparation with 5 times the platelet concentration of whole blood has become standard.¹⁷ Various PRP separation methods (ie, single-step or 2-step procedures) are also used; single-step procedures can produce sufficient concentrations.¹⁸

The basic steps for preparing the solution involve drawing approximately 20 to 60 cc of venous blood from the patient's antecubital vein and placing it in an FDA-approved centrifuge device that separates the PRP from platelet-poor plasma and red blood cells. The process takes about 15 minutes and typically generates about 3 to 6 cc of PRP, which is withdrawn by syringe from a port on the device. The physician then positions the patient, instills local anesthesia with lidocaine, uses image guidance (ultrasonography or fluoroscopy) to direct the needle into the site of pathology, and injects the PRP preparation.

At the 4-week postprocedure appointment, physical therapy follow-up should be initiated if neuromuscular re-education is needed. Most patients, however, do not require this. That said, I [WL] do initiate physical therapy for the professional athletes I treat with PRP therapy because of the expected physiologic stress that their training will put on their bodies.

One injection or more? In my [WL] experience, one injection is often sufficient, as seen in the 3 cases described on pages S13 and S14. At this time, however, neither the optimal

CASE #1**Active older woman with elbow pain**

A 74-year-old active, right-handed woman who, for many years, had progressive lateral epicondyle pain with activities involving wrist extension presented to the clinic to explore other conservative therapeutic options. She had previously tried physical therapy, bracing, cortisone injections, activity modification, NSAIDs, and various other pain medications without sustained relief. Her goal was to have her pain reduced and to be able to return to playing bocce.

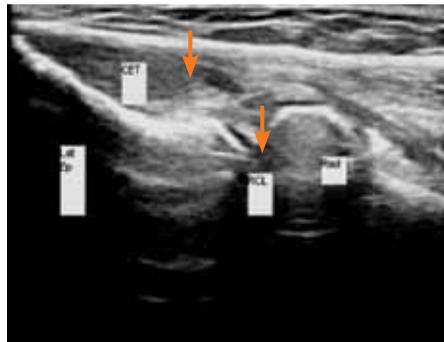
Magnetic resonance imaging (MRI) and ultrasound studies showed evidence of a common extensor tendon tear and radial collateral ligament tear.

PRP injection, under ultrasound guidance, was done once. Local anesthesia was used, and approximately 2 to 3 cc of PRP concentrate was injected.

At follow-up 2 months later, the patient's symptoms of tenderness, swelling, and pain with wrist extension/gripping had resolved. Repeat ultrasound examination revealed tendon healing. The patient was able to return to playing bocce.



Extensor tendon tear: Ultrasound scan at patient's first visit shows evidence of a common extensor tendon tear (arrow, left) and radial collateral ligament tear (arrow, right).



Tendon repair at 2 months post-PRP treatment: Ultrasound scan after one injection of PRP shows healed tendon (arrow, left) and radial collateral ligament (arrow, right).

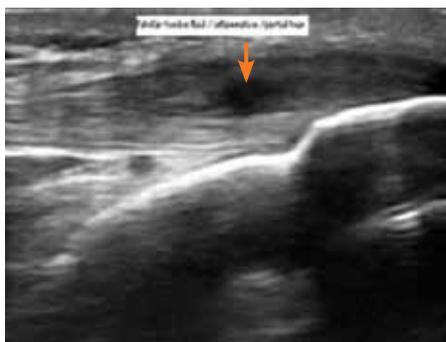
CASE #2**Athletic man with debilitating knee pain**

A 38-year-old man came to the clinic with patellar tendonitis. He had pain that was impacting his workout routines with squats. Physical therapy, modification of workout routine, and NSAIDs were all unsuccessful.

Ultrasound scan revealed evidence of a partial tear (50%) and fluid accumulation.

The patient underwent one injection with PRP concentrate utilizing a technique similar to that described for Case #1.

At the patient's 3-month follow-up visit, he reported experiencing only slight pain upon performing deep knee bends. Ultrasound was done at that time and revealed nearly complete healing of the tear and resolution of fluid.



Patellar tendon partial tear: Ultrasound scan shows partial tear (50%) of the patellar tendon and fluid accumulation (arrow).



Healing at 3 months post-PRP injection: Ultrasound image after one injection of PRP concentrate shows almost complete healing, with a patellar tendon thickness increase of 5 mm (arrow).

Ultrasound scans courtesy of Wendi Lundquist, DO, and Dale Glassley, MS, BA, INHE, ASMU.

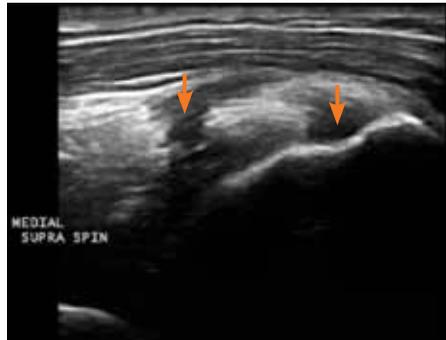
CASE #3

Older woman with painful shoulder

A 70-year-old right-handed woman came to our practice with a 15-month history of shoulder pain with abduction and evidence of a near full thickness tear of the supraspinatus muscle. She had been treated previously with an 8-week course of physical therapy, NSAIDs, ice, and cortisone injections without obtaining relief or functional improvement.

The patient was treated with one injection of PRP concentrate under ultrasound guidance.

At the 2-month follow-up exam, the patient reported that her pain with abduction had resolved. Ultrasound showed that the tear had healed.



