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REVIEW

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Paraspinal muscle pathophysiology associated with low back pain and spine degenerative disorders

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Abstract

Low back pain disorders affect more than 80% of adults in their lifetime and are the leading cause of global disability. The muscles attaching to the spine (ie, paraspinal muscles) are critical for proper spine health and play a crucial role in the functioning of the spine and whole body; however, reports of muscle dysfunction and insufficiency in chronic LBP (CLBP) patients are common. This article presents a review of the current understanding of the relationship between paraspinal muscle pathophysiology and spine-related disorders. Human literature demonstrates a clear association between altered muscle structure/function, most notably fatty infiltration and fibrosis, and low back pain disorders; other associations, including muscle cell atrophy and fiber type changes, are less clear. Animal literature then provides some mechanistic insight into the complex relationships, including initiating factors and time courses, between the spine and spine muscles under pathological conditions. It is apparent that spine pathology can directly lead to changes in the paraspinal muscle structure, function, and biology. It also appears that changes to the muscle structure and function can directly lead to changes in the spine (eg, deformity); however, this relationship is less well studied. Future work must focus on providing insight into possible mechanisms that regulate spine and paraspinal muscle health, as well as probing how muscle degeneration/dysfunction might be an initiating factor in the progression of spine pathology.

KEYWORDS
multifidus, erector spinae, degeneration, structure/function, fatty infiltration, fibrosis

1 | INTRODUCTION

1.1 | The problem

Low back pain disorders (LBPDs) are a complex, multifactorial condition that affect more than 80% of adults in their lifetime,[1,2] are the leading cause of global disability[3] and are the most common of all noncommunicable diseases.[4] LBPDs are responsible for enormous costs,[5] estimated at up to 200 billion dollars per year in the United States alone.[6] With the prevalence of LBP peaking in older age groups,[3] combined with an aging population,[7] spine related disorders and their associated costs are likely to rise.[8,9] The muscles surrounding and attaching to the spine (ie, paraspinal muscles) are responsible for both moving and stabilizing the spine and are the source of the majority of the loads that spine tissues experience; thus, they play an extremely crucial role in the proper functioning of the spine and

whole body. Reports of muscle dysfunction and insufficiency in chronic LBP (CLBP) patients are common and have included evidence of lower muscle strength,[10] endurance,[11] and greater fat content[12,13] compared to asymptomatic populations. Therefore, these muscles are a prime target for rehabilitation strategies in this patient group; though they are often reported as being unaffected by traditional rehabilitation methods.[14–16]

Numerous spine pathologies, including intervertebral disc (IVD) herniation,[17,18] sagittal balance disorder,[19–22] and nonspecific low back pain[12,23–25] are associated with paraspinal muscle adaptations; therefore, these muscle adaptations have been linked with a lowered quality of life for millions of patients annually.[26–28] Frequently reported muscle-specific adaptations to spine pathology and low back pain include: lower muscle endurance[11,29,30] and lower muscle strength,[10,11,31] muscle atrophy,[17,23,24] fiber type changes,[26,32,33] increased intramuscular fat[24,34] and connective tissue,[18,35,36] distorted cell populations,[18,37] and altered gene expression.[38–41] It should be noted that reported findings from some of these studies are unable to compare to true controls (ie, asymptomatic patients) due to the invasive nature of paraspinal muscle biopsies required to make certain measurements; the details of these comparisons will be discussed throughout the main section of the text.

The first part of this review article will aim to characterize the muscular pathology that is associated with LBPDs in humans. While much time, effort, and money has been dedicated to studying LBPDs, elucidation of the role that muscle pathology plays in LBPDs and whether the pathological features of muscle are causes or consequences of LBPDs still remains largely unknown. The second part of this review will thus aim to identify some of the direct temporal relationships between muscle pathology and LBPDs that have been established through the use of animal models. Note that when most appropriate, findings from human or animal studies will also be discussed in the opposing sections of the review. Understanding and resolving these cause-and-effect relationships will be crucial for the development of effective treatment plans and directing future studies in humans.

In order to appreciate the muscular adaptations that occur in LBPD patients, it is important to first understand the structure and function of the paraspinal muscles under healthy conditions.

1.2 | Healthy skeletal muscle

1.2.1 | Lumbar paraspinal muscle anatomy, architecture, and function

Lumbar multifidus fibers span two to five vertebral levels, originating on the spinous processes of the L1 to L5 vertebrae (Figure 1A). Most of the fibers attach caudally toward insertions on the mammillary processes, as well as the sacrum, soft tissues overlaying the sacrum, and erector spinae aponeurosis[42–44]; however, some deeper fibers attach to the capsules of the facet joints next to the mamillary processes.[45] The lumbar erector spinae are positioned laterally to the multifidus and consist of the longissimus thoracis and the iliocostalis lumborum (Figure 1B,C). The lumbar portion of the longissimus thoracis attaches cranially to the accessory processes and the medial part of the transverse processes, whereas the iliocostalis lumborum attaches cranially to the lateral parts of the transverse processes; both muscles terminate on the iliac crest with some fibers from the L5 longissimus terminating on the sacrum.[43,44,46] Other muscles, including the psoas major, quadratus lumborum, and the very small rotatores and intertransversarii also attach to the lumbar vertebrae; however, very little research has been performed in relation to these muscles and spine dysfunction/LBP. Therefore, this review will focus exclusively on the multifidus and erector spinae (Figure 1).

