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Systematic Review and Meta-analysis

Are the Pathologic Features of Enthesopathy, Tendinopathy, and Labral and Articular Disc Disease Related to Mucoid Degeneration? A Systematic Review

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Abstract

Background Tendinopathy, enthesopathy, labral degeneration, and pathologic conditions of the articular disc (knee meniscus and ulnocarpal) are sometimes described in terms of inflammation or damage, while the histopathologic findings are often consistent with mucoid degeneration. A systematic review of the histopathology of these structures at diverse locations might reconceptualize these diseases as expected aspects of human aging. The potential benefits of this evolution might include healthier patient and clinician mindsets as well as a reduced likelihood of overdiagnosis and overtreatment resulting from greater awareness of base rates of pathology.

Question/purpose In this systematic review of studies of surgical specimens, we asked: Are there are any differences in the histopathologic findings of structural soft tissue conditions (mucoid degeneration, inflammation, and vascularity) by anatomic site (foot, elbow, or knee) or structure (tendon body, muscle or tendon origin or insertion [enthesis], labrum, or articular disc)?

Methods Studies between 1980 and 2021 investigating the histopathologic findings of specimens from surgery for trigger digit, de Quervain tendinopathy, plantar fasciitis, lateral and medial elbow enthesopathy, rotator cuff tendinopathy, posterior tibial tendinopathy, patellar tendinopathy, Achilles tendinopathy, or disease of the hip labrum, ulnocarpal articular disc, or knee meniscus were searched for in the PubMed, EMBASE, and CINAHL databases. Inclusion criteria were the prespecified anatomic location or structure being analyzed histologically and any findings described with respect to inflammation, vascularity, or mucoid degeneration. Studies were excluded if they were nonhuman studies or review articles. Search terms included "anatomy," "pathology," and "histopathology." These terms were coupled with anatomic structures or disorders and included "trigger finger," "de Quervain," "fasciitis, plantar," "tennis elbow," "rotator cuff tendinopathy," "elbow tendinopathy," "patellar tendonitis," "posterior tibial tendon," and "triangular fibrocartilage." This resulted in 3196 studies. After applying the inclusion criteria, 559 articles were then assessed for eligibility according to our exclusion criteria, with 52 eventually included. We recorded whether the study identified the following histopathologic findings: inflammatory cells or molecular markers, greater than expected vascularity (categorized as quantitative count, with or without controls; molecular markers; or qualitative judgments), and features of mucoid degeneration (disorganized collagen, increased extracellular matrix, or chondroid metaplasia). In the absence of methods for systematically evaluating the pathophysiology of structural (collagenous) soft tissue

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structures and rating histopathologic study quality, all studies that interpreted histopathology results were included. The original authors' judgment regarding the presence or absence of inflammation, greater than expected vascularity, and elements of mucoid degeneration was recorded along with the type of data used to reach that conclusion.

Results Regarding differences in the histopathology of surgical specimens of structural soft tissue conditions by anatomic site, there were no differences in inflammation or mucoid degeneration, and the knee meniscus was less often described as having greater than normal vascularity. There were no differences by anatomic structure. Overall, 20% (10 of 51) of the studies that investigated for inflammation reported it (nine inflammatory cells and one inflammatory marker). Eighty-three percent (43 of 52) interpreted increased vascularity: 40% (17 of 43) using quantitative methods (14 with controls and three without) and 60% (26 of 43) using imprecise criteria. Additionally, 100% (all 52 studies) identified at least one element of mucoid degeneration: 69% (36 of 52) reported an increased extracellular matrix, 71% (37 of 52) reported disorganized collagen, and 33% (17 of 52) reported chondroid metaplasia.

Conclusion Our systematic review of the histopathology of diseases of soft tissue structures (enthesopathy, tendinopathy, and labral and articular disc) identified consistent mucoid degeneration, minimal inflammation, and imprecise assessment of relative vascularity; these findings were consistent across anatomic sites and structures, supporting a reconceptualization of these diseases as related to aging (senescence or degeneration) rather than injury or activity.

Clinical Relevance This reconceptualization supports accommodative mindsets known to be associated with greater comfort and capability. In addition, awareness of the notable base rates of structural soft tissue changes as people age might reduce overdiagnosis and overtreatment of incidental, benign, or inconsequential signal changes and pathophysiology.

