·REVIEWS· ·综 述·

Cellular and molecular mechanisms of fatty infiltration in paraspinal muscles in spine-specific sarcopenia

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ABSTRACT Spine-specific sarcopenia has recently been recognized as a localized degenerative disorder distinct from systemic sarcopenia. Its main symptom is selective degeneration of paraspinal muscles and is closely associated with various spinal disorders and postoperative prognosis. One of the core features of this condition is fatty infiltration (FI), which more accurately reflects muscle quality and functional impairment than muscle cross-sectional area (CSA). FI is closely associated with paraspinal muscle atrophy and is regulated by multiple interrelated mechanisms, including pathological activation of fibro-adipogenic progenitors (FAP), denervation-induced loss of trophic support, biomechanical alterations, and abnormal adipokine signaling pathways. At present, diagnostic indicators used for systemic sarcopenia show limited validity in the assessment of paraspinal muscles, highlighting the urgent need to establish an evaluation framework for spine-specific sarcopenia. By reviewing the major mechanisms underlying fatty infiltration of the paraspinal muscles and summarizing recent advances in imaging assessment of spine-specific sarcopenia, this article provides a basis for improving comprehensive evaluation of paraspinal muscle degeneration in both clinical and research settings.

KEY WORDS spine-specific sarcopenia; paraspinal muscle degeneration; fatty infiltration; fibro-adipogenic progenitors; imaging assessment

脊柱特异性肌少症椎旁肌脂肪浸润的细胞分子机制

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[摘 要] 脊柱特异性肌少症近年来被认为是1种不同于系统性肌少症的局部退行性病变，其主要表现为椎旁肌的选择性退变，并与多种脊柱疾病及其预后密切相关。该病的核心特征之一是脂肪浸润，其较肌肉横截面积更能准确反映肌肉质量与功能损害情况。脂肪浸润与椎旁肌萎缩密切相关，并受多种相互关联的机制调控，包括成纤维-脂肪祖细胞的病理性活化、去神经导致的营养支持缺失、生物力学改变以及异常的脂肪因子信号转导等。目前用于系统性肌少症的诊断指标在椎旁肌评估中效度较差，亟需构建脊柱特异性肌少症的评估框架。通过综述当前关于椎旁肌脂肪浸润的主要机制，总结脊柱特异性肌少症影像学评估的进展，可为提升临床及科研中对椎旁肌退变的综合评估提供依据。

[关键词] 脊柱特异性肌少症；椎旁肌退变；脂肪浸润；成纤维-脂肪祖细胞；影像学评估

With the rapid global aging of the population, age-related degenerative changes have attracted increasing attention[1]. Sarcopenia—characterized by progressive loss of skeletal muscle mass, strength, and physical performance—has become a major public health concern affecting the quality of life of older adults[2]. Although systemic sarcopenia has been widely studied, emerging evidence[3-4] indicates that whole-body muscle mass does not accurately reflect the degenerative status of paraspinal musculature. Many patients with normal appendicular muscle mass demonstrate marked degeneration of the multifidus muscles (MF) or erector spinae (ES)[5], suggesting that paraspinal muscle atrophy represents a unique, localized pathological entity.

In 2019, Kim, et al[6] introduced the concept of spine-specific sarcopenia, highlighting the independent and clinically meaningful role of paraspinal muscle degeneration in the onset, progression, and postoperative outcomes of spinal disorders. Although consensus diagnostic criteria are yet to be established, mounting evidence from imaging studies, basic research, and clinical investigations supports the validity of this concept. Compared with systemic sarcopenia, spine-specific sarcopenia shows superior sensitivity and specificity in predicting spinal degeneration severity, postoperative recovery, and spine-related functional outcomes[3].