Supraspinatus muscle tear: Ultrasound scan of the shoulder shows a near full thickness tear of the supraspinatus muscle in 2 places (arrows).



Healed muscle 2 months after PRP therapy: Ultrasound scan after PRP therapy shows healed supraspinatus muscle (arrows).

We have found that younger, nonsmoking patients who have a very specific problem respond best, while older patients who smoke and have more diffuse pain tend to have less benefit.

number of PRP injections needed nor the optimal time between injections has been determined. Although no definitive protocol has been established, the consensus at conferences and among practitioners that I have spoken with is that 2 to 4 weeks between injections is standard. This interval is derived from the understanding of the healing cascade⁵ (FIGURE).

Who benefits most?

As noted earlier, at the Active Life Physical Medicine & Pain Center we have administered PRP therapy to more than 400 patients for various tendinopathies, ligament strains, meniscal tears, degenerative joint disease, and various other nonhealing painful areas. Clinically, we have found that younger, nonsmoking patients who have a very specific problem respond best, while older patients who smoke and experience more chronic, diffuse pain tend to have less benefit. Also, non-weight-bearing areas are more responsive in our clinical experience. We have seen only 3 cases that came to follow-up without some degree of positive response, either functionally or in pain improvement.

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Neurogenic thoracic outlet syndrome: An often overlooked but treatable condition

Rely primarily on a patient's history and your physical examination findings in considering the diagnosis. Physical therapy, tricyclic antidepressants or SNRIs, and botulinum toxin type A injections can help control symptoms.

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Ms. R, a 25-year-old woman who sustained a whiplash injury in a car accident within the year, schedules an office visit for evaluation of pain she has been experiencing for 7 months in the right side of her neck and the trapezius. The pain radiates down the medial aspect of her right arm to the 4th and 5th digits, and it worsens when she brushes her hair or lifts bags of groceries. She feels her quality of life is significantly impaired because her limited arm movement makes it hard to hold her 1-year-old child. She also experiences headaches more frequently than she did before the accident.

Disclosure

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Photo: Thinkstock

A complex pain syndrome

This patient's clinical presentation of pain radiating from the neck to the arm and hand following trauma to the neck is typical of nerve irritation associated with neurogenic thoracic outlet syndrome (NTOS).¹ The disorder is complex and characterized by different neurovascular signs and symptoms involving the upper limbs.² Trauma from an external kinetic force is not the only cause of NTOS. Stresses from repetitive movement can also be at fault. Assembly line workers, violinists, and data entry professionals are especially vulnerable given the nature of their work. Athletes using frequent overhead arm motion in their sport (eg, volleyball players, baseball pitchers, weightlifters, swimmers) are also at risk for this syndrome.

Estimates of thoracic outlet syndrome frequency vary widely, from 3 to 80 cases per 1000 individuals.³ NTOS mainly affects patients in the third and fourth decades of life and has a female to male ratio of 3.5-4:1.⁴ Although NTOS is not common, family physicians are likely to be the first to evaluate patients who have symptoms and a history suggestive of the disorder. A lack of distinctive clinical indicators can make diagnosis difficult. But disregarded, this often underappreciated syndrome can lead to functional impairment, emotional upheaval, and impaired quality of life. For individuals with severe symptoms, the adverse impact on quality of life has been compared with that of patients suffering from chronic heart failure.⁵

A brief tour of the anatomy involved

Thoracic outlet syndrome manifests as "upper extremity symptoms due to compression of the neurovascular bundle by various structures in the area just above the first rib and behind the clavicle."⁶ This neurovascular bundle consists of the trunks of the brachial plexus and the subclavian vessels. As these vital structures course from the neck into the upper arm, potential sites for compression include the interscalene triangle, costoclavicular triangle, and subcoracoid space deep to the pectoralis minor tendon. In 1956, Peet and colleagues first coined the term *thoracic outlet syndrome* (TOS) to encompass previously described disorders involving compression of these neurovascular structures.⁷ Compression of the brachial plexus, a hallmark of NTOS, can occur in all 3 of these anatomic spaces. But most cases involve compression within the interscalene triangle.³

Congenital abnormalities, including first ribs

and fibrous bands, may also be sources of neurovascular compression. Although present in less than 1% of the population, cervical ribs and associated fibrous bands usually lie within the middle scalene muscle, thereby narrowing the space within the scalene triangle through which the nerve roots of the brachial plexus pass.¹

Factors that can precipitate NTOS

Virtually any injury that causes chronic cervical muscle spasm, such as hyperextension-flexion injuries, may precipitate NTOS.^{8,9} Whiplash injury, exercise-induced scalene muscle hypertrophy, hypertrophied anterior scalene muscles, and repetitive work-related injuries can bring on the syndrome. Risk factors for NTOS are not entirely understood, although many patients with NTOS exhibit a congenital predisposition, such as cervical ribs, in addition to a history of trauma or repetitive stress on the scalene muscles. Chronic stress of the cervical musculature, specifically the anterior scalene and middle scalene muscles (ASM and MSM, respectively), is strongly implicated in the development of NTOS and chronic pain. Cervical muscle spasm involving the ASM and MSM places traction on the brachial plexus/thoracic outlet.⁸ The mainstay of current minimally invasive treatment targets these muscles in an attempt to decrease spasm.¹⁰⁻¹⁴

Clinical presentation

Pain is a foremost feature of NTOS, although other symptoms can include sensory loss, shoulder and neck discomfort, arm paresthesia or edema, headache, and even sympathetic nervous system impairment.⁸

Arm exertion and elevation aggravate the symptoms, which typically occur after exercise rather than during exercise. Pain often radiates from the shoulder down along the inner aspect of the arm. Patients may also have pain in the neck, anterior chest wall, trapezius, or mastoid. Occipital headaches secondary to brachial plexus compression along C5-C7 are common.