The paraspinal muscles have unique architectural and design properties that are complex and different from the architecture and design of typically studied (ie, appendicular) muscles. For example, the paraspinal muscles have a broad range of skeletal attachments, with insertions at multiple vertebral levels (see above). In particular, the intersegmental nature of the multifidus is associated with its own architectural diversity,[42] with fiber lengths decreasing and fiber angles increasing from superficial to deep regions within the muscle.

Lumbar multifidus has been measured to have a larger overall physiological cross-sectional area (PCSA), and thus force generating capability, compared to erector spinae[47,48]; however, because multifidus fascicles span a fewer number of vertebral levels, biomechanical models estimate that its effective PCSA, and thus force and moment generating capability, at each intervertebral degree of freedom is lower than the erector spinae.[49–51] Multifidus (measured from both surgical patient biopsies[48] and cadavers[52]), as well as erector spinae[52] have short sarcomere lengths (ie, significantly below optimal force generating length), and thus a limited ability to generate force, when in the neutral spine posture. As the spine flexes, the muscles (and thus sarcomeres) lengthen and are able to generate maximum forces in mid-flexed to fully flexed spine positions.[48,52] Comparing passive mechanical properties of the multifidus and erector spinae in patients undergoing spine surgery has revealed that multifidus fiber bundles (muscle fibers ensheathed in their connective tissue matrix), but not individual fibers, have a significantly higher elastic modulus (higher stiffness).[53] Thus, in these patients the multifidus likely has a high capacity for passive force generation, suiting it for passive resistance to lumbar spine flexion. Whether this difference in passive mechanical function between multifidus and erector spinae exists in people with healthy backs is unknown, but model predictions have suggested that both these muscles play important roles in passively supporting the lumbar spine in flexion and modifying the well-known flexion-relaxation phenomenon.[54]

1.2.2 | Overview of skeletal muscle structure and function

The sarcomere is the fundamental unit of muscle force production. The contractile elements of the sarcomere consist of interdigitating actin (thin) and myosin (thick) filaments that bind and slide past one

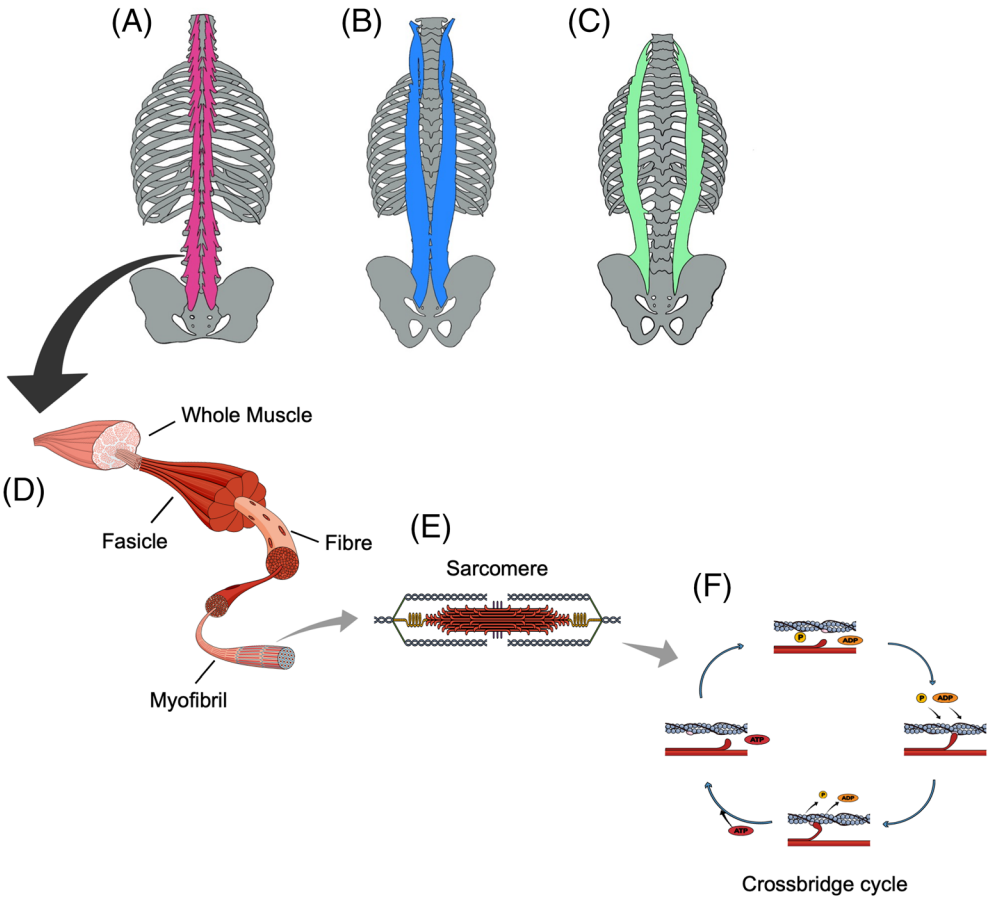

FIGURE 1 Schematic overview of paraspinal muscle anatomy: (A) multifidus (pink) is the most medial and deep of the paraspinal extensor muscles; (B) longissimus (blue) and (C) iliocostalis (green) make up the erector spinae muscle group. (D) Schematic overview of skeletal muscle structural hierarchy. Whole muscle can be broken down into fascicles, fibers, and myofibrils. Each of whole muscle, fascicles, and fibers are surrounded by connective tissues that bind these structural levels with each other and ultimately provide an interconnected network to other muscles and the skeleton. (E) Schematic representation of the sarcomere, the fundamental force-generating unit of skeletal muscle. (F) Actin-myosin cross-bridge cycle, which is responsible for the production of contractile force

