Clinical Review

Adipose Tissue as Pain Generator in the Lower Back and Lower Extremity: Application in Musculoskeletal Medicine

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Abstract

Description

Adipose tissue (AT) has diverse and important functions in body insulation, mechanical protection, energy metabolism and the endocrine system. Despite its relative abundance in the human body, the clinical significance of AT in musculoskeletal (MSK) medicine, particularly its role in painful MSK conditions, is under-recognized. Pain associated with AT can be divided into intrinsic (AT as a primary pain generator), extrinsic (AT as a secondary pain generator) or mixed origin. Understanding AT as an MSK pain generator, both by mechanism and its specific role in pain generation by body region, enhances the clinical decision-making process and guides therapeutic strategies in patients with AT-related MSK disorders. This article reviews the existing literature of AT in the context of pain generation in the lower back and lower extremity to increase clinician awareness and stimulate further investigation into AT in MSK medicine.

Keywords

adipose tissue; fat pad; musculoskeletal pain; connective tissue; lipodystrophy; lipoma; obesity; lipedema; pain generator

Introduction

Mounting evidence supports the various functions of adipose tissue (AT), most notably its link to obesity and metabolic dysfunction.[1-3] Aside from the impact of obesity on the musculoskeletal (MSK) system, the role of AT in painful MSK conditions is less established. Historically, AT masses/lipomas were considered common pain generators. However, the high prevalance of asymptomatic lipomas,[4,5] inconsistent responses to local injections and increasing awareness of other neighboring pain generators disputed their reputation in painful MSK conditions. AT has recently re-entered the focus of MSK clinicians, most notably for its use in regenerative medicine.[6] Moreover, localization and evaluation with high resolution imaging technologies has improved understanding of AT in other contexts, particularly pain generation. Therefore, our objective is to review the available literature on AT-related painful MSK disorders in the lower back and lower extremity, focusing on its pathogenic role as a pain generator as well as practical diagnosis and management.

Distribution, Physiologic Changes and Mechanical Properties of Adipose Tissue

AT is largely located in subcutaneous regions, followed by visceral regions. Ectopic areas of deposition include bone marrow and the retro-orbital, intramuscular, intermuscular and periarticular regions.[7] With aging, there is global redistribution of AT from subcutaneous to truncal/visceral regions.[8] Local redistribution also occurs, as seen in AT on the plantar aspect of the heel and metatarsophalangeal joints.[9] In addition, aging AT cells undergo cellular senescence, a process that promotes AT dysfunction through dysregulation of extracellular remodeling, inflammation and pathologic angiogenesis.[10]

AT is a highly expandable connective tissue comprised of adipocytes (lipid-filled cells) enclosed within collagen-based structures (basement membrane and interlobular septa) and smaller numbers of fibroblasts.[11] It protects the underlying MSK structures, contributes to mechanical stability and resists shear strain.[12] Nonetheless, the mechanical integrity of AT varies between individuals and over an individual's lifespan. For example, the stiffness and thickness of heel AT was found to be higher in overweight and obese individuals as compared to normal-weight individuals.[12] This discovery is partly explained by increased fibrosis, a process that limits the ability of adipocytes to expand.[13] Increased stiffness can also reflect a degenerative process, as repetitive microtrauma reduces water content and elastic fibrous tissues.[13-15] Furthermore, septal hypertrophy and fragmented elastic fibers in heel AT occurs with aging.[12] These changes can negatively impact the mechanical properties of AT and consequently its functions in shock absorption and resistance to compressive and sheer forces of gait.[12]

Adipose Tissue as an Intrinsic and Extrinsic Pain Generator

Pain-related to AT falls into two categories: 1) Intrinsic: pain originating directly from/within AT and 2) Extrinsic: pain related to the interaction of AT with surrounding structures. Mixed processes are not uncommon.