An estimated 95% of TOS cases are neurogenic in origin,¹⁵ with arterial or venous anomalies accounting for the remainder. True NTOS, characterized by objective findings consistent with brachial plexus compromise, account for just 1% of NTOS cases. The other 99% of neurogenic cases lack objective findings, are more difficult to define, and are deemed nonspecific NTOS.¹⁶

Virtually any injury that causes chronic cervical muscle spasm may precipitate NTOS.

Some experts believe the elevated arm stress test most consistently elicits NTOS symptoms.

Diagnosis

Physical examination findings are most important

A thorough history and physical examination are the basis for NTOS diagnosis.¹⁷

Palpation may elicit tenderness over the scalene muscles, subcoracoid space, anterior chest wall, or trapezius. There is often decreased sensation to light touch in the fingers, especially over the 4th and 5th digits.² Light percussion over the brachial plexus in the neck may elicit tingling or a “pins and needles” sensation—the Tinel sign—in the affected nerve distribution. These findings, as well as worsening symptoms with other provocative maneuvers, can help distinguish NTOS from other pathologies, such as carpal tunnel syndrome or degenerative disorders of the cervical spine.

Additional provocative tests (eg, Adson maneuver, nerve tension tests) have unknown reliability and specificity for NTOS. However, these examinations can assist in assessing patients. Some experts believe the elevated arm stress test (EAST) most consistently elicits NTOS symptoms.¹⁷ To perform the EAST, abduct the patient’s affected arm 90 degrees in external rotation while having the patient open and close the hand slowly over 3 minutes. A patient with NTOS typically reports neck and shoulder pain with paresthesias, often occurring in the medial aspects of the arm, forearm, and last 2 fingers.

Of note, a considerable proportion of the population will compress their radial pulse on hyperabduction maneuvers, but they do not have vascular TOS. Patients who present with neurogenic symptoms and have diminished pulse upon hyperabduction of the arm are frequently mislabeled as having vascular TOS. This sign, however, should make you suspect that the thoracic outlet could be tight and that the constellation of the neurogenic symptoms with the physical exam findings could be consistent with neurogenic TOS.

Imaging has limited usefulness

An x-ray of the chest or neck can identify cervical and anomalous first ribs.¹⁸ A growing body of research has also focused on using magnetic resonance imaging (MRI) to evaluate patients with suspected NTOS.¹⁹ In general, MRI and computed tomography (CT) are more useful for identifying other symptomatic conditions than for establishing a diagnosis of NTOS.³

Diagnostic anterior scalene block

One of the more effective methods for confirming a diagnosis of NTOS is the intramuscular anterior scalene block. The block temporarily paralyzes the muscle in spasm and allows the first rib to descend, which decompresses the thoracic outlet. Symptom reduction in response to the block correlates well with outcomes for surgical decompression. The block may be performed under guidance with electromyography (EMG), ultrasound, and, more recently, CT. Data on CT guidance indicate that this imaging modality minimizes such complications as brachial plexus block, dysphonia, and Horner’s sign.⁴

Electrodiagnostic studies more useful in excluding other disorders

There is no solid evidence to suggest that electrodiagnostic testing such as EMG and nerve conduction velocity (NCV) have diagnostic utility for NTOS, and results are often normal in patients with the syndrome.^{2,8} EMG and NCV are helpful to exclude other neurologic abnormalities, such as radiculopathy, carpal tunnel syndrome, cubital tunnel syndrome, polyneuropathy, and motor neuron disease.⁶

Additionally, the medial antebrachial cutaneous (MAC) nerve conduction study has been identified as a sensitive test to detect milder cases of NTOS.² It measures the sensory function of the lower trunk of the brachial plexus. Results of this test can be abnormal in patients whose EMGs and NCVs are normal. MAC studies may help to provide objective evidence of NTOS, but more research is needed to validate this test before its routine use can be recommended.

CASE: Ms. R’s exam findings

On physical examination, Ms. R has tenderness over the right anterolateral neck, just posterior to the sternocleidomastoid muscle. She has normal light touch and pinprick sensation in the right upper extremity. Strength is 4+/5 in the right arm and 5/5 in the left arm. Elevated arm stress testing reveals a reproduction of her symptoms at 15 seconds. MRI of her neck is negative for stenosis, disc bulge, or prior surgery. EMG conduction testing of her right arm is normal. Chest x-ray is negative for a cervical rib. Duplex scan of her right carotid, internal jugular, and axillary vessels is negative for stenosis and thrombosis.

Treatment

The clinical variability of NTOS is wide, and much debate continues regarding treatment strategies for these patients.

Medications and physiotherapy are first-line options

The initial approach to treating NTOS is conservative. A typical plan involves behavior modification, a course of physical therapy, and medication. Because NTOS displays neuropathic features, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), and membrane stabilizers (eg, gabapentin) may help to manage symptoms. Non-steroidal anti-inflammatory agents and muscle relaxants are frequently prescribed for pain, as well. If pain persists and a patient's quality of life continues to be impaired, sustained-release opioids may prove useful.⁸

Minimally invasive approaches

An area of increasing focus is nonsurgical, minimally invasive techniques to decompress the interscalene space. Injection of medications into the cervicothoracic musculature is a strategy aimed at diminishing pressure within the interscalene space by relaxing the scalene muscles, thereby decreasing compressive symptoms and nerve irritation.² Agents include local anesthetics, corticosteroids, and, more recently, botulinum toxin type A (BTX-A). Modalities employed to ensure accurate injection have included anatomical landmarks, EMG, ultrasound, CT, or a combination of ultrasound/EMG or fluoroscopy/EMG.