another to produce contractile force (Figure 1E,F). The sarcomere's ability to produce force is dependent on both its shortening or lengthening velocity,[55,56] as well as its length.[57–59] Sarcomeres are joined in series to form myofibrils. Bundles of myofibrils arranged in parallel form myofibers (muscle cells). These muscle fibers are then arranged in parallel (and in some instances in series) into bundles (fascicles) which make up the whole muscle (Figure 1D). In humans, skeletal muscle fibers can be classified into three groups: type I slow twitch oxidative, type IIa fast twitch oxidative/glycolytic, and type IIx fast twitch glycolytic. Muscle fiber type composition helps determine the metabolic capacity and contractile characteristics of a muscle and demonstrates considerable plasticity, in general manifesting as a slow to fast transformation with reduced muscle usage and a fast to slow transformation with increased muscle usage.[60] In healthy male and female subjects aged 25 to 60, the paraspinal muscles (both multifidus and erector spinae) have demonstrated fiber type percentages of ~60, 23, and 15% for type 1, type IIA, and type IIX fibers, respectively.[61] The predominance of type 1 fibers implies that these muscles are relatively slow contracting and fatigue resistant compared to most appendicular muscles in which faster type 2 fibers are more prevalent. Other myofilament (eg, titin, nebulin), cytoplasmic (eg, dystrophin), and intermediate filament (eg, desmin) proteins also contribute to muscle function and are implicated in some muscle diseases; however, these proteins have not been investigated in relation to LBPDs and a thorough discussion of all relevant muscle proteins is outside the scope of this review.

The three largest hierarchical scales of skeletal muscle (fibers, fascicles, and whole muscle) are surrounded by extracellular matrix (ECM) connective tissue.[62] In general, the endomysium surrounds individual muscle fibers,[63] the perimysium surrounds muscle fascicles[64] and the epimysium surrounds the whole muscle.[65,66] The composition and organization of the ECM is important to muscle function, specifically to scaffold and protect muscle cells, nerves and blood vessels, as well as to transmit force from the muscle cells longitudinally and laterally through the muscle to the tendon and aponeurosis and ultimately to the skeleton. The composition and arrangement of the ECM can vary in musculoskeletal disorders.[62,67]

Two cell types that are crucial to muscle growth, plasticity, and regeneration are muscle satellite cells[68] and fibro-adipogenic-progenitor cells (FAPs).[69,70] Satellite cells are muscle specific stem cells whose number and viability are known to decrease with age or in diseases that are characterized by extensive regeneration; the latter of which are thought to eventually exhaust the satellite cell population, therefore impeding the muscle's ability to adapt to its functional demands.[71,72] FAP cells are a subset of resident muscle stem cells which generally exert a positive regenerative effect; however, when efficient regeneration fails, they can quickly be recruited to generate fat and fibrosis to ensure the continuity of the tissue.[73]

1.2.3 | Muscle plasticity

As noted, muscles are adaptive tissues with a strong regenerative capacity. Under various stimuli (eg, neural activation, denervation, injury and inflammatory environment, exercise, stretch, and overload) changes can occur across muscle scales which ultimately affect the muscle force generation capability.[60]

2 | MUSCLE PATHOLOGY IN LBPDs

2.1 | Human studies

2.1.1 | Tissue composition

The paraspinal muscles of patients with LBPDs are prone to developing fatty infiltration (intrusion of fatty tissue into the body of the muscle), fibrosis (tissue remodeling whereby normal tissue is replaced by collagen-based connective tissue), and possibly atrophy (the loss of contractile protein volume, ie, reduced cross-sectional area of muscle cells and whole muscle); all of which can be considered features of muscle degeneration. For example, fatty and/or fibrotic changes have been regularly observed using noninvasive imaging in IVD herniation (eg, References 12,38,74), facet joint osteoarthritis (eg, Reference 75), nonspecific low back pain (eg, References 13,76–79), and spinal stenosis,[80] including greater fatty/fibrotic infiltration in patients who have a lower compared to higher functional status (eg, References 80,81). Interestingly, a statistically significant difference in multifidus fat content between CLBP and asymptomatic volunteers was only found in the intramyocellular (0.61 ± 0.27 ($\times 10^3$) mmol L^{-1} vs 0.26 ± 0.14 ($\times 10^3$) mmol L^{-1}, respectively) rather than extramyocellular (2.63 ± 1.75 ($\times 10^3$) mmol L^{-1} vs 1.52 ± 1.54 ($\times 10^3$) mmol L^{-1}, respectively) stores,[78] and a statistically significant correlation between multifidus fat content and visual analog scale (VAS) for pain in CLBP patients was again only found intracellularly and not extracellularly,[79] both in studies using MR spectroscopy. Further, reported magnitudes of fatty infiltration appear to be similar in both the multifidus and erector spinae[82,83]; however, this may be influenced by ethnicity, with erector spinae having greater fatty infiltration in Korean,[30] Finnish,[84] and Hungarian cohorts,[74] but multifidus having greater fatty infiltration in a Swiss population.[85] In addition, fatty infiltration increases with age,[79,84,85] is greater in women,[79,86] and greater fatty infiltration is predictive of continued and frequent LBP at 1 year follow up[82] in both muscles.