Introduction

Painful musculoskeletal diseases, many of them conditions of senescence (biological deterioration with age), are often described in terms that imply inflammation or injury [54, 55]. For instance, the MRI signal changes associated with tendinopathy and enthesopathy are often referred to as "tears" in the absence of traumatic rupture [27, 90]. Experimental evidence has contributed to some notable, albeit incomplete, transitions in the conceptualization of musculoskeletal disease. For instance, "impingement syndrome"—implying mechanical tendon damage because of shoulder motion—was replaced by "rotator cuff tendinopathy" [47]. This change recognizes the evidence that rotator cuff tendinopathy is nearly universal with age regardless of activity, is symmetric in symptomatic and asymptomatic shoulders, is often misperceived as an injury, and has histopathologic findings consistent with myxoid degeneration rather than injury and repair [50, 73, 79, 85]. We have noted similar findings for soft tissue structures at various anatomic sites, but we could not find a systematic review of the histopathology of tendons, entheses, labrums, and articular discs that addressed this possibility.

Accurate and healthful concepts are important for several reasons. First, unhelpful thoughts, including misinterpretation of symptoms related to an injury or activity, are a notable contributor to a patient's level of discomfort and incapability [11, 18, 65, 78]. Common unhelpful thoughts include the misinterpretation of new symptoms as representing a new disease or an injury, a belief that painful activity will make a disease worse, and the misconception that the absence of pain is necessary to continue cherished activities [13, 16, 35, 38, 78]. If the evidence from studies of the histopathology of surgical specimens of structural (collagenous) soft tissue musculoskeletal diseases is consistent with mucoid degeneration and suggests senescence, our conceptualization of these diseases as being related to use or injury might be tempered. A mindset that these structures are structurally sound and that painful activity does not alter the natural history of the pathophysiology could help reorient some of the unhelpful thoughts associated with people feeling worse and doing less [4, 51, 78]. Even if the finding of such a systematic review was inconclusive regarding histopathology and etiology, it likely would temper the frequent and potentially harmful description of many of these conditions as injuries either from a single event or related to frequent activities. Additionally, given that MRI signal changes associated with diseases of structural (collagenous) soft tissue structures are highly prevalent with advancing age and may never normalize even if symptoms decline or resolve, a systematic review identifying these conditions as mucoid degeneration and likely related to senescence (programmed biological deterioration) might establish a notable base rate of MRI changes with a corresponding decreased potential for misdiagnosis or overdiagnosis, along with corresponding mistreatment or overtreatment [32, 37].

In this systematic review of studies of surgical specimens, we asked: Are there are any differences in the histopathologic findings of structural soft tissue conditions (mucoid degeneration, inflammation, and vascularity) by anatomic site (foot, elbow, or knee) or structure (tendon body, muscle or tendon origin or insertion [enthesis], labrum, or articular disc)?

Materials and Methods

Search Strategy

We systematically searched PubMed, EMBASE, and CINAHL for studies reporting the results of histopathologic analyses of the human tendon, enthesis, labrum, or articular disc at various anatomic locations. Electronic searches were performed using Medical Subject Heading terms and corresponding key terms for anatomic location. Medical Subject Heading search terms included "anatomy," "pathology," and "histopathology." These terms were coupled with anatomic structures or disorders and included "trigger finger," "de Quervain," "fasciitis, plantar," "tennis elbow," "rotator cuff tendinopathy," "elbow tendinopathy," "patellar tendonitis," "posterior tibial tendon," and "triangular fibrocartilage."

Eligibility Criteria

This initial query yielded 3196 studies. We excluded articles not written in the English language, review articles, and articles that were not electronically available. Abstracts were initially scanned for eligibility. If there was insufficient information in the abstract, the full-text article was reviewed. Study reference lists were scanned to identify studies that might not have been found in the initial database search, which resulted in the addition of one study. Abstracts not published in peer-reviewed journals (such as preprint server articles) were excluded from review.

Selection Process

After the authors (DFB, SRP, FS, DR) manually screened 3196 article abstracts, 2637 articles were excluded. After evaluating the full text of the remaining 559 articles, we selected 72 for further evaluation, 52 of which met the inclusion criteria (Fig. 1). The included studies addressed 12 anatomic structures in seven anatomic locations (Table 1).