Intrinsic Pain Generation

Dye et al. described pain perception of different intraarticular structures in a conscious individual by arthroscopic probing and found the infrapatellar fat pad to be both highly localized and sensitive compared to neighboring structures.[16] In an alternative study, similar noxious responses were induced by injecting hypertonic saline (5%) into the infrapatellar fat pad.[17] Such findings underscore the rich nociceptive innervation of fat pads by substance-P and calcitonin gene-related peptide nerve fibers and lend credibility to pain originating directly from AT.[18] Moreover, AT is metabolically active and produces proinflammatory adipokines such as tumor necrosis factor-alpha, leptin, vaspin, chemerin and interleukin-6.[3,19,20] As an example, pain syndromes due to inflamed fat pads are well described in patients with HIV. These pain syndromes include retrocalcaneal pain from isolated inflammation of Kager's fat pad and nonspecific anterior knee pain related to inflammation of the infrapatellar fat pad.[21] AT torsion resulting in inflammation and/or ischemic necrosis is amongst other proposed mechanisms of AT-based pain.[22]

Extrinsic Pain Generation

Painful MSK conditions can be related to the interaction of AT with surrounding structures, i.e., extrinsic pain generator. Lipomas, for example, are AT masses that can arise from any location where fat is normally present. Local pain in lipomas can result from irritation of a fascial layer or other neighboring structures, such as bursa and nerve.[23] If nerve irritation occurs, distant pain (either radiating or referred) can be experienced.[24] The pain characteristics and presentation of painful fat pads/symptomatic lipoma will vary based on the body region and surrounding structures. (**Table 1**) As another example, increased adiposity can cause tendinopathy due to direct mechanical loading and biochemical alterations caused by systemic dysmetabolic factors.[25] Rich neovascularization and sensory innervation of AT surrounding tendons may also play a role in chronic tendon pain.[26] In addition, there is evidence that AT can contribute to the development of osteoarthritis via adipokines, such as leptin, visfatin and resistin.[19] Other processes, such as the loss of the AT structural integrity, can contribute to pain generation. This loss is observed in plantar fat pad atrophy.[27]

Mechanisms and Biomechanics of Musculoskeletal Pain Generation: Regional Approach

Lower Back and Buttock

Episacroiliac subcutaneous lipomas, or "back mice," are subfascial fat herniations that may be encountered in patients with nonspecific low back pain.[4] These lipomas are often bilateral and located near the sacroiliac "dimple," posterior iliac crest and lumbar paraspinal area. (**Figure 1**) There appears to be a female predilection. Subfascial herniation to the myofascial layer makes symptomatic lipoma difficult to distinguish from myofascial pain syndrome. A discrete, large and painful palpable nodule favors lipoma herniation rather than a myofascial trigger point.[23]

Table 1. Classification of painful adipose tissue/fat pad disorders affecting lower back and lower extremity

Location	Common pathologies	Characteristics and suggested mechanisms of pain
Systemic Adipose Tissue Disorders		
General	Lipodystrophy (congenital and acquired)	Chronic pain with neuropathic pain most common, followed by arthralgia, muscle pain Common chronic peripheral neuropathy
Partial	Lipedema	Pain and tenderness in the bilateral lower extremities, skin hypersensitivity, neural tissue compression within the septa surrounding fat lobules
	Partial lipodystrophy (acquired)	Hoffa's fat pad with anterior (infrapatellar) knee pain and Kager's fat pad with posterior heel pain, anterior to the Achilles tendon in patients with HIV infection
	Adiposis dolorosa (Dercum's disease)	Painful subcutaneous adipose tissues involving extremities, torso and even face
Adipose Tissue Pain Generation by Body Region		
Lower back and buttock	Subcutaneous painful fat pad	Episacroiliac subcutaneous lipomas, "back mice", irritating myofascia, fascial herniation and torsion of fat pad, commonly in the episacral region, often bilateral Can cause neuropathic pain by irritation of cluneal nerves
	Spinal lipoma	Lipomyelomeningocele (fatty mass in conus medullaris), lipoma of the terminal filum causing tethered cord/root syndrome Spinal epidural lipomatosis (primary and secondary) with lumbosacral radiculopathy
Hip and thigh	Painful fat pad	Femoral fat pad entrapment with femoroacetabular impingement, anterior inferior iliac spine fat pad causing adhesion of joint capsule and gluteal muscle
	Lipoma	Deep large intramuscular lipoma with thigh pain
Knee	Painful fat pad	Hoffa's infrapatellar fat pad impingement, suprapatellar, prefemoral fat pad impingement syndrome (hyperextension of knee) with anterior knee pain
	Lipoma arborescens	Involving suprapatellar recess
Ankel and foot	Lipoma	Retrocalcaneal bursitis
	Painful fat pad	Insertional Achilles tendinopathy
	Fat pad atrophy and migration	Nociceptive pain on the heel (plantar aspect) and forefoot (metatarsalgia)
	Piezogenic pedal papules	Subcutaneous fat herniation in the heel, especially in weight bearing