Fatty-fibrotic changes have also been observed histologically using muscle biopsies taken from patients during surgery to treat IVD herniation.[18,35,36] Further, it appears that spinal pathology leading to kyphotic deformation of the lumbar spine involves greater degeneration of the paraspinal muscles compared to patients without deformity.[35] For example, Delisle et al[35] found that the paraspinal muscles from kyphotic patients had more extensive fibrosis than patients being treated for IVD herniations. Few histological studies have compared paraspinal muscle pathology to "true" control muscle; however, Agha et al[18] discovered that the multifidus from patients being surgically treated for IVD herniations had higher amounts of fatty and fibrotic tissue than hamstring muscle harvested from patients during ACL reconstruction surgery (~14% each vs <1 %). It has been suggested that the greater fatty infiltration is related to the inflammatory dysregulation found in the multifidus of degenerative spine patients[39]; however, others[18] have suggested, based on mouse data, that the healthy multifidus may have amplified baseline concentrations of FAPs with increased adipogenicity compared to other muscles, which could then play a role in the amplified fatty infiltration reported in the multifidus of degenerative spine patients. Future work will need to confirm if this is true in human multifidus and further explore if the multifidus and erector spinae have baseline properties in other biological and functional measures that are different from more commonly studied muscles in the body.

Associations between muscle atrophy and LBPDs have shown mixed results. Imaging studies have revealed both atrophic[23,87–93] and nonatrophic or inconclusive findings,[74,94–97] in the paraspinal muscles of people with LBPDs. Two recent systematic reviews[94,96] agreed that in CLBP patients, there is moderate evidence of muscle atrophy in the multifidus, whereas in the erector spinae and other paraspinal muscles (psoas and quadratus lumborum), the results are inconclusive. It has been shown that multifidus cross-sectional area (CSA) is reduced on the affected side in patients with an identified IVD herniation presenting for longer than three months but not in those presenting for less than one month.[92] Similar conclusions were reported in a recent systematic review[97] indicating that patients with chronic IVD herniation and radiculopathy had a reduction in multifidus CSA on the affected side. However, many of the studies included in the review did not differentiate between chronic and acute patient groups, therefore it is difficult to say how exactly the muscle atrophy was related to chronicity.

Histological investigations of paraspinal muscle atrophy in patients with LBPDs are also inconsistent, with atrophic,[17,97–99] nonatrophic,[100,101] or even hypertrophic[36,102] findings reported across various LBPD populations. The predominate spine pathology investigated using histological techniques is lumbar IVD herniation, which largely suggests that atrophy is present in paraspinal muscle fibers.[17,98,99] However, others[36,102] have shown that the muscle fibers from IVD herniation patients had larger multifidus fiber CSAs (ie, hypertrophy) compared to controls (young individuals who died suddenly with no signs of neuromuscular disorder)[102] and literature norms for healthy multifidus fibers,[36] suggesting muscle fiber atrophy may not be the primary factor accounting for muscle loss and degeneration in LBPD patients. Further, a recent article by Agten et al[101] suggests there are no differences in multifidus and erector spinae muscle fiber CSAs in patients with nonspecific CLBP compared to healthy aged-matched controls. Likewise, Ford et al[100] demonstrated that patients undergoing surgery for an acute IVD postero-lateral protrusion demonstrated no differences in paraspinal muscle fiber CSAs compared to the less-affected side (note that, the definition of acute was not reported in this article).

Ultimately, the reduced lumbar extensor muscle strength that has been reported in low back pain patient groups (eg, Refereences10,

11, 31) is thus better explained (at least in part) by muscle fatty and fibrotic infiltration than by muscle atrophy. Interestingly, recent mouse work has demonstrated that the loss of force generating capability in fatty muscle is not simply due to a replacement of contractile tissue by fat, but also due to an intrinsic decrease in the contractile output of muscle.[103]

2.1.2 | Fiber type changes

It has been reported that patients with nonspecific CLBP[32,33,104] and IVD herniation[105] have a higher proportion of type IIX (fast twitch glycolytic) at the expense of type I (slow twitch oxidative) fibers in both the multifidus[104] and erector spinae[33,105] which manifests itself with symptom duration,[33] suggesting that this phenotype could lead to paraspinal muscles that are less fatigue resistant.[32] In contrast, results have also shown a greater proportion of type I relative to type IIa and IIx fibers in multifidus biopsies from male patients (but not female patients) undergoing surgery for IVD degeneration (compared to cadaver controls),[102] as well as when comparing the affected vs non-affected side multifidus in IVD herniation patients.[98] Further, Agten et al,[101] using anthropometrically matched subjects, found that the erector spinae in patients with nonspecific CLBP had a greater proportion of type I (slow oxidative) and a lower proportion of type IIx (fast twitch glycolytic) fibers when compared to healthy controls; no significant difference was found in their multifidus samples. However, not all studies have found differences in fiber type characteristics in either LBP patients compared to healthy subjects[106] or IVD herniation patients compared to cadavers.[107] In summary, there are conflicting data regarding fiber type distribution between LBPDs and controls.[108] Thus, the commonly reported lower spine extensor muscle endurance in CLBP patients[11,29,30] is likely not simply explained by fiber type characteristics (see also Reference 109).