Data Items

We sought information regarding histopathologic analyses in three broad categories: inflammation (cell or markers that were present or not), vascularity (greater than expected: yes or no), and mucoid degeneration (at least one feature present or not present). Vascularity was assessed in all 52 studies and was categorized as quantitative (such as vessel counting, vessel size, or Bonar scale), qualitative judgments ("vessel aggregation" or "vessel clustering"), or molecular markers associated with angiogenesis (such as vascular endothelial growth factor or CD31). We also addressed comparisons of vascularity with control tissues and recorded the type of control tissue used. Thirty-three percent (17 of 52) of the studies used quantitative methods and 67% (35 of 52) made qualitative judgments. Ten percent (five studies) also addressed molecular markers such as vascular endothelial growth factor in addition to a quantitative (three studies) or qualitative (two studies) assessment of vascularity. Fourteen of the 17 quantitative assessments also included a comparison with control specimens from live or cadaver tissue without symptoms, signs, or imaging evidence of pathology. Six studies used cadaver control tissue that was deemed healthy (presumably meaning no diagnosed pathophysiology) based on either medical record or family report. Live control tissue was taken from asymptomatic patients undergoing unrelated procedures at other anatomic locations, such as hamstring grafting in ACL reconstruction [89]. Three of 11 studies used live age-matched controls and one used nonage-matched controls with the same anatomic location [59]. One of the studies of the long head of the biceps investigated the intra-articular portion of the tendon and used the extra-articular portion of the tendon as a control. In the absence of control specimens, one study relied on pathologists to assess that vascularity was more than expected [12]. Included studies were inconsistent in classifying specimens by sex; thus, this factor was not included in our analysis.

Three features of mucoid degeneration were assessed as present or absent: alterations of the extracellular matrix, collagen derangement, and fibrocartilaginous metaplasia. We considered the following terms to be consistent with an altered extracellular matrix: mucoid, mucinous, or myxoid "degeneration" and increased mucin, glycosaminoglycans, mucopolysaccharides, or proteoglycans. We considered the following terms to be consistent with collagen derangement: collagen degeneration, hyaline degeneration, and increased collagen. We considered the following terms to be consistent with fibrocartilaginous metaplasia: chondroid metaplasia and fibroblastic proliferation. When included studies did not address a component under investigation (for example, inflammation), it was noted, and the study was excluded from statistical analysis for that category.

Study Characteristics

The 52 included studies performed histopathologic analyses of surgical specimens of structural soft tissue diseases (Supplemental Table 1; http://links.lww.com/CORR/A995). Five studies evaluated trigger digit, seven studies evaluated rotator cuff tendinopathy, six studies evaluated de Quervain tendinopathy (first dorsal compartment of the wrist), three evaluated posterior tibialis tendinopathy, three evaluated

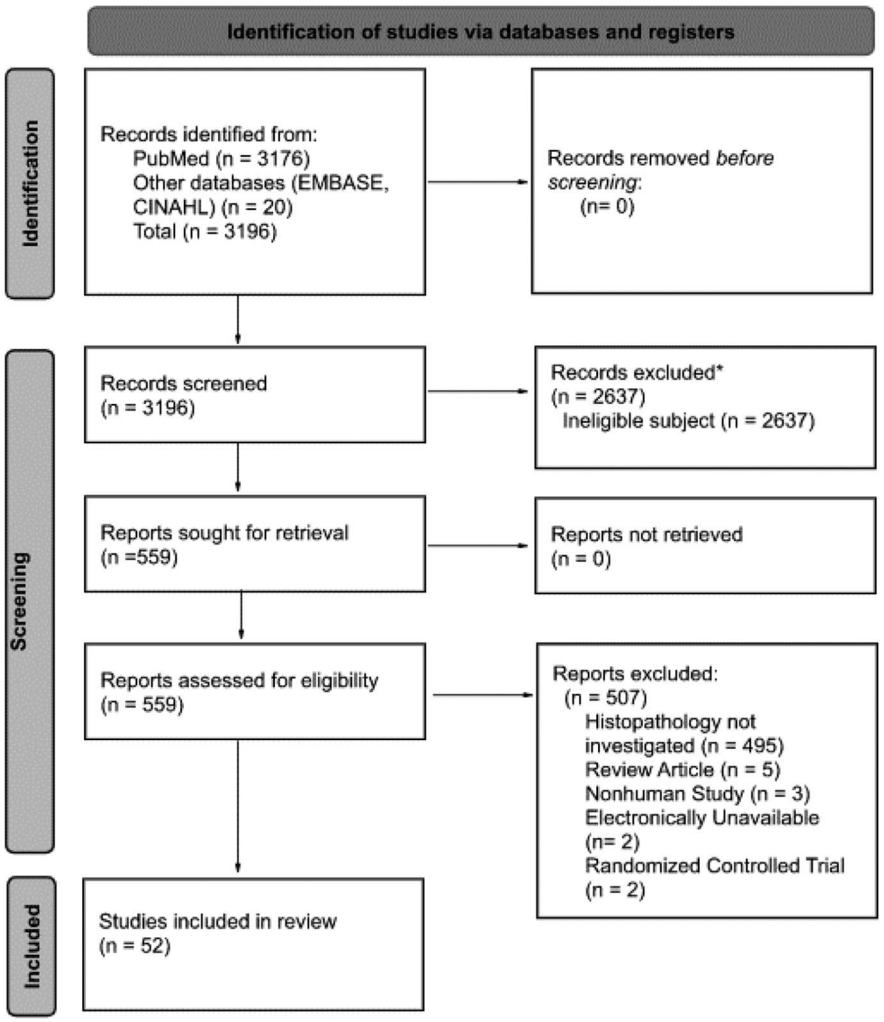

Fig. 1 This study flow diagram shows the studies that were included in this review.

