

TOPICS IN PAIN MANAGEMENT

Multidisciplinary Continuing Education for Pain Management Practice

CONTINUING EDUCATION ACTIVITY

Diagnosis and Management in Patients With Pain in the Setting of Obesity

Sydney C. Karnovsky, MD, Rachel Souza, DO, and MaryAnn Dakkak, MD, MPH

Learning Objectives: After participating in this continuing professional development activity, the provider should be better able to:

1. Describe how stigma related to chronic pain and obesity can affect patient care and outcomes.
2. Explain the relationships among obesity, inflammation, and pain.
3. List 2 key differences to consider in the approach to pain management for patients with obesity compared with patients with healthy weight.

Key Words: Chronic pain, Inflammation, Obesity

Editors' note: In the first article in this 2-part series (*Topics in Pain Management* 2023;39:8), the authors discussed the importance of listening to the patient and identifying any misconceptions of the origins and causes of continuation of pain leading to chronic pain conditions and how these situations can be mitigated. In this second article, the

primary author will review the literature of causes, prevention, and management of chronic pain, especially as it relates to obesity.

The prevalence of chronic pain in the United States is dramatic, with reports citing between 11% and 51% of the US population.¹ Obesity prevalence was 41.9% in 2017–2020, with 9.3% of persons having a body mass index (BMI) qualifying for severe obesity.² Relative to normal-weight people, overweight individuals report a 20% increase in recurrent pain, and an increase of 68% with obesity.³ Chronic pain and obesity are among the most challenging conditions to treat in primary care. Both are highly complex, often involving

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psychosocial and economic factors as major contributors. Another similarity between pain and obesity is that there is significant stigma around both, from differences in the diagnostic and treatment modalities used by the health system, to patients expressing self-doubt, to internalized shame leading to untold and unfulfilled goals. Therefore, in this article, we attempt to untangle some of the web of these 2 topics, both looking at how stigma affects pain and obesity, and how as primary care health care workers, we can begin to create positive change in how we treat both chronic conditions.

Stigma Around Pain Diagnoses

Recent literature has supported a biopsychosocial model of pain that shows how biological, psychological and societal/cultural factors all shape an individual's perception of and response to chronic pain.⁴ Stigma surrounding pain diagnoses can take the form of public/societal shame, structural inequalities, and internalized stigma, all of which can perpetuate the perception of pain for the individual. Patients face stigma around pain in their families and workplaces and the health care system. The US Department of Health and Human Services reported up to 20.5% of patients delayed seeking care for pain due to negative consequences at their workplaces such as fear of stigma, different treatment, or retaliation at the workplace; 17% were concerned about judgment from friends and community.

As well as patients, clinicians who treat acute and chronic pain may experience stigma from colleagues and fear of scrutiny from medical licensure boards, which can lead to over-referral and delays in care.⁵ Acute pain and chronic pain can be managed

by many primary care physicians. The stigma surrounding pain management can lead to over-referral to pain specialists, causing a backlog and delayed care for the patient.

Stigma Around Obesity Diagnoses

There is a widespread stigma surrounding obesity, particularly as a medical diagnosis. Society holds misbeliefs that weight-based stigma must be helpful, serving as motivation to lose weight. Instead, this stigma around obesity propagates unhealthy and often weight-promoting behaviors such as binge eating, social isolation, and decreased physical activity, often leading to avoidance of health care services, which in turn leads to worse health outcomes for obese individuals.⁶ Not only does society stigmatize obesity, but it has been studied that among health care providers, about 30% of providers have negative views of obese patients, often equating their patients' obesity to a lack of motivation and decreased exercise as compared with their nonobese patients.⁷ This is particularly devastating when considering the large percent of Americans who are overweight or obese (>30%).⁸

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The stigma surrounding obesity has also been shown to correlate with other stigmatized diagnoses like anxiety and depression, which only adds to the shame felt by obese

The continuing education activity in *Topics in Pain Management* is intended for clinical and academic physicians from the specialties of anesthesiology, neurology, psychiatry, physical and rehabilitative medicine, and neurosurgery, as well as residents in those fields and other practitioners interested in pain management.