2.1.3 | Stem cell and gene expression

The above sections have established that muscle tissue compositional differences, such as fatty-fibrotic infiltration, and conflicting reports of muscle atrophy and fiber type disparities, exist in this patient population compared to controls. This begs the question, what are the mechanistic pathways that drive these muscle specific tissue changes? To begin to answer this, information is needed regarding the cellular and molecular factors that could be involved, which will ultimately propel the development and refinement of effective treatment strategies.

Only a handful of studies to date have explored the relationship between spine pathology and paraspinal muscle stem cell (satellite and FAP) populations.[18,37] Agha et al[18] found that the multifidus from IVD herniation patients contained more FAPs and elevated percentages of satellite cells than biopsies from the hamstring muscle in ACL reconstruction patients, and that these FAPs had greater fibrogenic and adipogenic gene expression than FAPs from the hamstring; whether these differences are related to the IVD herniation or to fundamental baseline differences between the multifidus and hamstring is unknown. Meanwhile, Shahidi et al[37] found that muscle fibers from patients being treated for both acute and chronic IVD herniations had focal regions of degeneration, and that the most common cell type observed within the degenerating regions were PDGFRβ-positive (FAP) cells, particularly in the acute (symptom duration <6 months) phase. This suggests that FAP cells may be a key player contributing to the tissue compositional differences observed in the spine muscles. Indeed, this cell population has been implicated in the fatty and fibrotic composition of muscles in other diseases.[82,110]

Equally few articles have studied the effects of spine pathology on the gene expression of the paraspinal muscles.[38,40–42] Kudo et al[38] discovered that genes associated with impaired muscle function (PGC-1α) as well as proinflammatory genes (tumor necrosis factor (TNF)-α and interleukin (IL)-6) were greater in multifidus samples from patients undergoing posterior lumbar spinal surgery who had a reduced lumbar lordosis (ie., lumbar kyphosis) when compared to patients with normal lumbar lordosis. Likewise, greater expression of pro-inflammatory and lower expression of anti-inflammatory genes have been found in the multifidus as well as adipose (intramuscular and subcutaneous) tissue of patients with high vs low muscle fatty infiltration (Kjaer grade).[40] Further, a study by Shahidi et al[41] that measured muscle specific gene expression in the multifidus from patients with acute vs chronic spine pathology, found an upregulation of fibrogenic genes in the chronic (symptom duration >6 months) vs acute (symptom duration <6 months) group; based on this they suggested that early efforts should be targeted at preventing or reversing muscle fibrosis. Most recently, Chen et al[41] demonstrated that markers for impaired muscle regeneration were related with poorer outcomes (measured as improvement <33% vs >33% on pain VAS) in patients undergoing microdiscectomy for lumbar IVD herniation with radiculopathy. Together, these findings may have important implications for treating muscle degeneration in the spine.

2.2 | Animal studies

While there is a growing body of human literature demonstrating links between altered muscle structure/function and LBPDs, much is still unknown regarding the direct mechanistic interplay between paraspinal muscle pathology and both acute and chronic LBPDs.

Due to the many challenges in conducting studies on human LBPD patients (e.g., accessing healthy and pathological spine muscle tissue and conducting longitudinal studies probing cause-and-effect), animal experiments can provide a means to study mechanistic cause-effect relationships between muscle and spine degeneration/dysfunction. Each of experimental (for example, References 111–115), naturally developing[116] and genetically induced (for example,[117–120]) animal models have been utilized to answer important fundamental and clinical questions. As such, the following section will be divided into animal models that are (a) experimentally (surgically) induced and (b) naturally occurring and genetically induced.

2.2.1 | Experimental models

Generally, experimentally induced spine injury studies have been performed in sheep,[113,114,121] pigs,[122] rabbits,[111,115] and rats.[112,123,124] Therefore, the following section will focus on these animal models.

Likely the most studied experimentally induced spine pathology is IVD injury, performed with the intent of inducing degenerative changes in the IVD. In these models, caution is taken when accessing and injuring the IVD, thereby sparing the paraspinal muscles themselves from direct disruption. Using a porcine IVD stab incision model, Hodges et al[122] found degenerative changes in the multifidus 3 days following injury, including atrophy and an increase in intramuscular fat. Studies assessing the more chronic effects of experimental IVD injury through needle puncture in rabbits[111] and stab incision in sheep[114] found no histological signs of multifidus fatty infiltration 12 weeks after injury,[111] while Hodges et al[114] did find histological evidence of increased multifidus adipose and connective tissue, but not atrophy, 6 months following IVD injury. These latter histological findings were consistent with their gene expression data, showing increased expression of genes responsible for cytokines implicated in both adipogeneses and fibrosis[114]; this upregulation of pro-inflammatory gene expression is comparable to the findings from human patients with IVD herniation[38] and degenerative spine pathology.[39,40] The discrepancy in muscle atrophy findings between References 114 and 122 is not clear. The authors suggest that the earliest changes may be modulated by vascular and/or reflex inhibition effects; however, discrepancies in the methodologies used (ultrasound vs whole muscle/muscle fiber histology) as well as temporal differences in the measurements (eg, Reference 114 did not examine an early timepoint), were likely also a factor. Consistent with the increased multifidus connective tissue (ie, fibrosis) noted 6 months following IVD injury,[114] Brown et al[111] observed a proliferation of the multifidus connective tissue and a corresponding increase in the passive stiffness of the muscle. This passive muscle stiffening was suggested to be an adaptive mechanism to compensate for a possible loss of spine stiffness due to the early stages of IVD degeneration. It should be noted that all of the findings described in this paragraph are limited to the multifidus, as none of these articles tested for similar effects in the erector spinae.