Lipomas of the spinal cord are rare tumors often associated with occult spinal dysraphism.[24] Spinal lipomas are more commonly located in the conus medullaris and called lipomyelomeningocele. Lipomyelomeningocele is characterized by a subcutaneous fibrofatty mass, lamina defect, compressive myelopathy and tethered cord syndrome.[28] It can present with progressive neurological deficit in the lower extremities with the loss of bladder function.[24] Lipoma of the terminal filum is another common cause of tethered cord syndrome with lower back pain as the first presenting symptom.[29] Spinal epidural lipomatosis is extremely uncommon and can be found incidentally or present symptomatically as radiculopathy, neurogenic claudication and

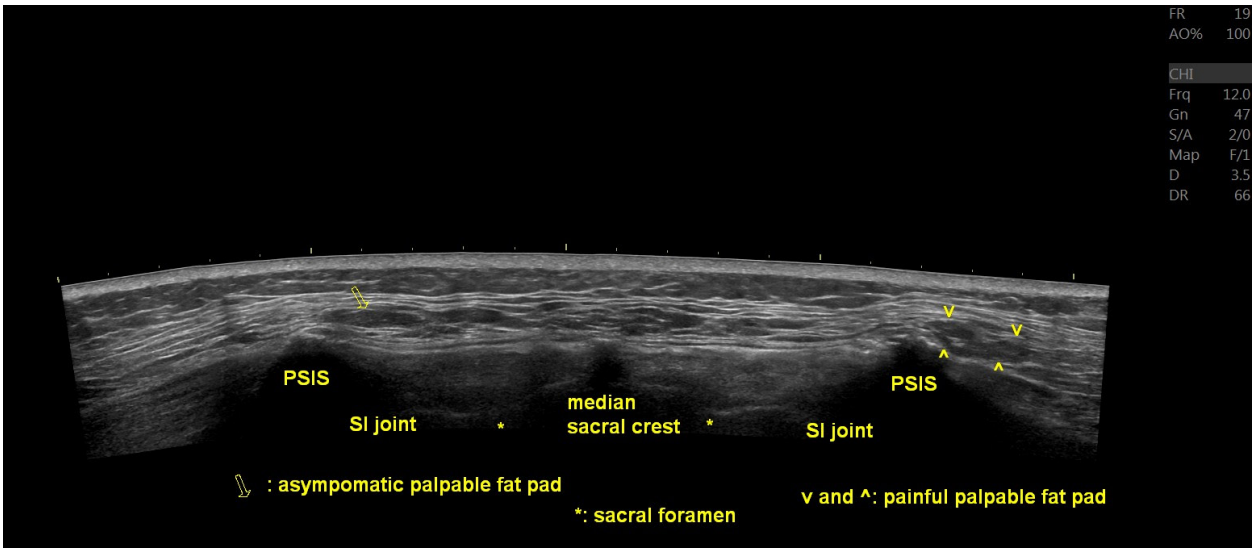

Figure 1. Ultrasonographic figure of multiple fat pads on the lumbosacral region in a patient with chronic low back pain.