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individuals and increases the likelihood of disengaging with medical care.⁹ Even the tone in which we speak while discussing topics like obesity enhances the negative health outcomes experienced by those with obesity as a diagnosis.⁹ The pessimistic and negative tone observed in health care providers adds to the stigma surrounding obesity. Weight stigma negatively impacts physiological and psychological outcomes, putting individuals at increased risk for obesity, diabetes, and low self-esteem.¹⁰ Furthermore, it has been shown that, due to this stigma, people with obesity are not only less willing to engage with health care professionals, but also are less likely to participate in physical activity and exercise.⁸ With these substantial impacts, it is important to work to reduce bias in medical care for obese individuals.

How Is Adipose Implicated in Inflammation?

Adipose tissue is metabolically active and produces many cytokines implicated in inflammatory processes that may lead to further pain for individuals with higher levels of adiposity.¹¹ These proinflammatory cytokines also activate the c-Jun-N-terminal kinase (JNK) pathways, which can lead to insulin resistance. It has also been proposed that, in obese individuals, macrophages in adipose tissue undergo “phenotype switching” to more proinflammatory cell types that dominate in stressed, overnutrition states,¹¹ which could lead to further weight gain due to inflammation. Visceral adipose is more inflammatory than subcutaneous fat with more immune cells found infiltrating those fat stores. This inflammation has been linked as a mechanism by which obesity can cause metabolic syndrome¹¹; however, a link to pain has not been established.¹²

Does Obesity Cause Pain?

Multiple studies and reviews outlined below have analyzed the relationship between obesity and pain. Most of these studies aim to elucidate whether weight management can be considered an appropriate course of action and treatment recommendation for patients experiencing pain. In one study reviewing obesity and low back pain, researchers discovered an association between obesity and pain only for those within the highest quartile of obesity but found no evidence to show a temporal relationship between changes in weight and changes in low back pain.¹³

Another study demonstrated that higher BMI may have a causal relationship with risk factors for dorsopathies, but also noted that the relationship between obesity and intervertebral disc disease and sciatica is still unclear, and patients’ experience of pain with these conditions is not proven to change based on changes in their weight.¹⁴

Yet another study involved a chronic pain clinic and separated out 372 patients seeking care for chronic pain by BMI and demonstrated no relationship between weight and pain severity and frequency of pain episodes.¹⁵

Although studies consistently failed to show a direct correlation between BMI and pain intensity, many do show an increase in physical activity, quality of life, and psychiatric well-being.^{16,17}

These findings suggest that the effects of obesity, perhaps even the stigma surrounding obesity—which has been shown to have negative implications for mood—have more to do with the pain obese patients experience than with

actual weight. Many studies have shown an association between abdominal obesity and general obesity with risk of low back pain, but within the same studies, they also show associations between lifestyle, physical workload, and age as risk factors for this same pain,¹⁸ making a causal relationship between obesity and pain difficult to prove.

These findings suggest that the effects of obesity, perhaps even the stigma surrounding obesity, have more to do with the pain obese patients experience than with weight.

One theory that links obesity and pain posits that obesity leads to a proinflammatory state which, after time, leads to systemic inflammation.¹ Studies also show that adipose tissue can lead directly to neuroinflammation, which may worsen chronic pain¹ and as an inflammatory state can lead to increased irritation of surrounding muscles and nerves, worsening the experience of pain. Although the studies show neuroinflammation affecting cognitive changes from excess adiposity,¹⁹ this may be extrapolated to theorize on how pain may be affected. Obesity leads to an increased amount of adipose tissue, which perpetuates further insulin and leptin resistance contributing to metabolic syndrome.²⁰ This then leads to increased amounts of leptin, which has been shown to lead to cartilage degradation through inflammatory means such as increased proinflammatory mediators and matrix metalloproteinases.²⁰ Studies on adiposity and pain often conclude that exercise is good for both decreasing adiposity and pain, but the data cannot be linked linearly from obesity reduction causing pain reduction, and in fact many studies do not show weight loss as effective for pain attenuation.^{15,19}

Despite evidence suggesting no causal relationship between obesity and pain, there is evidence to show that chronic pain increases disability and decreases overall physical functioning in those patients with an elevated BMI as compared with their BMI less than 25 counterparts,¹⁵ most likely related to the factors mentioned above, including increased mood disorders.

Does Pain Cause Obesity?