Although local anesthetics may help to reduce pain, relief is brief. Such injections are more useful in confirming the diagnosis, predicting surgical outcomes, assessing candidacy for BTX-A therapy, and determining the reversibility of symptoms.²

BTX-A. This toxin, derived from *Clostridium botulinum*, has been a scientific curiosity since its discovery in 1897. Its mechanism of action targets the neuromuscular junction, blocking the release of acetylcholine from presynaptic terminals. By the mid-1980s, BTX-A emerged as an effective therapy for strabismus and blepharospasm.²⁰ Since that time, BTX-A has been approved to treat hemifacial spasm, cervical dystonia, glabellar lines, hyperhidrosis, and chronic migraine.

BTX-A works by reducing muscle overactivity

and, possibly, decreasing pain and inflammation. BTX-A injected into the anterior scalene muscle alone, or into more than one scalene muscle along with the upper thoracic or chest wall muscles, has effectively reduced symptoms of NTOS.^{10,21}

Histologic studies demonstrate that injury to either the anterior or middle scalene muscles contributes to most of the pathology in NTOS.^{1,10} Muscle fibrosis is the most significant histologic finding, showing that scar tissue occurs 3 times more frequently than other pathologic changes.¹⁰ Interestingly, some animal data suggest that BTX-A may improve wound healing in injured muscles and reduce the risk of scarring. Human studies show benefit from BTX-A injection into muscles affected by radiation fibrosis syndrome.¹⁰

Cervical muscle spasm and, probably, fibrosis place traction on the brachial plexus/thoracic outlet and lead to muscle and nerve edema, neural compromise, and spatial narrowing of the outlet. The application of BTX-A to targeted scalene muscles can ease the symptoms of NTOS.

Although the use of BTX-A for NTOS is off label, so is its use for many other non-FDA-approved applications. Due to its history of safety and therapeutic benefit, BTX-A is also used to treat piriformis syndrome, lateral epicondylitis, achalasia, and oromandibular dystonia.

In clinical practice, doses of BTX-A injections into the ASM range between 12 and 25 units¹⁰; however, much study and debate continues regarding the optimal dosage, targeting of muscle groups, and patient selection. Symptomatic relief can last up to 6 months, although the average duration of pain relief is slightly beyond 3 months,⁸ which is the approximate duration of action of BTX-A in other applications.²²

Larger doses of BTX-A, more frequent use, and higher protein load increase the chance that patients will develop neutralizing antibodies.²² Antibodies often diminish the duration of action and the maximal therapeutic effect of BTX-A. Therefore, it's prudent to use the lowest effective dose over the greatest time interval while still aiming for a reasonable duration of pain relief. Author PC does not repeat dosing until 3 months have passed.

Several studies have shown BTX-A injection into the ASM alone, or into more than one scalene muscle along the upper thoracic or chest wall muscles, to be effective in NTOS patients.⁸ In a prospective longitudinal study by

BTX-A works by reducing muscle overactivity and, possibly, decreasing pain and inflammation.

Surgical decompression of the thoracic outlet is an option for patients who have not obtained adequate relief with conservative therapies.

Christo et al, patients underwent CT-guided BTX-A injections of the ASM.¹⁰ After 3 months, patients experienced a 29% decrease in their pain as well as an approximate 15% reduction in their visual analog scale score. A prior study by Torriani and colleagues also showed similar promising results, but the mean duration of improvement after BTX-A injection was 31 days.²¹

To date, only one randomized controlled trial involving BTX-A for TOS has been completed.¹¹ Interestingly, it failed to detect a clinically or statistically significant reduction in pain for subjects treated with BTX-A. This study had several limitations, thus making it difficult to interpret the results. For instance, patients in the BTX-A treatment group had experienced, on average, nearly 6 years of symptoms. The investigators noted that many of these patients had already developed chronic pain with central sensitization, making it unlikely that a single intervention would significantly reduce pain. Injections were also guided with EMG as opposed to more precise modalities, such as MRI, CT, or ultrasound.^{10,11,23}

Surgical intervention

Surgical decompression of the thoracic outlet is an option for patients who have not obtained adequate relief with conservative therapies.²⁴ However, the benefits of surgery are controversial given the difficulties in objectively establishing a diagnosis, a lack of uniform indications for surgery, variations in surgical technique, and a lack of objective postoperative outcomes metrics.²⁵ Many studies are based on small sample sizes and do not report long-term data.

A variety of surgical techniques, used for more than 50 years in the treatment of NTOS, include scalenectomy alone, first rib resection alone, or first rib resection with scalenectomy (FRRS). Overall, surgical success rates can be as high as 90% with low complication rates, but persistent disability in 60% of patients one year following surgery with more than a 30% complication rate has also been reported.^{26,27}

Predictors of success with surgery. Predicting which patients will benefit from surgical intervention has been a challenge for surgeons and pain specialists. Recent studies have looked at patient selection and factors that may be associated with surgical failure. Rochlin et al retrospectively reviewed 161 patients with NTOS who underwent surgical intervention (182 FRRS procedures) from 2003 to 2011, and looked

for evidence of unresolved, recurrent, or contralateral neurogenic symptoms after FRRS.²⁸ Patients with poorer outcomes tended to be older and actively smoking, have more comorbid pain syndromes and neck or shoulder disease, and have experienced a long duration of symptoms.