myelopathy.[30] It has been associated with exogenous steroid use (epidural or chronic systemic steroids), endogenous hypercortisolism (Cushing's syndrome), hypothyroidism, hyperprolactinemia and protease inhibitors in patients with HIV.[31] Spinal epidural lipomatosis is most often localized to the thoracic spine followed by lumbosacral spine.[30,32]

Hip and Thigh

Femoral fat pads were recently recognized as a source of pain in femoroacetabular impingement syndrome, with fat pad entrapment occurring between the femoral head-neck junction and labrum. In patients with cam-type femoroacetabular impingement, Jayasekera et al. observed similar clinical outcomes with arthroscopic resection of the femoral fat pads in the anterior head-neck junction with or without creating a spherical femoral head.[33] In addition, anterior inferior iliac spine fat pads have been implicated in anterior groin pain as a consequence of inflammation, fibrosis, scar and adhesion (between the joint capsule, rectus femoris and gluteus muscles).[34]

Most lipomas in the thigh are asymptomatic but can be painful when situated deep (under the enclosing fascia, in the intramuscular and intermuscular layers) or if they are large (usually due to the expansion of soft tissue or compression of the peripheral nerve).[35,36]

Knee

Infrapatellar or Hoffa's fat pad impingement syndrome is a well-known cause of anterior knee pain that occurs at either the infrapatellar or peri-patellar region during knee hyperextension. Hoffa's fat pad can be impinged by any combination of neighboring structures, including the patella and patellar tendon anteriorly, femoral condyle posteriorly and proximal tibia caudally.[37] (**Figure 2**) A minor injury to Hoffa's fat pad, including hyperextension with or without twisting and a direct trauma, can cause swelling, inflammation, fibrosis and scarring that contributes to the altered biomechanics and increased pain perception.[37] Anterior knee pain can also result from anterior suprapatellar fat pad impingement. This triangular-shaped fat pad is located on the superior edge of the patella (underneath the quadriceps tendon, anterior/superficial to the suprapatellar recess).[38,39] Impingement occurs during maximal knee flexion. Lastly, the prefemoral fat pad, located proximal to the femoral trochlea, can be impinged between the patella and anterolateral surface of the distal femur during flexion and extension of the knee.[40,41]

Lipoma arborescens is a benign, "tree-like" AT lesion characterized by the replacement of subsynovial connective tissue with AT and synovial villous proliferation. This replacement can result in intermittent painful swelling of the knee joint, typically involving the suprapa-

tellar bursa.[42] Other reported locations include the hip and ankle joints. It is more common in males between the 5th and 6th decades of life and is associated with osteoarthritis and inflammatory arthropathy.[43]

Ankle and Foot

Kager's fat pad is bordered by the Achilles tendon, retrocalcaneal bursa and flexor hallucis longus tendon in the posterior ankle.[44] (**Figure 2**) It reduces tendon kinking and minimizes pressure on the bursa.[45] Patients with Kager's fat pad impingement can present with a painful bulging mass at the retrocalcaneal space of the posterior ankle. Symptoms are exacerbated by ankle plantarflexion with a knee hyperextension (recurvatum) momentum in a closed kinetic chain movement. Pathologies of the neighboring structures and lipodystrophy (LD) of the fat pad can also contribute to impingement.[21]

A lipoma beneath the flexor retinaculum of the tarsal tunnel can cause tarsal tunnel syndrome. It manifests with pain behind the medial malleolus that radiates to the plantar aspect of the foot.[46,47]

Fat pad atrophy and migration occurs in the sole of an aging foot at the superficial to medial calcaneal tuberosity[48] and under the metatarsal heads. It is often associated with plantar heel pain, metatarsalgia and metatarsal subluxation. In addition to normal age-related changes, fat pad atrophy can occur as a consequence of steroid injections.[49,50]