Previously normal-weight patients with newly diagnosed chronic pain are at higher risk of developing obesity than counterparts without chronic pain.^{7,12} The relationship between pain and obesity is multifactorial and can also be cyclical. Pain can lead to increase in weight due to physical activity avoidance, mood disorders worsened by pain, increased energy intake (eating), and disability.²¹ Both weight loss and pain improvement independently improve mood, which can, in turn, decrease pain.³ Patients with chronic pain and obesity are more likely to report decreased physical activity and increased levels of disability even in the absence of worsening pain.²¹

Does Losing Weight Reduce Pain?

Ultimately, the mechanisms that link obesity and pain are still poorly understood. Therefore, most studies around this topic show a correlation between weight loss and pain

reduction but are unable to define a causal relationship or demonstrate the mechanistic pathways influenced by weight reduction that may lead to a decreased experience of pain. Many of the links between weight loss and pain reduction are multifactorial and hypothetical. In one review, authors posit that because obesity can increase mechanical stress and lead to metabolic disruptions, that a reduction in BMI may reduce the risk of developing pain in the first place and potentially aid in recovery of those already experiencing pain.²² Some of the strongest evidence for weight loss as a method to reduce pain is with osteoarthritis, showing small to moderate improvements. The same meta-analysis did not show differences in back pain.²³

Many of the links between weight loss and pain reduction are multifactorial and hypothetical.

Multimodal approaches to weight loss and obesity often encompass many of the same behavioral and functional goals. Both sleep and physical activity are disrupted more in patients with both obesity and chronic pain. Targeting both of these in a multimodal approach can improve quality of life and function. For example, obstructive sleep apnea, which is strongly linked to obesity, when treated, can decrease pain. Studies have shown that improvement in sleep can improve reported pain levels.²¹

Are There Differences in Medication Management for Pain in Obese Patients?

Traditionally, chronic pain is treated with a variety of medications, most typically including nonsteroidal anti-inflammatory drugs, antidepressants, anticonvulsants, topical agents, acetaminophen, and opioids.²⁴ Despite new FDA approvals for medications such as pregabalin for chronic pain, the success of medication alone is often quite limited.²⁴

Recently, nonpharmacologic attempts to treat chronic pain have been studied more frequently, with evidence often pointing to a significant role these may play in successfully mitigating chronic pain. Examples of these less traditional treatments include cognitive behavioral therapy (CBT) for pain, acupuncture, meditation, tai chi, virtual reality, graded motor imagery, and physical movement.^{24,25} Although a multimodal combination of these therapies shows great promise for all patients, there is the risk that, as with medications, practitioners will not offer these alternative or adjunct treatments for chronic pain to obese patients in the same way they offer them to nonobese patients.

Interestingly, more obese patients than healthy weight comparisons are counseled on the importance of exercise, but it is most typically with the goal of weight loss in mind instead of functional improvement.⁸ Although exercise can lead to modest changes in weight (~2% to 6% weight loss within the first 6 months), it is insufficient to maintain long-term significant weight loss and how it is presented can cause further stigma, worsening the patient's engagement with care. Instead of being strictly thought of as a tool for

weight loss (as it is in many physicians' offices), exercise should be discussed as a critical piece of the puzzle for all patients as part of a multimodal approach to improvements in overall health, including improving their chronic pain and quality of life.⁸

In fact, one study looking at how health care personnel counsel patients on weight loss and exercise showed that patients in higher BMI classes, who received more counseling on weight loss and exercise, ended up with higher BMIs 1 year later.²⁶ Possible reasons, the study states, include loss and gain of weight worsens weight gain over time (the "yo-yo" effect), that no weight management program had been proposed—that it was just counseling, or that these were clinician-initiated conversations. Although the study cannot elucidate exactly what or how these patients are being counseled, it suggests that patients are not hearing the same universal messaging from their doctors and that this is having an impact on their long-term obesity levels, perhaps even related to the stigma the patient might have felt after hearing the non-standardized weight-loss counseling in the first place.