Spinal degeneration is no longer considered a process driven solely by intervertebral disc, facet joint, or ligamentous changes. Degeneration of the paraspinal muscles—manifested primarily as muscle atrophy and fatty infiltration (FI)—is increasingly recognized as a critical component of spine degenerative disorders[7-9]. Structural remodeling of the paraspinal muscles, including FI, asymmetry, and volume reduction, has been consistently observed in lumbar degenerative disorders (LDD)[7, 10-11]. FI, in particular, is a key imaging biomarker of muscle quality, reflecting the severity of local degenerative changes, and contributing to altered biomechanics, inflammatory microenvironmental shifts, and accelerated spinal degeneration[10]. Given the rising prevalence of lumbar degenerative diseases, a deeper understanding of the mechanisms and evaluation strategies related to FI within the framework of spine-specific sarcopenia is urgently needed.

Therefore, this review aims to elucidate the key cellular and molecular mechanisms underlying paraspinal muscle FI in spine-specific sarcopenia, focusing on activation of fibro-adipogenic progenitors (FAPs), denervation, biomechanical alterations, and adipokine dysregulation. It also seeks to evaluate current imaging-based assessment methods and explore the relationship between FI and clinical outcomes, including functional impairment and postoperative recovery.

1 FI as the structural basis of spine-specific sarcopenia

The paraspinal muscles—including the MF, ES, psoas major, and quadratus lumborum—play essential roles in spinal stability and sagittal and coronal alignment[12-13]. The MF provides segmental stabilization, whereas the ES primarily contributes to global postural control. Despite their anatomical proximity, these muscles differ substantially in innervation, architecture, and biomechanical function, leading to distinct degenerative patterns. Deep muscles such as the MF undergo more rapid degeneration and are strongly associated with postoperative dysfunction, increased complication rates, and poor clinical prognosis[13-17].

With advancing age, paraspinal muscles undergo

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structural changes characterized by loss of contractile fibers, decreased muscle density, and progressive lipid infiltration within and between fascicles[18]. Severe MF FI—often defined as >50% on magnetic resonance imaging (MRI)—is increasingly used as an imaging criterion for spine-specific sarcopenia[3]. Higher FI levels correlate with greater symptom severity, impaired functional status, and suboptimal postoperative recovery. FI not only diminishes contractile capacity and metabolic activity but also profoundly alters the local inflammatory and biomechanical environment, contributing to progressive spinal dysfunction.

The process of FI in paraspinal muscles is driven by a combination of factors. Aging, pathological conditions, and muscle injury have all been shown to promote lipid accumulation within skeletal muscles. This process is tightly regulated by a network of molecular factors, genetic determinants, and signaling pathways, which together orchestrate the progression of FI and contribute to the structural and functional decline of the paraspinal musculature[19-20].

2 Mechanisms underlying paraspinal muscle FI

2.1 Pathological activation of FAPs

FAPs are resident mesenchymal stromal cells within skeletal muscle and are widely regarded as the principal cellular source of intramuscular adipose deposition[21-22]. Under homeostatic conditions, FAPs support muscle maintenance and regeneration by secreting paracrine factors that regulate the activation, proliferation, and differentiation of muscle stem cells (MuSCs). Notably, FAPs exhibit a dual functional nature: while essential for orchestrating effective myogenesis, aberrant or prolonged activation drives their pathological differentiation into adipocytes, thereby promoting the accumulation of intramuscular adipose tissues (IMAT) and contributing to fibro-fatty muscle degeneration[22].

Aging imposes profound alterations on FAPs biology. A study[23] demonstrates that aging diminishes the ability of FAPs to facilitate MuSCs-mediated myogenesis and reshapes their proliferative dynamics and lineage commitment. Compared with young muscle, aged muscle contains fewer FAPs, and these cells exhibit delayed activation and expansion following injury[23]. Despite this numerical decline, aged FAPs possess an intrinsically heightened adipogenic potential, forming a key cellular mechanism underlying age-associated IMAT accumulation[22, 24].