Piezogenic pedal papules are herniations of the subcutaneous fat into the plantar fascia retinaculum. They are common incidental findings in weight-bearing areas of the foot, particularly the plantar heel fat pad.[51] The papules may only be visible in full weight-bearing. Although a

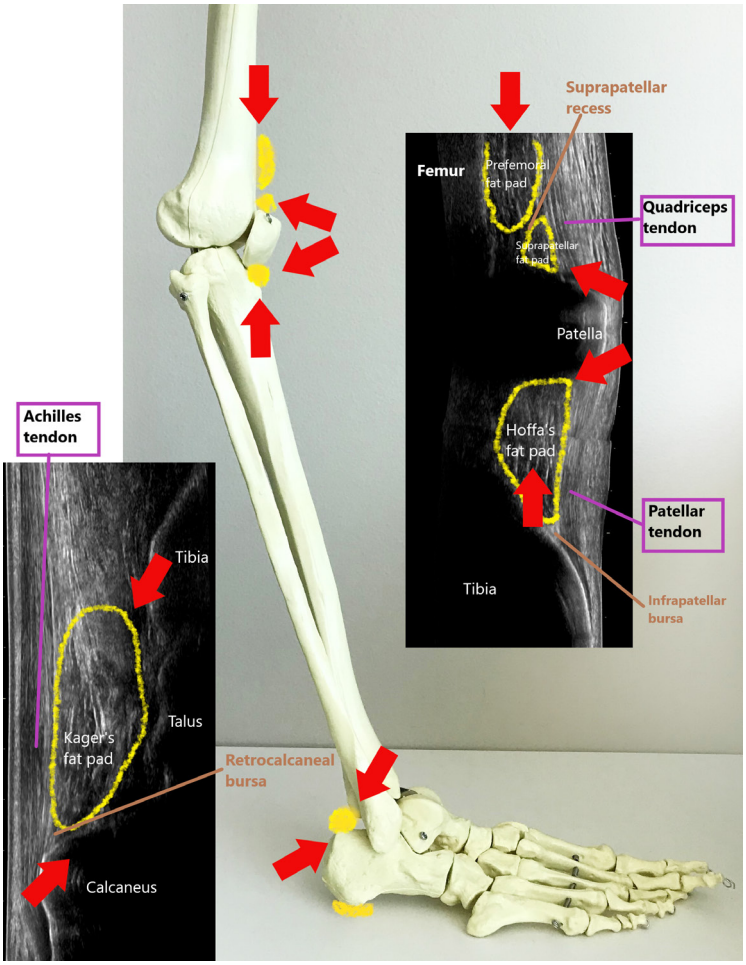

Figure 2. Ultrasonographic figures of fat pads (yellow colored line) in the anterior knee (right upper corner) and the posterior ankle (left lower corner). Red arrows indicate proposed impingement mechanisms of these fat pads.

majority of lesions are asymptomatic, papules may be discretely tender on palpation. Irritation of local nerves and blood vessels by repetitive trauma can contribute to pain.[52]

Systemic Adipose Disorders

Although painful MSK conditions related to focal AT are the main focus of this paper, systemic adipose disorders, in particular lipedema and lipodystrophy (LD), may likewise cause lower back and lower extremity pain and, therefore, will be briefly reviewed.

LD is a heterogeneous group of disorders characterized by abnormal distribution of AT, including AT loss or hypertrophy.[53,54] LD can be classified into primary (idiopathic or familial) versus secondary depending on the underlying etiology (HIV, panniculitis, autoimmune, medication, trauma), or general versus partial depending on the extent of involvement.[55-57] More than 70% of patients with LD suffer from chronic pain, most commonly neuropathic pain, followed by arthralgia and muscle pain amongst others. Peripheral sensory-motor neuropathy is found in more than 60% of patients with LD and diabetes.[58] Underlying mechanisms for peripheral neuropathy in LD are not entirely clear but likely include a combination of metabolic dysfunction and a failure of the shock-absorbing function of peripheral nerves. Specifically, loss of epineural fat components is thought to contribute to chronic trauma, inflammation/pressure palsies and denervation.[58-61] Muscle pain is common in congenital LD, but readily apparent myopathy is not common in LD other than a late complication of juvenile dermatomyositis.[58]