Caputo et al showed that younger patients tend to be better surgical candidates.²⁹ In this retrospective review of 189 patients undergoing supraclavicular decompression (scalenectomy, brachial plexus neurolysis, and first rib resection, with or without pectoralis minor tenotomy) for NTOS, adolescents had more favorable preoperative characteristics and enhanced 3-month and 6-month functional outcomes than adults.²⁹

In general, preoperative factors associated with a poor postoperative course are active smoking, age >40 years, and a need for opioids to control pain.³⁰ A need postoperatively for opioids or injections of BTX-A, steroids, or local anesthetics likely indicates that surgery has failed.³⁰ Strict patient selection for surgery has become a critical determinant of the NTOS treatment algorithm.

CASE: Ms. R obtains pain relief

Ms. R was treated with physical therapy for 2 months, NSAIDs, and a muscle relaxant. She noted a 20% improvement in pain, but she requested more relief. A CT-guided anterior scalene block was then performed, producing 50% relief of her symptoms. Next, she was offered the choice of decompressive surgery or BTX-A therapy, and she elected to try BTX-A. She was treated with 25 units of BTX-A injected into the anterior scalene muscle. At the 2-month follow-up, Ms. R reported 60% relief of her pain, improved functional use of her arm, and better strength.

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Obesity-related pain: Time for a new approach that targets systemic inflammation

We may be able to reduce pain, disability, and related comorbidities in obese patients by implementing modest weight loss and fitness interventions to address systemic inflammation.

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Pain with obesity is an increasingly common problem in the patients who walk into our clinics. Unfortunately, the overlap of these 2 conditions can seem like too much for us to address in one office visit. If the patient is in pain, we start there. I would argue, however, that we need to begin viewing obesity in our patients as an opportunity to improve their pain.

People with obesity-related pain represent 2 epidemics: the 100 million Americans with chronic pain and the 150 million who are overweight or obese.^{1,2} In June 2013, the American Medical Association declared obesity a disease.³ Similarly, the Institute of Medicine has called for a “cultural transformation” to better assess and treat pain.⁴

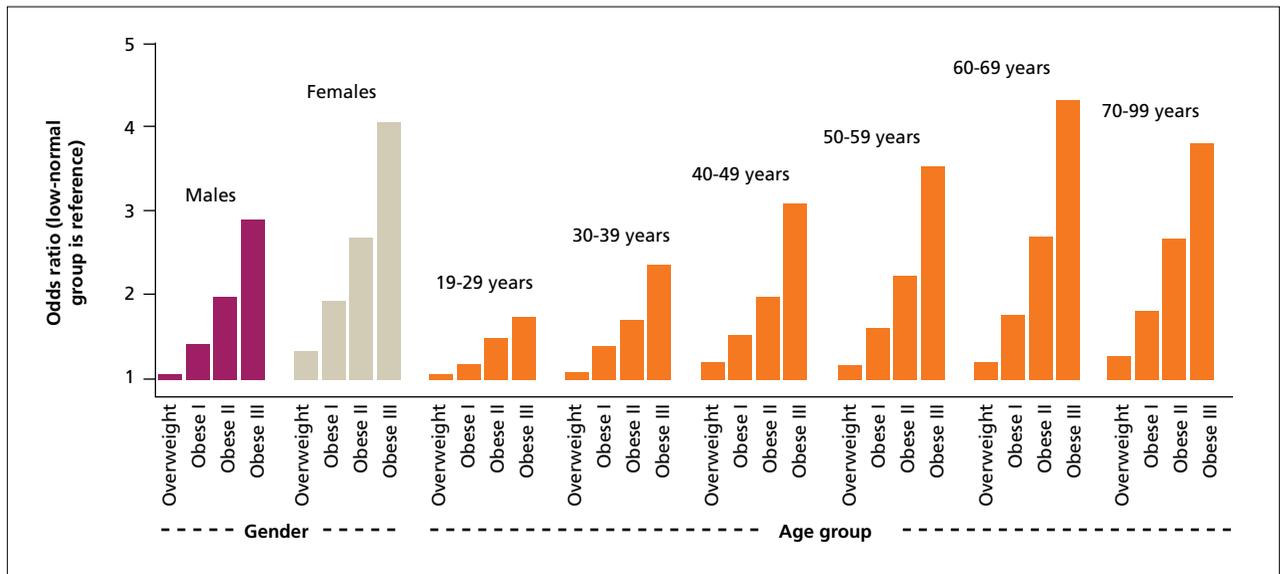
With those calls for action in mind, this article explores the idea of a negative association

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Illustration: Dave Cutler

FIGURE 1: Odds ratios for “pain yesterday” for BMI classifications* by gender and age group^{†6}



*Body mass index (BMI) classifications: low through normal, <25; overweight = 25 to <30; obese I = 30 to <35; obese II = 35 to <40; obese III, ≥40.

[†]Based on a survey of >1 million Americans.

Source: Reprinted with permission from Stone AA, Broderick JE. Obesity and pain are associated in the United States. *Obesity (Silver Spring)*. 2012;20:1491-1495.⁶

between pain and obesity that goes beyond mechanical overload. The emerging evidence reviewed here elucidates potential connections between these conditions, including systemic inflammation. It suggests that we can reduce pain, disability, and related comorbidities for our patients with even modest weight loss and fitness interventions.