Adipogenic commitment of FAPs is tightly regulated by cues from the local microenvironment. Among these regulators, fibroblast growth factor-2 (FGF2)—secreted by FAPs, MuSCs, and myofibers—plays an age-dependent and dualistic role in skeletal muscle homeostasis. FGF2 is a critical growth factor within the adult MuSC niche, and its abundance increases in aging muscle[24-25]. While FGF2 promotes muscle growth and regeneration, accumulating evidence[24, 26] indicates that it concurrently drives the formation of IMAT, an effect that becomes more pronounced with advancing age. Mechanistically, researchers have identified an FGF2-Fos-related antigen 1 (FRA-1)-miR-29a-secreted protein acidic and rich in cysteine (SPARC) signaling axis as a central regulator of FAPs adipogenic fate. FGF2 activates the FGFR-mitogen-activated protein kinase 1/2 (MEK1/2)-extracellular signal-regulated kinase 1/2 (ERK1/2) cascade, resulting in upregulation of the transcription factor FRA-1. Elevated FRA-1 suppresses miR-29a expression, leading to increased expression and secretion of its downstream target, SPARC—a matricellular glycoprotein whose levels typically decline during aging[24]. Increased SPARC promotes the adipogenic differentiation of FAPs by functioning as a molecular “decoy” for c-Fos, preventing c-Fos/c-Jun heterodimerization, reducing activator protein-1 (AP-1) transcriptional activity, and ultimately downregulating adipogenic genes such as peroxisome proliferator-activated receptor gamma (PPARγ) [26]. Through this pathway, age-related increases in FGF2 signaling shift FAPs toward an adipogenic phenotype, thereby accelerating IMAT accumulation and contributing to muscle quality decline.

Pathological conditions further amplify the adipogenic bias of FAPs. In aged mdx mice, a model of muscular dystrophy, although the absolute number of FAPs is reduced, the proportion expressing the key adipogenic regulator PPARγ is markedly increased. This shift indicates that chronic disease or aging-associated

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microenvironments reprogram FAPs populations toward adipogenesis, ultimately accelerating muscle FI and functional decline[27].

2.2 Neurogenic degeneration

FI of the paraspinal muscles exhibits a distinct neurogenic pattern, closely linked to the anatomical organization of their innervation. The MF, the largest and most medially located deep paraspinal muscle, originates from the sacrum and ilium and inserts onto the lumbar spinous processes and laminae. Each MF fascicle is innervated in a strictly segmental fashion by the medial branch of the dorsal ramus, receiving motor input exclusively from a single spinal segment[28]. This highly segmental innervation renders the MF particularly vulnerable to mechanical compression or injury of the corresponding segmental nerve. A clinical imaging study[29] demonstrates that MF FI displays a segmental pattern in patients with degenerative lumbar scoliosis (DLS) and degenerative lumbar kyphosis (DLK), with the most pronounced changes observed in the lower lumbar levels.

In contrast, the ES, comprising the longissimus and iliocostalis muscles, receives its innervation from the lateral branches of the dorsal rami, which form an interconnected, multi-segmental lattice of collateral branches[30]. Consequently, when neural compromise occurs, degenerative changes in the ES are less restricted to a single spinal level and instead manifest as diffuse, multisegmental FI. This distribution pattern has been consistently observed in an imaging study[29] of patients with DLK. These anatomical differences in innervation between MF and ES provide a mechanistic explanation for their distinct spatial patterns of fatty degeneration and the heterogeneity commonly seen in clinical practice.

Compression of the spinal nerves—such as from disc herniation, ligamentum flavum hypertrophy, facet joint osteoarthritis, or spinal canal stenosis—can directly impair the dorsal rami and induce denervation atrophy. Following nerve injury or loss of neural input, the number and adipogenic/fibrogenic differentiation potential of FAPs increase markedly within the affected muscle[31]. Normally, neural innervation through the neuromuscular junction (NMJ) and sensory organs suppresses the expression of glial cell-derived neurotrophic factor (GDNF) in muscle[32]. In a rat tibial nerve transection model, GDNF levels in skeletal muscle remain persistently elevated after denervation[31]. An in vitro study[31] further demonstrates that exogenous GDNF induces adipogenic differentiation of healthy FAPs in a dose-dependent manner. This neurotrophic factor-mediated shift promotes excessive deposition of IMAT, ultimately accelerating structural degeneration and functional decline of the paraspinal muscles[31-33].