Understanding the temporal changes to paraspinal muscle structure and function and correlating these changes with the appropriate mechanisms will be important for developing proper treatment strategies in humans. Synthesizing what we know from animal studies suggests that fatty infiltration can occur at multiple stages following IVD injury, with evidence of adipogenesis at both early (3 days in pigs) and later (>6months sheep) stages following injury.[125] This is suggested to be mediated by muscle inhibition in the acute phase and proinflammatory cytokines and disuse in the later stages.[125] Meanwhile, it appears that fibrosis develops in the later stages (>6 months in sheep) following IVD injury, possibly mediated by more slowly developing proinflammatory cytokines, as well as long-term unloading of the muscle.[125] This is in slight temporal disagreement with animal studies investigating direct paraspinal muscle injury to rabbits[115,126] using the muscle splitting approach, which have demonstrated fibrotic changes between 3 and 6 weeks (earlier), with fatty infiltration mostly occurring between 12 and 24 weeks (later only). Further, Brown et al[111] reported evidence of multifidus fibrosis but not fatty infiltration at 12 weeks after IVD injury in rabbits. Human studies[40] have demonstrated an upregulation in the genes associated with fibrosis but not adipogenesis in chronic (symptoms >6 months) compared to acute (symptoms < 6 months) spine pathology patients. However, due to the cross-sectional nature of this last study, more longitudinal work will be needed to elucidate the precise timelines and compare with the findings from animal studies.

Some animal studies have reported a transformation from type 1 (slow) to type 2 (fast) muscle fibers in the multifidus of IVD injury groups compared to controls (References 113,114—both in sheep), while others have reported no change (Reference 111—in rabbits); matching the inconsistency reported in the human literature. Hodges' group[113,114] suggested that the increased expression of proinflammatory cytokines (particularly TNF-α) in the multifidus may drive the fiber type changes associated with IVD injury in their studies. In support of this, there is evidence of a greater proportion of M1 (pro-inflammatory) macrophages in IVD injury groups compared to control, suggesting that following IVD injury, macrophages may play an active role in the early remodeling phase of muscle.[121] This is reinforced by the known role macrophages have in determining satellite cell function in normal muscle regeneration.[127] However, macrophages can play both a beneficial and detrimental role in skeletal muscle regeneration. This is dependent on the timely switching from M1 to M2 macrophages during the regeneration process, which promotes both FAP cell death and survival, respectively. Under normal circumstances M1 macrophages promote FAP cell death following satellite cell differentiation, giving way to a rise in M2 macrophages which promote the survival of any remaining FAP cells. However, premature switching from M1 to M2 macrophages can give rise to fibrosis due to excessive FAP survival and differentiation.[127]

Using mesenchymal stem cell (MSC) injections into injured IVDs, James et al[128] found that adipose (at both 3 and 6 months) and connective tissue (at 3 months only) CSAs within the multifidus were reduced when compared to control (no treatment) animals (sheep). However, MSC injections did not prevent fiber type transformation (slow to fast) within the multifidus, and there was a variable response in the treatment's ability to normalize the gene expression of various inflammatory cytokines within the muscle. Some inflammatory cytokines were prevented (IL-1ß) (at 3 months) from increasing in response to treatment while others increased (TNF and TGF-ß1; at 6 months) following treatment. The authors suggest that timing of the IVD MSC therapy is important in the inflammatory response of the muscle. Future efforts will need to explore stem cell treatments further with an emphasis on prevention of muscle degeneration via treatment of the paraspinal muscles directly.

While it is clear that experimental IVD injury leads to paraspinal muscle changes, only one study has looked at the effect of injury to other spinal structures on paraspinal muscle changes. Zwambag et al[124] created a mild injury to the facet joint of rat spines, with

specific care being taken to minimize direct disruption to the paraspinal muscles, to determine if facet degeneration would also lead to changes in the passive mechanical properties of the surrounding musculature. While the facet injury led to mild cartilage degeneration and bony remodeling, there was no effect on either the passive stress or stiffness of the multifidus or erector spinae; it is important to note that other degenerative properties of muscle such as fatty infiltration and fibrosis were not examined.

Few studies have attempted to directly probe the opposite relationship between spine and muscle pathology; specifically, the question of whether muscle injury/degeneration can initiate a degenerative cascade in the spine? Maas et al[123] attempted to answer this question by completely removing the lumbar multifidus bilaterally in rats to determine if the muscle loss would lead to degenerative IVD changes. The authors reported no effect on the IVD or nucleus pulposus areas, concluding that multifidus disruption does not lead to IVD degeneration within the time frame studied (28 days). In contrast to this, Cho et al[112] found that severe injury (2-week ischemia) to the paraspinal muscles (multifidus and erector spinae were not specified in their description) of rats led to a thoracolumbar kyphotic deformity that persisted for the remainder of the study (12 weeks); however, the authors did not quantify the degenerative changes in either the muscles or specific spine tissues.