Obesity complicates pain management

Obesity is associated with increased pain and reduced benefit from pain treatments. More than one-third of adult Americans (35.7%) are obese (body mass index [BMI] ≥30).⁵ Individuals with obesity experience daily pain at much higher rates than those of low to normal weight. A survey of >1 million Americans found that pain rates were 68% to 254% higher in individuals classified as obese compared with nonobese groups.⁶ The association held for both men and women, became stronger in older age groups, and persisted in higher-weight groups even when controlled for other pain conditions (FIGURE 1).⁶

Broader definitions of obesity. BMI calculations based on weight and height (kg/m²) are the traditional definition of obesity recognized by the World Health Organization and Centers for Disease Control and Prevention (TABLE 1). In addition, obesity is now recognized in normal-weight individuals with elevated body fat percentage (normal-weight

obesity [NWO])⁷ and in individuals with signs of metabolic syndrome (ie, metabolic obesity), characterized by elevated waist circumference, fasting blood glucose, triglycerides, and blood pressure, as well as reduced HDL cholesterol.⁸

Visceral fat is an independent risk factor for cardiovascular disease. Individuals with central abdominal obesity appear to be at higher risk of atherogenesis than those with peripheral obesity. Insulin resistance, a sequela of intra-abdominal fat accumulation, increases the risk of stroke, type 2 diabetes, and heart disease.⁸

Adding waist circumference to the BMI calculation can help you identify abdominal distribution of obesity.⁸ Waist circumference

TABLE 1

World Health Organization definition of obesity based on body mass index (BMI)

Weight status	BMI (kg/m ²)
Underweight	<18.5
Normal	18.5 to 24.9
Overweight (pre-obese)	25.0 to 29.9
Obese class I	30.0 to 34.9
Obese class II	35 to 39.9
Obese class III (morbid obesity)	≥40

Online BMI calculators are available from the Centers for Disease Control and Prevention at: <http://www.cdc.gov/healthyweight/assessing/bmi>.

Source: World Health Organization. BMI classification. Available at: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html.

>40 inches for men and >35 inches for women substantially increases the risk of metabolic complications.⁹

A clinical tool developed by Sharma and Kushner (TABLE 2)¹⁰ identifies 5 stages of disability from obesity-related medical conditions and recommends a management approach at each stage. This Edmonton Obesity Staging System is complementary to the BMI classifications of obesity. It recognizes that patients—

whatever their BMI—may have no apparent risk factors or functional impairments (stage 0); subclinical disease, with mild impairment such as mild aches, pain, and fatigue (stage 1); or moderate to severe organ damage and disability (stages 2 to 4).

A predictor of reduced pain relief. Pain clinicians feel frustration when interventions that generally have a good chance of working fall short. Evidence supports the observa-

TABLE 2
The Edmonton Obesity Staging System for managing metabolic and functional risk¹⁰

Stage	Patient characteristics	Management approaches
0	<p>No apparent obesity-related risk factors, eg, blood pressure, serum lipids, fasting glucose levels are within normal range</p> <p>No physical symptoms</p> <p>No psychopathology</p> <p>No functional limitations and/or impairment of well-being</p>	<p>Identify factors contributing to increased body weight.</p> <p>Counsel patient on lifestyle measures, including healthy eating and increased physical activity, to prevent further weight gain.</p>
1	<p>Obesity-related subclinical risk factor(s), eg, borderline hypertension, impaired fasting glucose, elevated liver enzymes</p> <p>Mild physical symptoms, eg, dyspnea on moderate exertion, occasional aches and pains, fatigue</p> <p>Mild psychopathology</p> <p>Mild functional limitations and/or mild impairment of well-being</p>	<p>Investigate for other (non-weight-related) contributors to risk factors.</p> <p>Institute more intense lifestyle interventions, including diet and exercise, to prevent further weight gain.</p> <p>Monitor risk factors and health status.</p>
2	<p>Established obesity-related chronic disease(s), eg, hypertension, type 2 diabetes, sleep apnea, osteoarthritis, reflux disease, polycystic ovary syndrome, anxiety disorder</p> <p>Moderate limitations in activities of daily living and/or well-being</p>	<p>Initiate obesity treatments, including considerations of all behavioral, pharmacologic, and surgical treatment options.</p> <p>Maintain close monitoring and management of comorbidities as indicated.</p>
3	<p>Established end-organ damage, eg, myocardial infarction, heart failure, diabetic complications, incapacitating osteoarthritis</p> <p>Significant psychopathology</p> <p>Significant functional limitation(s) and/or impairment of well-being</p>	<p>Initiate more intensive obesity treatment, including consideration of all behavioral, pharmacologic, and surgical treatment options.</p> <p>Aggressively manage comorbidities as indicated.</p>
4	<p>Severe (potentially end-stage) disability/ies from obesity-related chronic diseases</p> <p>Severe disabling psychopathology</p> <p>Severe functional limitation(s) and/or severe impairment of well-being</p>	<p>Institute aggressive obesity management as deemed feasible.</p> <p>Prescribe palliative measures, including pain management, occupational therapy, and psychosocial support.</p>

tion that pain treatments are less effective in patients with obesity compared with those who are not obese.