Neurogenic atrophy is further characterized by molecular changes that favor adipogenesis[34]. In denervation conditions such as amyotrophic lateral sclerosis, the expression of the Wnt antagonist frizzled-related protein (FRZB) is markedly upregulated in muscle tissue[34]. FRZB inhibits the Wnt signaling pathway by preventing ligand-receptor interactions and blocking β-catenin nuclear translocation[34] . Given that Wnt/β-catenin signaling is a well-established inhibitor of adipogenic differentiation in FAPs—where activated β-catenin suppresses PPARγ expression and restricts the commitment of FAPs to the adipocyte lineage—its inhibition directly facilitates fat accumulation[35]. Consistently, in a rat tibial nerve transection model, denervated soleus muscle exhibited increased numbers of FAPs with enhanced adipogenic and fibrogenic differentiation potential[31].

2.3 Altered mechanical loading and biomechanical imbalance

Alterations in mechanical loading and global spinal biomechanics represent key drivers of FI and structural degeneration in the paraspinal muscles. The MF and ES exhibit distinct biomechanical roles: MF functions primarily as a segmental stabilizer, whereas ES contributes to maintaining global sagittal alignment. Consistent with these roles, the relative cross-sectional area (rCSA) of MF correlates strongly with global sagittal parameters—such as sagittal vertical axis (SVA), thoracic kyphosis (TK), lumbar lordosis (LL), and thoracolumbar kyphosis (TLK) —whereas ES rCSA correlates more closely with pelvic parameters including pelvic incidence (PI) and sacral slope (SS) [29]. These findings indicate that MF and ES respond differently to spinal degeneration due to their unique mechanical demands.

In patients with DLS, the MF frequently exhibits

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segmental atrophy, whereas the ES may show compensatory hypertrophy in some cases, likely reflecting the increased mechanical demand required to preserve postural balance[36-37]. Under normal physiological conditions, the cross-sectional area (CSA) of the MF increases progressively from the cranial to caudal levels, consistent with greater physiological loading in the lower lumbar spine[38-39]. However, when intervertebral discs and facet joints degenerate, passive spinal stability is compromised, forcing the MF and other deep stabilizers to increase their contractile activity. Chronic overload predisposes these muscles to fatigue and microinjury[14], which in turn triggers a state of chronic low-grade inflammation. Mechanistically, chronic inflammation drives FI primarily through its direct effects on FAPs[31]. Activation of the transforming growth factor (TGF)-β signaling pathway under inflammatory conditions promotes the differentiation of FAPs toward fibrogenic and adipogenic lineages[40]. Inflammation suppresses Wnt/β-catenin signaling, a pathway that ordinarily inhibits adipogenesis of FAPs by restricting their commitment to the adipocyte lineage; its downregulation therefore enhances the adipogenic potential of FAPs. Chronic inflammation impairs Notch signaling, which in healthy muscle maintains quiescence of FAPs and suppresses adipogenic differentiation[41]. Collectively, these inflammation-induced alterations in behavior of FAPs accelerate MF degeneration and FI.

A clinical imaging study[42] supports this load-related degeneration. FI of the lumbar paraspinal muscles is more severe in the lower lumbar region (L_4 to S_1) than in the upper lumbar region (L_2 to L_4). In patients with DLS, FI of MF is significantly more pronounced than in patients with other lumbar degenerative conditions and is particularly severe on the concave side of the curve[43]. In contrast, ES degeneration tends to be diffuse rather than segment-specific, consistent with its multilevel mechanical role[44]. Additionally, FI of ES correlates positively with SVA deviation[44], suggesting that mechanical imbalance and compensatory loading are major contributors to its degenerative changes.