The stigma in medicine surrounding treatment of obese patients affects their treatment by health care professionals. In a study looking at how providers view and treat pain, 616 clinicians were exposed to videos of patients who were healthy weight, overweight, and obese discuss their pain. The subjects were asked to make recommendations about pain control for these 6 patients. The study demonstrated that overweight women's pain and obese men's pain were more likely to be "less intense, less interfering, and more exaggerated than their healthy weight counterparts."²⁷ As a result, in the study, these overweight and obese patients were less likely to receive medications and workplace accommodations.²⁷

Approaches to Treating Chronic Pain in Patients With Obesity

To start, practitioners can help center the patient in the conversation by first asking the patient for permission to be weighed, permission to speak about weight, and having the patient lead with what their weight goals are. Treating chronic pain in patients with obesity, much like treating obesity or pain alone, requires careful attention to the patient and avoidance of accidentally (or intentionally) portraying any sense of mistrust or judgment.

In addition to traditional pain methodologies, there is strong evidence for adjuvant care in these patients. One type of therapy that is very promising for patients with pain and obesity is electroacupuncture. Electroacupuncture targeted at the lower limbs and abdomen has shown promising success in both decreasing obesity and treating pain by lowering serum leptin, tumor necrosis factor, and other proinflammatory markers that contribute to worsening pain and obesity.²⁰

Meta-analyses and systematic reviews looking specifically at lower back pain and obesity demonstrate that weight loss does not affect the pain.

Interestingly, despite common beliefs (or stigma-caused beliefs), there are meta-analyses and systematic reviews that show when looking specifically at lower back pain and obesity, weight loss does not affect the pain.²⁰ This is contrary to chronic pain in most other locations in the body and very notable given the high frequency of chronic back pain in the general population. Instead, physical therapy was shown to be the best intervention for chronic low back pain across a systematic review of pain intervention modalities and obesity.²⁰

When treating chronic pain in patients with obesity pharmacologically, it is necessary to recall that the pharmacokinetics in people with significantly increased amounts of adipose tissue vary from normal. Obese patients often have differences in how drugs work based on how lipophilic the drug is and which organ metabolizes it; that is, if someone with obesity has fatty liver disease and a drug is metabolized in the liver, the degree of liver disease as reflected by altered liver function tests may affect the way the drug is absorbed in the body.²⁰

Another form of treatment for chronic pain, injections, must be seen with a different lens when comparing obese and healthy-weight people. For example, epidural injections, one of the most common treatments that exist for chronic lower back pain, need to be done carefully for obese patients. A physician must choose a needle length based on presumed depth of tissue and an imaging technique (ie, x-ray vs ultrasonography) that will enable vision of the target.²⁰ Data show that epidural injections under US guidance for the lumbar facet have a lower success rate than those done on normal-weight patients.²⁰ Fortunately, studies show that epidural injections had similar outcomes across BMI without increase in adverse effects.²⁸

Conclusion

The relationship between weight and pain is complex, with multiple comorbidities that contribute to both. Both can increase the other, and yet there is no strong evidence that changing one definitely decreases the other. Both require a destigmatized approach that centers patient goals, their function, and evidence-based medicine with multimodal approaches for weight loss and pain management.

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ICYMI: IN CASE YOU MISSED IT

News from recent studies related to pain management, compiled by Elizabeth A.M. Frost, MD, co-editor of *Topics in Pain Management*

Chronic Low Back Pain Improves More With Cognitive Functional Therapy Than With Core Exercises

This study compared the effectiveness of cognitive functional therapy (CFT) over core exercises and manual therapy (CORE-MT) in improving pain and function for patients with chronic low back pain after spinal surgery.

The authors conducted a randomized controlled superiority trial in a university hospital and a private physical therapist clinic in Santa Catarina, Brazil, involving 80 participants ages 18 to 75 years who had chronic low back pain after spinal surgery. Patients were given 4 to 12 treatment sessions of CFT or CORE-MT once per week for a maximum period of 12 weeks. Primary outcomes measured were pain intensity (numeric pain rating scale, scored from 0 to 10) and function (Patient-Specific Functional Scale, scored from 0 to 10) after intervention.

Data were obtained for 75 participants (93.7%). CFT was more effective, with a large effect size, than CORE-MT in reducing pain intensity [mean difference (MD) = 2.42; 95% confidence interval (CI) = 1.69 to 3.14; effect size (d) = 0.85] and improving function (MD = -2.47; 95% CI = -3.08 to -1.87; effect size = 0.95) after intervention [mean = 10.4 weeks (standard deviation = 2.17) after the beginning of

treatment]. These differences were maintained at 22 weeks for pain intensity (MD = 1.64; 95% CI = 0.98 to 2.3; effect size = 0.68) and function (MD = -2.01; 95% CI = -2.6 to -1.41; effect size = 0.81).