This pattern has been noted with behavioral pain interventions¹¹ and in clinical trials. For example, the Spine Patient Outcomes Research Trial (SPORT) for the treatment of lumbar disc herniation examined the benefit of operative and nonoperative treatments in more than 1000 participants. At 4-year follow-up, individuals who were obese had improved significantly less in both treatment groups than did their nonobese counterparts.¹²

Obesity-related pain as systemic inflammation

Obesity causes mechanical disruption, including joint compression and alignment changes that can lead to pain.¹³ The association of obesity to pain is often related to areas with mechanical overload (eg, symptomatic knee osteoarthritis [OA] and chronic back pain), and is evidenced by the fact that the rate of early retirement, disability, and risk of requiring surgical treatment are several times higher among people who are overweight or obese.¹⁴

Pain that occurs with obesity is not exclusively mechanical, however. Increased rates of pain in locations above the knees and low back also have been associated with obesity, including the thoracic spine, neck, upper extremities (rotator cuff tendinitis and carpal tunnel syndrome), as well as with conditions including fibromyalgia, migraine, and headache (TABLE 3).^{13,15-17}

Obesity-related pain is a conceptual framework to describe pain and related disability in individuals with obesity and metabolic dysregulation.⁷ This concept suggests that systemic inflammation is likely additive in individuals with pain and obesity. Thus, interventions such as exercise that target systemic inflammation and obesity could be important in relieving pain as well.¹⁸

A number of adipocyte-derived cytokines and markers of systemic inflammation have been associated with obesity and metabolic syndrome.¹⁹ Interestingly, C-reactive protein (CRP) and tumor necrosis factor α (TNF- α) are related both to inflammation and to the progression of OA and low back pain.^{20,21} (See FIGURE 2.)

Briggs et al showed increased reporting of low back pain among individuals with elevated CRP, particularly those classified as obese.¹⁸

TABLE 3
Pain conditions associated with obesity^{13,15-17}

- Carpal tunnel syndrome
- Connective tissue disorders (eg, rheumatoid arthritis)
- Fibromyalgia
- Gastrointestinal disorders*
- Gout
- Low back pain
- Migraine and headache
- Neuropathy*
- Osteoarthritis: multiple sites (eg, knee, hip, hand)
- Plantar fasciitis
- Rotator cuff tendonitis

*Refers to subtypes of the condition.

Hormones traditionally viewed as playing a role in obesity, such as leptin and adiponectin, have been linked with upregulation of matrix metalloproteinase and joint degeneration.²²

A 20-year study by Schett and colleagues²³ found type 2 diabetes to be an independent predictor of severe OA progressing to joint replacement in a group of >900 patients. These authors noted that evidence linking type 2 diabetes with joint degeneration supports the concept that OA is part of the metabolic syndrome. Their data suggest that glucose metabolism directly affects joint integrity, independent of body weight.

Opportunity: Weight loss, pain, and function

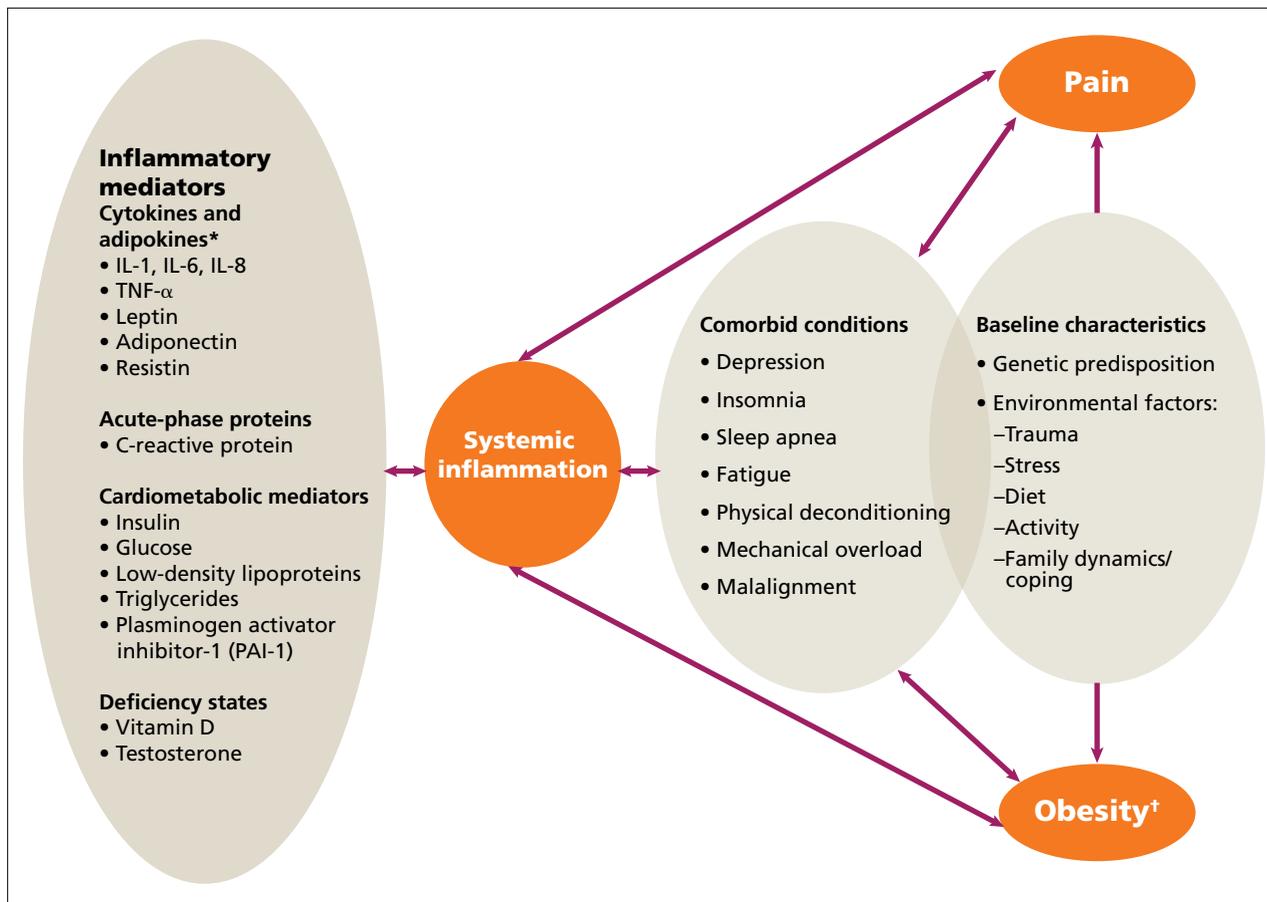
Weight loss provides important and often overlooked potential in reducing pain. Although the additive burden of pain and obesity can seem overwhelming to patients and clinicians, even modest weight loss can produce positive results.²⁴