Achilles tendinopathy, eight evaluated long head of the biceps tendinopathy, four evaluated patellar tendinopathy, three evaluated the plantar fascia, five evaluated enthesopathy of the extensor carpi radialis brevis origin (lateral epicondylitis), two evaluated enthesopathy of the flexor-pronator origin (medial epicondylitis), five addressed the knee meniscus, and one addressed the labrum of the hip.

Study Quality and Risk of Bias

To our knowledge, there are no metrics for reporting a study's histopathologic findings or for assessing the quality of histopathologic studies. We were mostly limited to recording the authors' judgment that inflammation and mucoid degeneration were present and that vascularity was greater than expected. Studies varied in how inflammation, vascularity, and degeneration were assessed. Of the studies that used objective means, inflammation was largely assessed by quantifying inflammatory cells or cytokines. For vascularity, vessel count per unit of area was often used (unit of measurement differed between studies). Several studies used objective scales such as the Bonar scale to quantify vascularity and mucoid degeneration. Studies also varied regarding the number of pathologists reviewing data, with many studies using only a single pathologist and no assessments of reliability.

Primary Study Outcomes

We categorized histopathologic findings by anatomic structure, as follows: enthesis, tendon, labrum, and articular

Table 1. Study findings of inflammation, greater vascularity, and mucoid degeneration by anatomic site

	Inflammation			Greater vascularity				Mucoid degeneration			
Diagnosis	Number of studies	Inflammation cells or markers	Inflammatory cells	Any assessment of vascularity	Quantitative vessel count	Qualitative judgment	Markers	Any mucoid degeneration	Extracellular matrix	Collagen derangement	Fibrocartilaginous metaplasia
Tendinopathy											
Trigger finger	5	1	1	3	1	2		5	5	2	3
Rotator cuff	7	0	0	6	3	3		7	5	7	3
De Quervain	6	2	2	6	1	5	2	6	3	4	2
Posterior tibial	3	0	0	3	3	0		3	3	2	0
Achilles	3	2	2	3	2	1	1	3	2	2	0
Long head of biceps	8	2	1	6	4	2	2	8	6	6	2
Patellar	4	1	1	4	1	3		4	1	3	1
Enthesopathy											
Plantar fascia	3	0	0	3	0	3		3	3	3	1
Extensor carpi radialis brevis origin	5	1	1	5	1	4		5	3	4	2
Flexor-pronator origin	2	1	1	2	0	2		2	1	2	1
Other											
Knee meniscus	5	0	0	1	0	1		5	4	2	3
Hip labrum	1			1	1	0		1	1	1	0
Total	52	10	9	43	17	26		52	37	38	18

Table 2. Summary of study characteristics (inflammation, angiogenesis, and mucoid degeneration)

All studies	Category	% (n)
Inflammation (51 studies)	Inflammatory cells or markers	22 (11)
	Inflammatory cells	16 (8)
Greater vascularity (52 studies)	Any assessment of greater vascularity	83 (43)
	Quantitative vessel count	33 (17)
	Qualitative judgment	48 (25)
Mucoid degeneration (52 studies)	At least one element of mucoid degeneration	100 (52)
	Extracellular matrix	69 (36)
	Collagen derangement	73 (38)
	Fibrocartilaginous metaplasia	69 (36)

disc. We categorized the anatomic location as hand and wrist, elbow, shoulder, hip, knee, or foot and ankle.

Effect Measures and Statistical Analysis

To investigate the factors associated with finding evidence of inflammation, angiogenesis, and mucoid degeneration, including anatomic sites and type of pathologic finding, we performed a bivariate analysis using Fisher exact tests because at least one value in the bivariate table was less than 5. The significance level was set at $p < 0.05$ (Supplemental Table 2; http://links.lww.com/CORR/A996).

Results

Differences in the Histologic Findings of Structural Soft Tissue Conditions by Anatomic Site

Regarding differences in the histopathologic findings of surgical specimens with structural soft tissue conditions by anatomic site, there were no differences in inflammation or mucoid degeneration, and the knee meniscus was less often described as having greater than normal vascularity.