Lipedema, a type of LD, is characterized by abnormal deposition of subcutaneous AT, frequently involving the lower extremities symmetrically.[62-64] There is a demographic predilection for females of a younger age and commonly a family history.[62] A typical patient complaint is pressure,-mediated leg pain and tenderness. These symptoms may be a consequence of neural compression within the septa surrounding fat lobules. Other potential mechanisms include hypersensitivity, mechanical friction and skin irritation.[62] As the hypertrophy extends from hips to ankles, lipedema may be misdiagnosed as lymphedema.[62] In comparison, lymphedema is typically painless and involves the foot, whereas lipedema commonly spares the foot with a step-off (cuff sign) at the ankle.[65] The absence of pain and edema can differentiate lipohypertrophy from lipedema.[64] Adiposis dolorosa, also known as Dercum's disease, shares similar clinical features with lipedema, such as painful subcutaneous AT and a predominance in females between the ages of 35–50 years.[66,67] Fat involvement of the torso in early stages of the disease, greater pain severity and comorbidities such as fibromyalgia and metabolic disease distinguishes adiposis dolorosa from lipedema.[68,69]

Evaluation with Imaging Modalities

A majority of MSK disorders related to AT are clinically diagnosed. Imaging modalities are helpful to confirm the clinical diagnosis, evaluate differential diagnoses and aid in the identification of indiscrete masses in patients with larger body habitus. With the increasing availability of ultrasonography (US) in outpatient clinics, lipomas can be easily visualized in-office (**Figure 1**). Typical findings include a partially or well-encapsulated mobile mass with similar echogenicity to the neighboring fat (hypoechoic or isoechoic depending on the heterogenicity of AT and water components) and absence of acoustic shadowing.[70,71] Differential diagnoses for subcutaneous AT masses include epidermal cyst, ganglion cyst and malignant neoplasm. Epidermal cysts are isoechogenic, which is similar to subcutaneous lipomas. However, post-acoustic enhancement and lateral shadowing are differentiating characteristics. Ganglion cysts typically demonstrate anechogenicity within the cyst, with protrusion towards a neighboring joint.[72] US imaging of soft tissue malignant neoplasms, most commonly pleomorphic sarcoma and liposarcoma, can mimic a lipoma. However, they typically demonstrate larger size (≥ 5 cm), are intramuscular, have an infiltrative border, grow rapidly and violate tissue planes.[71] Differential diagnoses for deep-lying lipomas in US evaluation are extensive and vary depending on mass location. These differential diagnoses may include congenital cysts, ganglion cyst, heterotopic ossification, hemangiomas, angiolipoma, hematoma, lymph nodes, normal muscle/muscle herniation and malignant tumors, amongst others.[36,73] Sonoelastography provides information on intrinsic tissue

properties. This information aides in the delineation of malignant tumors, which are generally stiffer than benign masses.[74,75] Any suspicion for malignant neoplasm requires further imaging studies and the definite diagnosis with histopathologic and molecular examination.

MRI is useful when US assessment is difficult. Examples include deeper, intraarticular or intracortical lesions.[76] On both T1 and T2 weighted images, lipomas demonstrate high signal intensity, while fat-suppression sequences show decreased signal intensity.[36] Increased lipoma signal intensity on fat-suppression sequences may indicate edema/fluid, necrosis or mass heterogeneity (as seen in an atypical tumor or liposarcoma).[77] An MRI can also evaluate neighboring structures such as ganglion cyst, plica, synovium, ligament, meniscus, bony/tendon edema or any neoplastic lesions.[37] A CT can similarly be utilized to evaluate lipomas, which would appear as a hypodense mass with attenuation similar to fat tissue. A CT can be particularly useful to delineate subtle ossification/calcification and associated cortical bony lesions.[78] An x-ray is limited in the evaluation of soft tissue lesions (lipoma) in general but serves utility in the identification of intraosseous lipomas mimicking other diseases such as fibrous dysplasia, aneurysmal bone cysts, simple cysts, bone infarcts and chondral tumors.[79]