The researchers concluded from their findings that CFT was more effective than CORE-MT, with large and long-lasting effect sizes and may be an option for patients with chronic low back pain after spinal surgery.

The researchers concluded from their findings that CFT was more effective than CORE-MT, with large and long-lasting effect sizes, and it may be an option for patients with chronic low back pain after spinal surgery. (See Avila L, da Silva MD, Neves ML, et al. Effectiveness of cognitive functional therapy versus core exercises and manual therapy in patients with chronic low back pain after spinal surgery: randomized controlled trial. *Phys Ther.* 2024;104(1):pzad105. doi:10.1093/ptj/pzad105. PMID: 37548608.)

Minimal Effect of Corticosteroids in Preventing Postherpetic Neuralgia

Postherpetic neuralgia (PHN) is a common and painful complication of herpes zoster. It has been postulated that the anti-inflammatory properties of corticosteroids might be beneficial in preventing this complication.

The authors updated searches for randomized controlled trials (RCTs) of corticosteroids for preventing PHN in the Cochrane Neuromuscular Specialised Register, CENTRAL, MEDLINE, Embase, 2 other databases, and 2 trials registers (June 2022). They also reviewed the bibliographies of identified trials, contacted authors, and approached pharmaceutical companies to identify additional data. All RCTs involving corticosteroids were given by any routes to people of all ages, with herpes zoster of all degrees of severity within 7 days after onset as compared with no treatment or placebo.

Five randomized, double-blind, placebo-controlled parallel-group study trials with a total of 787 participants met inclusion criteria. Evidence is very uncertain about the effects of corticosteroids given orally during an acute herpes zoster infection in preventing PHN 6 months after the onset of herpes [risk ratio (RR) 0.95, 95% confidence interval (CI) 0.45 to 1.99; 2 trials, 114 participants; very low-certainty evidence (downgraded for serious risk of bias and very serious imprecision)]. Three other trials that fulfilled inclusion criteria were not included in the meta-analysis because they did not provide separate information on the number of

participants with PHN at 6 months. Adverse events during or within 2 weeks after stopping treatment were reported in all 5 included trials. There were no observed differences in serious [RR 1.65, 95% CI 0.51 to 5.29; 5 trials, 755 participants; very low-certainty evidence (downgraded for serious risk of bias and very serious imprecision)] or nonserious adverse events [RR 1.30, 95% CI 0.90 to 1.87; 5 trials, 755 participants; low-certainty evidence (downgraded for serious risk of bias and serious imprecision)] between the corticosteroid and placebo groups. One of these trials was at high risk of bias because of incomplete outcome data, 2 were at unclear risk of bias, and the other was at low risk of bias.

Based on the current available evidence, corticosteroids given orally during an acute herpes zoster infection do not appear to prevent PHN.

The authors concluded that, based on the current available evidence, the effect of corticosteroids given orally during an acute herpes zoster infection does not appear to prevent PHN. Corticosteroids given orally or intramuscularly may result in little to no difference in the risk of adverse events in people with acute herpes zoster. Corticosteroids

may relieve the zoster-associated pain in the acute phase of the disease. Further research is needed to evaluate the efficacy of corticosteroids for herpes zoster and long-term follow-up should be included to observe effects on the transition from acute pain to PHN. Future trials should include

measurements of function and quality of life, and updated measures of pain. (See Jiang X, Li Y, Chen N, et al. Corticosteroids for preventing postherpetic neuralgia. *Cochrane Database Syst Rev.* 2023;12(12):CD005582. doi:10.1002/14651858.CD005582.pub5.)

Management of Chronic Pain Associated With Temporomandibular Disorders: Hope on the Horizon

In this systematic review, the authors looked at the comparative effectiveness of available therapies for chronic pain associated with temporomandibular disorders (TMDs). Data sources included MEDLINE, EMBASE, CINAHL, CENTRAL, and SCOPUS, searched to May 2021, and again in January 2023.