2.2.2 | Naturally occurring and genetically induced models

The disadvantage of experimental animal models of spine pathology is that they require an overt injury to initiate the progressive degenerative changes; a sequence which may not mimic the naturally developing process in humans. Therefore, naturally occurring or genetically induced spine pathology models in dogs[116] and mice,[117–120] respectively, have also been used, which may provide additional insight into how pathological changes to the spine interact with the surrounding muscles in a more progressively developing manner.

Dogs have often served as models of human IVD degeneration due to similarities in gross pathology and histology.[129] An MRI based study examined paraspinal muscle fatty infiltration in dogs being treated for either IVD herniation or other (non-IVD herniation) spine pathologies.[116] They found greater fatty infiltration in the erector spinae than in the multifidus, but no difference in the magnitude of fatty infiltration in the dogs being treated for IVD herniation compared to other spine pathology. They thus concluded that paraspinal muscle degeneration (fatty infiltration) was not specific to IVD-related disorders (despite these being the most commonly studied type of spine pathology in this field) but instead was likely related to the severity or chronicity of general spine pathology. Although, recent human data suggest that multifidus degeneration is not different between acute (symptoms <6 months) and chronic (symptoms >6 months) spine patients[37] and that only fibrotic genes (and not adipogenic, inflammatory, atrophy, or myogenic genes) are significantly upregulated when comparing chronic to acute patient groups.[40]

Using the SPARC-null mouse as a model of age-accelerated IVD degeneration[130] and LBP,[131–133] James et al[118,119] investigated the inflammatory pathways[118] and fibrotic development[119] in the multifidus at levels where IVD degeneration was most pronounced, and whether or not this could be improved by physical activity.[118,119] The authors found that IVD degeneration was associated with a dysregulation of the inflammatory and adiponectin pathways,[118] and greater IVD degeneration was associated with more intramuscular connective tissue and a dysregulation of fibrotic genes.[119] Chronic physical activity via voluntary wheel running was able to prevent much of the (apparently) detrimental effects in both instances by reducing the pro-inflammatory response to IVD degeneration[118] and reducing fibrosis and regulating the fibrotic gene network[119] in the multifidus. These studies are in general agreement with recent human reports showing inflammatory dysregulation within the multifidus of disc herniation patients[38]; future work will need to assess whether these detrimental pathways can be reversed with physical activity in humans.

Using the ENT1 deficient (KO) mouse model of progressive mineralization of spine soft tissues,[134,135] Gsell et al[117] found a clear inverse relationship between the passive mechanical properties of the spine and the surrounding paraspinal muscles. Specifically, the mineralized spines from the ENT1$^{-/-}$ (KO) mice were stiffer than WT (control) spines, while the passive stiffness of both the multifidus and erector spinae was lower in the ENT1$^{-/-}$ (KO) mice compared to WT control. This reduced paraspinal muscle passive stiffness was hypothesized to have developed to counteract the increased stiffness of the spine. Interestingly, the reduced multifidus and erector spinae stiffness was apparent only within individual muscle fibers and not bundles of fibers, suggesting that remodeling was limited to the muscle cells themselves and not their connective tissue extracellular matrix. Recently, the paraspinal muscles from these ENT1$^{-/-}$ (KO) mice have also been shown to have impaired active contractile function.[120] Particularly, specific force (maximal isometric force normalized to CSA), unloaded shortening velocity (proxy for contractile speed of cross-bridge interactions) and active modulus (proxy for number of attached cross-bridges normalized to CSA) were all lower in the multifidus of the ENT1$^{-/-}$ (KO) compared to the WT mice. Meanwhile, only the specific force was lower in the erector spinae KO group when compared to WT controls. This is the first study to demonstrate a fundamental impairment in the active contractile capabilities of spine muscles in response to a spine disorder; whether this is a compensatory functional consequence of the mineralization and progressive stiffening of the spine in this animal model is unknown.

Finally, Rederstorff et al,[136] using SEPN1 KO mice that have a reduced muscle cellular ability to deal with oxidative stress and maintain calcium homeostasis, reported that exercise-induced stress resulted in paraspinal muscle atrophy and a progressive hyperkyphosis of the thoracic spine. Similar to the experimental muscle damage model of Cho et al,[112] this suggests that paraspinal muscle weakness can lead to spine deformity. More detailed degenerative changes to spine tissues were not examined.