Clinicians should be aware of the limitation of imaging modalities, including inconsistent relationships between the imaging findings and the local pain.[80]

Management

The first step for the successful management of symptomatic AT is to recognize AT as a pain generator and investigate the underlying mechanisms for the pain. This review primarily focuses on the management of focal AT-related painful MSK disorders; LD will be briefly covered.

Local, non-pharmacological interventions that may improve AT-related disorders in the lower back and lower extremities include orthotics, taping and modification of daily activity. For fat pad atrophy and migration in the foot, heel cups (rubber or felt pad) and low dye taping can be tried for heel pain and a metatarsal pad for metatarsalgia.[81] Repeat steroid injections through the plantar fat (during plantar fascia and intermetatarsal bursa/neuroma injections) should be avoided to prevent atrophy. Ethanol-based nerve fiber ablation has been previously attempted to mitigate pain associated with AT. However, caution is required as AT scarring and denaturing can occur. Biomechanical evaluation and avoiding faulty training (with repetitive trauma) should be considered a means to alleviate pain and prevent progression and recurrence. Symptomatic Hoffa's fat pad impingement with pes cavus may respond to heel lift placement by mitigating knee extension moments known to aggravate symptoms.[82] Placing a pillow under the knee avoids full knee extension, relieving pain associated with sleeping in the supine position.

Weight loss should also be emphasized to decrease metabolic dysfunction and the biomechanical disadvantages associated with increased weight. Weight loss has favorable impacts on pain and biomechanics of the lower extremity, including decreased foot plantar loading pressure, increased ankle plantarflexion, knee joint motion (maximal knee flexion), compressive force and peak moments around the hip and knee.[83-85] However, evidence reflecting the impact of weight loss in AT-related painful MSK disorders is scarce and unclear. Okifuji and Hare suggested obesity may not impact pain response in the absence of inflammation or nerve injury, though obesity can potentiate inflammatory response.[86] Dodet et al.[87] and Zahorska-Markiewicz et al.[88] reported higher pain thresholds among the obese population compared to the nonobese population. Although the exact mechanisms were not clear, ghrelin and galanin were suggested for modulation of the obesity-induced change in pain threshold.[89,90] Regardless of the direct impact of obesity and weight loss on AT-related pain, aerobic endurance exercise is important to decrease complications related to chronic MSK pain and to improve metabolic dysfunction.[91]

Surgical options can be considered in patients who fail conservative treatment and have disabling pain. Potential interventions include fat pad resection in impingement syndrome. These interventions include intraarticular or extraarticular fat pad resection in anterior groin pain, Hoffa's fat pad resection in anterior knee pain and Kager's fat pad resection in retrocalcaneal

heel pain.[34,92,93] Scarring of the surgical site and the impact of regional stability can be challenging postoperatively. Alternatively, US guided scraping of vascularized fat pads can relieve pain from neighboring chronic tendinopathy.[26] A few studies highlight the non-cosmetic implantation of fat for fat pad atrophy, such as fat grafting for metatarsalgia and chronic heel pain.[27,94,95]

As it pertains to LD, management should focus on symptomatic manifestations and metabolic syndrome. Recombinant human leptin (metreleptin) is considered for generalized LD, with low serum leptin levels to improve metabolic syndrome and weight loss.[96,97] In secondary LD, recognizing and managing the underlying etiology is useful for successful treatment.[98]

Conclusion

AT should be recognized as one of the pain generators in painful musculoskeletal disorders. Therapeutic strategies for adipose tissue-related pain disorders could be better guided by understanding the mechanism by which AT-related pain is occurring.

Conflicts of Interest

The authors declare they have no conflicts of interest.

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