Pairs of reviewers independently identified patient-important outcomes, including pain relief, physical functioning, emotional functioning, role functioning, social functioning, sleep quality, and adverse events. The GRADE approach rated the certainty of evidence and categorized interventions from most to least beneficial. Identified were 233 trials, of which 153—enrolling 8713 participants and exploring 59 interventions or combinations of interventions—were included in network meta-analyses. All subsequent effects refer to comparisons with placebo or sham procedures. Effects on pain for 8 interventions were supported by high- to moderate-certainty evidence. The 3 therapies probably most effective for pain relief were CBT augmented with biofeedback or relaxation therapy [risk difference (RD) for achieving the minimally important difference (MID) in pain relief of 1 cm on a 10-cm visual analogue scale: 36% (95% confidence interval (CI) 33 to 39)], therapist-assisted jaw mobilization [RD 36% (95% CI 31 to 40)], and manual trigger point therapy [RD 32% (29 to 34)]. Five interventions were less effective, yet more effective than placebo, showing RDs ranging between 23% and 30%: CBT, supervised postural exercise, supervised jaw exercise and stretching, supervised jaw exercise and stretching with

manual trigger point therapy, and usual care (such as home exercises, self-stretching, and reassurance). Four interventions had moderate evidence (improved physical functioning: supervised jaw exercise and stretching [RD for achieving the MID of 5 points on the short form-36 physical component summary score: 43% (95% CI 33 to 51)], manipulation [RD 43% (25 to 56)], acupuncture [RD 42% (33 to 50)], and supervised jaw exercise and mobilization [RD 36% (19 to 51)]. The evidence for pain relief or physical functioning among other interventions, and all evidence for adverse events, was low or very low certainty.

With moderate- or high-certainty evidence, interventions that promote coping and encourage movement and activity were most effective for reducing chronic TMD pain.

Conclusions drawn were that when restricted to moderate- or high-certainty evidence, interventions that promote coping and encourage movement and activity were found to be most effective for reducing chronic TMD pain. (See Yao L, Sadeghirad B, Li M, et al. Management of chronic pain secondary to temporomandibular disorders: a systematic review and network meta-analysis of randomised trials. *BMJ.* 2023;383:e076226. doi:10.1136/bmj-2023-076226.)

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1. People with obesity report a ___ increase in recurrent pain compared with normal-weight people.
 - A. 5%
 - B. 10%
 - C. 15%
 - D. 20%
2. Which one of the following is a major contributor to obesity and chronic pain?
 - A. employment status
 - B. psychosocial factors
 - C. advanced level of education
 - D. marriage status
3. Stigma surrounding pain diagnoses can take the form of ____, which can perpetuate the perception of pain for the individual.
 - A. public/societal shame
 - B. motivation
 - C. facilitating weight loss
 - D. support
4. Similar to anxiety and depression, the stigma surrounding obesity can increase shame and the likelihood of
 - A. obtaining an accurate diagnosis.
 - B. retention in care.
 - C. disengaging with medical care.
 - D. adherence with the medical plan.
5. For individuals with higher levels of adiposity, the cytokines released from adipose tissue can lead to
 - A. less pain.
 - B. renal failure.
 - C. increased metabolic rate.
 - D. insulin resistance.
6. Previously normal-weight patients with newly diagnosed chronic pain are at higher risk of developing obesity than their counterparts without chronic pain.
 - A. True
 - B. False
7. Some of the strongest evidence for weight loss as a method to reduce pain, which shows small to moderate improvements, is in
 - A. migraine.
 - B. osteoarthritis.
 - C. spinal stenosis.
 - D. rheumatoid arthritis.
8. Exercise for patients with obesity should be presented
 - A. to initiate substantial weight loss (eg, >20% in 6 months).
 - B. as a method to maintain significant weight loss.
 - C. in a way that does not increase stigma.
 - D. as a way to demonstrate motivation for reducing pain.
9. In a study that examined how health care professionals view and treat pain, in 616 people who viewed videos of healthy weight, overweight, and obese patients with pain,
 - A. the pain of overweight women and obese men was underestimated.
 - B. the estimation of pain was congruent with the patient's report of pain.
 - C. pain ratings of the health care professionals were significantly higher.
 - D. the impact of pain in obese women and men was significantly overemphasized.
10. Electroacupuncture targeted at the lower limbs and abdomen has shown promising success in both decreasing obesity and treating pain by
 - A. increasing proinflammatory cytokines.
 - B. facilitating release of serum leptin.
 - C. lowering proinflammatory markers.
 - D. reducing the likelihood of fatty liver disease.