2.4 Adipokine imbalance and metabolic dysregulation

Sarcopenia and obesity often coexist in the elderly population, and this state is called sarcopenic obesity[45-46]. Lineage-tracing studies using platelet-derived growth factor receptor alpha-Cre estrogen receptor T2 (Pdgfrα-CreERT2)×Rosa26 reporter-enhanced yellow fluorescent protein (R26R-EYFP) mice have demonstrated that high-fat diet (HFD)-induced IMAT arises predominantly from FAP-derived adipocytes. In this metabolic context, skeletal muscle exhibits reduced myofiber CSA accompanied by transient accumulation of senescent FAPs. These senescent FAPs in HFD-fed mice show marked upregulation of PPARγ signaling and adipogenic genes, including perilipin 1 (PLIN1), fatty acid-binding protein 4 (Fabp4), and CD36[47], which is consistent with findings from others across different muscle injury and degenerative models[48-49]. Collectively, these observations suggest that HFD reshapes the muscle microenvironment toward a pro-adipogenic state, facilitating FAP-driven adipogenesis and exacerbating muscle atrophy.

During ectopic fat deposition within skeletal muscle, the expression of pro-adipogenic transcription factors—such as PPARγ and CCAAT/enhancer-binding protein alpha (C/EBPα) —is markedly elevated[50], further promoting adipocyte differentiation within the muscle tissues. Metabolic dysregulation associated with obesity or insulin resistance contributes to this process. When adipose tissue fails to adequately buffer circulating lipids, plasma free fatty acids (FFAs) rise, leading to excessive lipid uptake by skeletal muscle. This results in the accumulation of intramuscular triglycerides (IMTG) and harmful lipid intermediates, including diacylglycerol (DAG) and ceramides[51-52]. These metabolites activate protein kinase C (PKC) isoforms, which disrupt insulin signaling by impairing the insulin receptor substrate 1 (IRS-1)/phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway, thereby reducing glucose uptake and contributing to insulin resistance and muscle dysfunction[51, 53].

The PI3K/Akt axis is a key regulator of glucose transport, fatty acid metabolism, and cellular growth. Impairment of this pathway decreases fatty acid oxidation, exacerbates lipid accumulation, and further inhibits insulin signaling[54-55]. Together, these metabolic alterations create a feed-forward loop that accelerates muscle degeneration and promotes progressive FI. The pathological mechanisms and related signaling pathways of spine-specific sarcopenia are summarized in Figure 1.