In the Framingham study, an 11-pound weight loss was associated with a 50% reduction in the risk of symptomatic knee arthritis.²⁵ In another study of knee OA, an 11% loss of body weight from diet alone resulted in a 50% decrease in pain across 8 weeks in patients with a mean BMI of 35.9.²⁶

An integrative approach that combines nutrition, activity, and behavioral strategies appears to provide maximum benefit. In the

Data suggest that glucose metabolism directly affects joint integrity— independent of body weight.

FIGURE 2: Obesity-related pain: A proposed framework related to systemic inflammation



*Adipokines are cytokines secreted by adipose tissue.

†Includes various definitions of obesity as discussed in the article, including normal-weight obesity (NWO) and metabolic obesity.

IL, interleukin; TNF- α , tumor necrosis factor α .

Sources: Briggs MS, Givens DL, Schmitt LC, et al. Relations of C-reactive protein and obesity to the prevalence and the odds of reporting low back pain. *Arch Phys Med Rehabil.* 2013;94:745-752. Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. *Annu Rev Immunol.* 2011;29:415-445. Vodo S, Bechi N, Petroni A, et al. Testosterone-induced effects on lipids and inflammation. *Mediators Inflamm.* 2013;2013:183041.

18-month Arthritis, Diet, and Activity Promotion Trial (ADAPT), weight loss plus moderate exercise provided greater improvement in function and pain in overweight and obese adults with knee OA, compared with either intervention alone. A 5% weight loss resulted in a 24% improvement in function and a 30% reduction in pain.²⁷

Weight loss can reduce pain in patients with obesity and knee OA regardless of the degree of joint damage (as assessed by magnetic resonance imaging [MRI]), muscle strength, or knee-joint alignment, reported Gudbergson et al.²⁸ Some aspects of structural deformity may stabilize or reverse with weight loss.²⁹

Effective for knee pain and more.

Although most trials have evaluated weight loss in people with symptomatic OA, several trials have found benefit in other common pain conditions, such as fibromyalgia and low back pain.

Dietary weight loss resulted in reduced

tender points and significantly improved quality of life in obese patients with fibromyalgia, as assessed by the Fibromyalgia Impact Questionnaire in a 6-month controlled trial by Senna et al.³⁰ Patients who lost weight also slept better and were less depressed than those without weight loss. The investigators also observed an association between weight loss and reduced levels of proinflammatory mediators interleukin 6 (IL-6) and CRP.

Other studies also note that weight loss appears to improve depression and sleep dysfunction, which may contribute to obesity's symptomatic burden. IL-6, linked to these common comorbidities, also is associated with the progression of OA and degree of obesity.^{31,32}

A 52-week program of diet and exercise, along with regular group and educational meetings, was effective in reducing BMI in obese patients with low back pain, reported Roffey et al.³³ The interventions also were asso-

ciated with a trend toward improved pain and clinically significant improvements in function.

Exercise does not worsen pain conditions. Patients with pain and obesity may feel discomfort as they begin an exercise program, but postexertional soreness does not represent long-term worsening of a pain condition. Longitudinal data from the 30,000-patient Norwegian HUNT study confirm that exercise overall does not appear to increase the risk of osteoarthritis at any level of BMI.³⁴ An exhaustive literature review suggested that moderate exercise did not cause progression of osteoarthritis.³⁵

A better way to assess and treat pain

Comorbid obesity and pain conditions may be related to subtle processes that start early in life, including genetics, environmental stress, and trauma. Cultural and familial coping patterns, fear avoidance, maladaptive stress coping, and autonomic dysfunction can influence motivation and behavior.³⁶

In interviewing primary care patients with coexisting pain and obesity, Janke and Kozak³⁷ found 5 major behavioral themes:

- Depression can magnify comorbid physical symptoms and complicate treatment.
- Physical pain may trigger hedonic hunger (eating for pleasure rather than to satisfy a biological need), associated with depression and shame.
- Pain may lead to emotional or “binge” eating.
- Pain may result in altered dietary choices.
- Pain may lead to feelings of low self-efficacy for physical activity.

Pain clinicians know the obstacles faced by patients with chronic pain and obesity. We realize how hard it is for them to move, that exercise can flare their pain, and that they may not make the best food choices.

The next logical step is to routinely include weight reduction as a component of pain treatment for our patients with comorbid obesity or metabolic dysregulation. The evidence points to the potential for increased benefit from pain treatments and reduction in obesity-related comorbidities. This would represent what the Institute of Medicine calls a “cultural transformation” in our understanding of pain states and our approach to the clinical encounter.

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