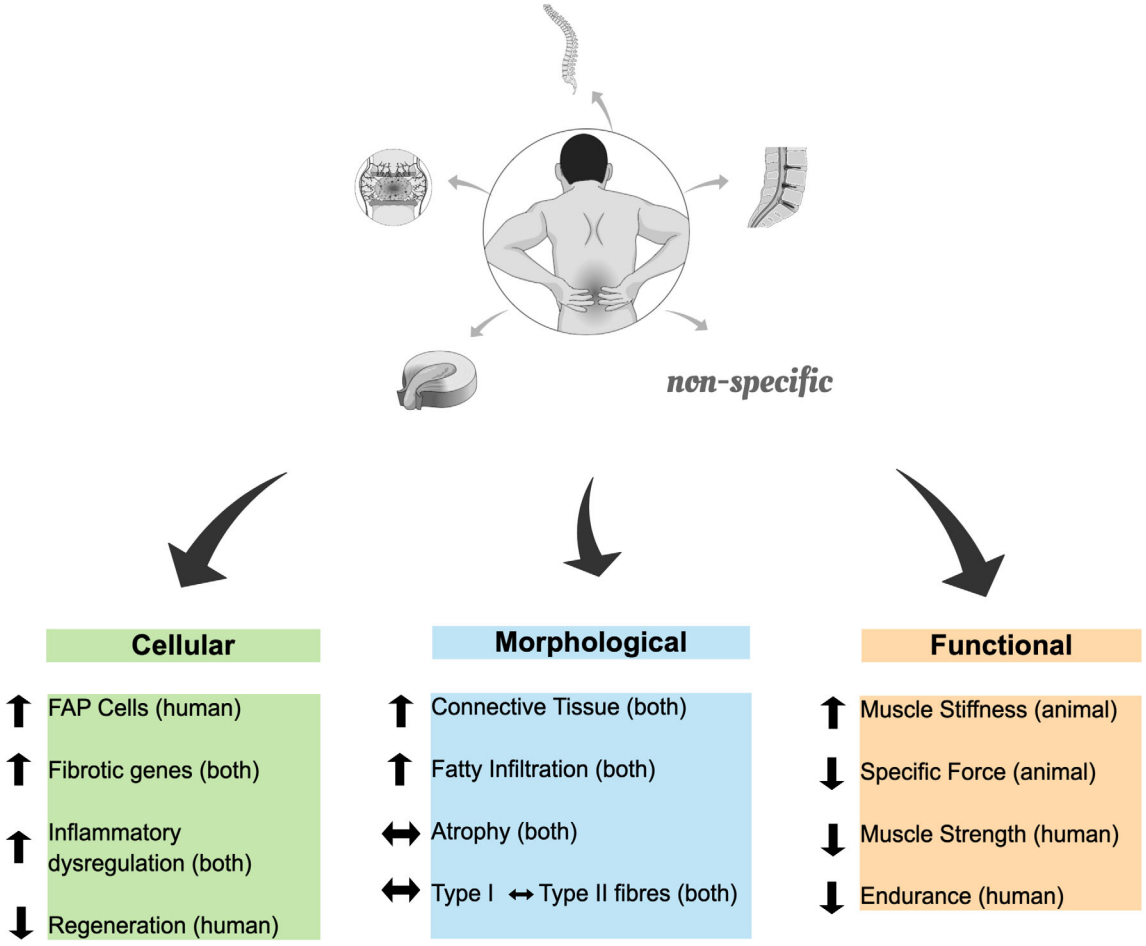

FIGURE 2 General overview of the cellular, morphological, and functional muscle characteristics associated with low back pain and spine degenerative disorders. Human = evidence from human studies; animal = evidence from animal studies; both = evidence from both. ↑ = greater; ↓ = lesser; ↔ = evidence of differences in both directions

Together, these animal models provide some clarity and mechanistic insight into the complex relationships between the spine and spine muscles under pathological conditions. IVD injury and degeneration can directly lead to changes in the paraspinal muscle structure, function, and biology. However, the precise mechanisms responsible for these changes are still uncertain. Whether other degenerative changes in the spine can lead to similar muscular changes, and whether muscle degeneration can lead to distinct changes in the spine tissues themselves, are less clear. Future work must focus on providing insight into possible mechanisms, as well as probing how muscle degeneration/dysfunction might be an initiating factor in the progression of spine pathology.

2.2.3 | Limitations of animal models

Much of the animal findings are consistent with those found in humans (see above Reference 114). However, there are obvious functional differences between humans and animals (biped vs quadruped) and while it is not entirely clear how these functional differences may impact either the muscular response to spine injury or vice versa, a review by Smit et al[137] provided evidence that in both standing and walking, the quadruped spine is primarily loaded similar to the human spine (along its long axis, in axial compression). This is largely due to the muscle, and to a lesser extent the ligaments, which exert tensile forces to counterbalance the bending and torsional moments. Quadruped vertebrae show architecture that supports this, with trabeculae that are oriented from endplate to endplate, just as the human spine, suggesting that the main loading direction is in axial compression.[138] Similarly, rodents and humans have similar muscle architectural properties in both the spine[139] and abdominal wall.[140] One additional difference is that while humans have a lordosis of the lumbar spine, rodents have a flatter or even slightly kyphotic lumbar region.

3 | CONCLUSION

This review aimed to summarize the current knowledge of the pathophysiological characteristics of the paraspinal muscles frequently observed in chronic LBPDs. The exact cause-effect relationships

between muscle and spine degeneration are not clear; however, it is evident that significant pathology manifests within the muscles that affect their structure, function, and rehabilitative potential (Figure 2). This information must be considered when developing prevention and rehabilitation strategies. Prospective work will need to focus on the mechanisms leading to and progressing the musculoskeletal degeneration of the spine. Future treatment strategies will likely involve a combination of surgical, biological, and engineering interventions.

AUTHOR CONTRIBUTIONS

Alex M. Noonan reviewed the literature, performed the first interpretation of the literature, and wrote the first draft of the manuscript. Stephen H. M. Brown further reviewed and interpreted the literature and reviewed and edited the manuscript.

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