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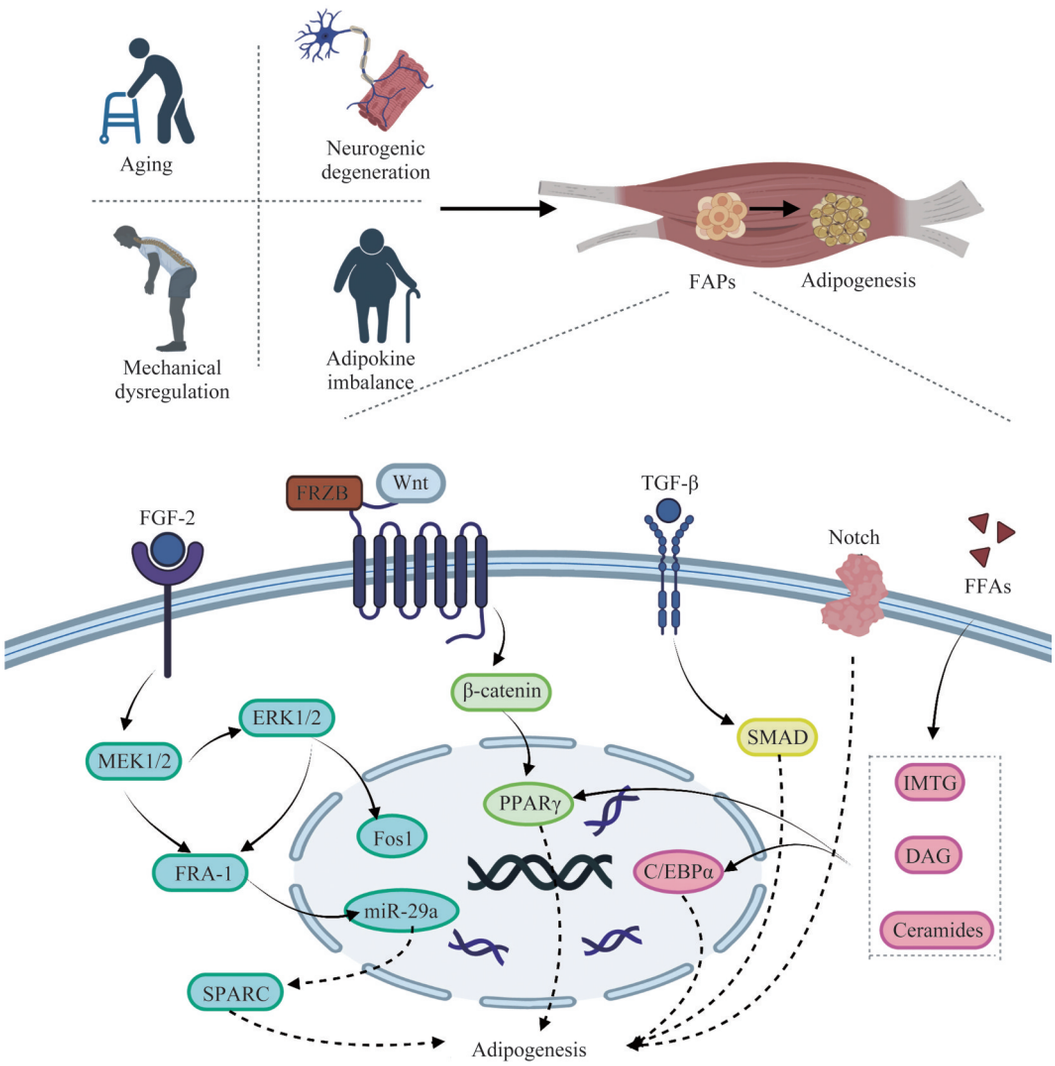


Figure 1 Pathological mechanisms and related signaling pathways regarding spinal-specific sarcopenia

FAPs: Fibro-adipogenic progenitors; FGF-2: Fibroblast growth factor-2; FRZB: Frizzled related protein; TGF-β: Transforming growth factor-beta; FFAs: Free fatty acids; MEK1/2: Mitogen-activated protein kinase 1/2; ERK1/2: Extracellular signal-regulated kinase 1/2; FRA-1: Fos-related antigen 1; SMAD: Sma- and Mad-related proteins; C/EBPα: CCAAT/enhancer-binding protein alpha; DAG: Diacylglycerol; IMTG: Intramyocellular triglycerides; PPARγ: Peroxisome proliferator-activated receptor gamma; SPARC: Secreted protein acidic and rich in cysteine.

3 Assessment strategies and future directions

Spine-specific sarcopenia currently lacks a globally accepted diagnostic framework, representing a major barrier to its clinical translation and standardization. Existing assessment strategies are largely extrapolated from consensus definitions of generalized sarcopenia, particularly those proposed by the Asian Working Group for Sarcopenia (AWGS) [56], and are complemented by imaging and function-based evaluations targeting the paraspinal musculature. According to the AWGS 2019 criteria[56], low muscle mass is defined as an appendicular skeletal muscle index (ASMI) <7.0 kg/m² for men and <5.4 kg/m² for women, while low muscle strength is defined as handgrip strength <28 kg for men and <18 kg for women. Despite their clinical utility, these approaches are limited in their ability to assess localized muscle alterations, particularly paraspinal muscle atrophy, FI, and intermuscular heterogeneity.

In contrast, computed tomography (CT) and MRI provide high-resolution cross-sectional imaging,

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enabling precise quantification of muscle volume, density, and fat content at specific anatomical levels. Quantitative imaging approaches based on CSA have become increasingly standardized and widely applied in recent years. CSA measurements at different lumbar levels (L_1 to L_5) have been shown to correlate with functional indicators such as handgrip strength and Short Physical Performance Battery scores, suggesting their value in assessing muscle function[38]. Notably, measurements at the L_1 level appear to demonstrate stronger correlations in male and sarcopenic populations[57], indicating potential anatomical variability.

The skeletal muscle index (SMI), defined as the total skeletal muscle area at the L_3 level normalized by height squared, has been widely adopted as a key diagnostic parameter[58-59], with commonly used cutoff values of <52.4 cm^2/m^2 for men and <38.5 cm^2/m^2 for women[60]. In addition, emerging indices such as the psoas muscle index (PMI) and gluteus maximus index (GMI)—defined as the CSA of the respective muscles normalized by height squared—have been proposed as predictors of sarcopenia risk in patients with lumbar degenerative diseases. Higher PMI and GMI values are generally associated with a lower risk of sarcopenia[61]. However, whether these indices accurately reflect paraspinal muscle degeneration remains to be fully elucidated.

Beyond muscle quantity, muscle quality, particularly FI, has gained increasing attention as a core feature of spine-specific sarcopenia. Growing evidence[62-63] suggests that FI may be more sensitive than muscle mass in reflecting functional decline. MRI-based quantification of FI in lumbar paraspinal muscles is increasingly utilized, with FI ≥50% commonly regarded as indicative of severe degeneration[3]. The Goutallier grading system, originally developed for rotator cuff assessment, has been widely adapted for evaluating paraspinal muscle FI. In this system, Grade 0 indicates no fat, Grade 1 minimal fatty streaks, Grade 2 fat less than muscle, Grade 3 equal amounts of fat and muscle, and Grade 4 fat greater than muscle; typically, Grade ≥2 is considered pathological[64]. Although this semi-quantitative method is easy to apply and demonstrates good interobserver reliability, it remains limited by subjectivity and lacks a spine-specific standardized classification. Given its relative accuracy and clinical relevance, the Goutallier grading system has been increasingly adopted as a practical tool for assessing paraspinal muscle quality and predicting clinical outcomes.

Accumulating evidence[17, 62] indicates that spine-specific sarcopenia is an important predictor of postoperative outcomes. It has been shown to be significantly associated with postoperative pain, physical function, and alterations in lumbar sagittal alignment parameters[65]. Therefore, incorporating muscle quality assessment into preoperative risk stratification and individualized surgical planning is of critical importance.

Overall, current assessment of spine-specific sarcopenia continues to face several key challenges, including the lack of standardized diagnostic criteria, variability in measurement across imaging devices and anatomical levels, and the high cost and limited accessibility of CT/MRI in community settings. Continued efforts are required to establish unified and clinically applicable evaluation frameworks.

4 Conclusion

Spine-specific sarcopenia represents a distinct, localized form of muscle degeneration that disproportionately affects the paraspinal musculature, with FI as its hallmark feature. FI is not merely a passive marker of aging but a dynamic, multifactorial process driven by pathological activation of FAPs, neurogenic degeneration, mechanical overload, and metabolic dysregulation. These mechanisms collectively disrupt muscle structure, impair contractile and metabolic function, and alter the local inflammatory and biomechanical environment, thereby accelerating spinal degeneration and negatively influencing clinical outcomes. Despite advances in imaging modalities such as MRI and CT, which allow for detailed quantification of muscle atrophy and FI, standardized diagnostic criteria and assessment frameworks for spine-specific sarcopenia remain lacking. Future research should focus on developing unified, region-specific evaluation protocols, integrating mechanistic insights with quantitative imaging biomarkers, and exploring targeted interventions aimed at mitigating FI and preserving

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paraspinal muscle function. Establishing such approaches will be critical for improving the prevention, diagnosis, and management of spinal degenerative disorders in aging populations.

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