A single study of the hip labrum [70] did not investigate inflammation, and only 20% (10 of 51) noted some element of inflammation. Of those 10 studies, nine identified inflammatory cells in tissue and one [68] identified a molecular marker of inflammation alone. There were no statistical differences in inflammation by location (Table 2). The three studies of plantar fasciitis, seven of rotator cuff tendinopathy, and five of disease of the knee meniscus reported no tissue inflammation (Table 1). Of eight studies investigating the long head of the biceps tendon, two reported inflammation, and one of the two based this only on the presence of inflammatory markers and not the presence of inflammatory cells (Table 1).

With respect to vascularity, 83% (43 of 52 studies) reported increased vascularity: 67% (35 of 52) used qualitative judgments and 33% (17 of 52) used quantitative measures. All of the five studies that used molecular markers reported greater vascularity.

One hundred percent (all 52 studies) identified some element of mucoid degeneration: 71% (37 of 52) reported an increased extracellular matrix, 73% (38 of 52) reported disorganized collagen, and 35% (18 of 52) reported chondroid metaplasia (Table 1). There were no differences in components of mucoid degeneration by anatomic site (Table 2).

Differences in the Histologic Findings of Structural Soft Tissue Conditions by Structure

There were no differences in inflammation, vascularity, or mucoid degeneration by anatomic structure (Table 2).

Discussion

Soft tissue conditions such as tendinopathy, enthesopathy, labral degeneration, and articular disc degeneration are often described as "tears" or ascribed to use of the limb (for example, wear and tear, repetitive motion, or overuse) [2, 84]. Not only are these concepts unsupported by epidemiologic and pathophysiologic evidence, but they also reinforce unhelpful patient thoughts [13, 65, 79] and behaviors, and are known to increase symptom intensity and the magnitude of incapability [5, 76]. Based on studies of the histopathology and epidemiology of rotator cuff tendinopathy, conceptualization of this condition evolved from "impingement" (activity-related) to an intrinsic and age-related pathophysiology [50, 85]. We are aware that the histopathologic finding of surgical specimens of structural (collagenous) soft tissue disease is often

consistent with mucoid degeneration, but we did not find a systematic review of histopathologic studies. This systematic review of the histopathologic evidence of operative specimens from procedures addressing various diseases of structural and collagenous soft tissues found consistent signs of mucoid degeneration at all structures and sites, minimal evidence of inflammation, and imprecise and uncontrolled evaluations of vascularity, which seems inconclusive and unsupportive of injury or inflammation. Reconceptualizing tendinopathy, enthesopathy, and labral and articular disc pathologic findings as being inconsistent with damage from a single event or repeated activity based on this evidence might foster healthier mindsets with corresponding alleviation of symptoms, and help patients and surgeons be mindful of the notable base rate of these conditions as people age, with corresponding reductions in overdiagnosis and overtreatment [35].

Limitations

This review has several limitations. One is the imprecise, variable, and sometimes idiosyncratic descriptions authors used of inflammation, repair, and mucoid degeneration in tissue samples. To our knowledge, there is no standardized method for evaluating and reporting histopathologic findings in tissue samples. A few studies used scales such as the Bonar scale, which unhelpfully mixes evaluations of vascularity with myxoid degeneration. Most only reported the pathologist's judgment. Of the measured variables, greater than expected vascularity was measured the most inconsistently. The presence or absence of changes consistent with myxoid degeneration or inflammation seems more reliable. However, our review represents the best available evidence to date and includes these limitations. A second limitation is that most of the samples were reviewed by a single pathologist with no testing of reliability. For most of the studies, the interpretations and descriptions inadequately account for the beliefs and biases of the investigators using more rigorous experimental techniques. Again, the current systematic review can serve as a cataloging of shortcomings of the current evidence and indicate where the evidence currently is. A third limitation is that many of the studies did not quantify myxoid degeneration, inflammation, or vascularity as a primary goal of the study and consequently did not elaborate on methods. A final limitation is that control tissue from either living or cadaver sources that may be deemed healthy might not be. The absence of pain or symptomatology does not qualify a tendon as not having the possibility for degeneration or any other cellular alteration. Future studies of histopathology can use standardized methods, test reliability among multiple pathologists, and report experimental techniques in greater detail. A fourth limitation is that the controls for many of the vascular assessments may not have been normal. We cannot assume the absence of a diagnosis or symptoms reported by a patient's family means there are no pathologic changes. Future studies will need to be more rigorous in their selection of controls.

Differences by Anatomic Site

The observation of consistent histopathologic findings of mucoid degeneration across anatomic sites suggests a common, nonrepair, noninflammatory pathophysiology. Combined with evidence on prevalence and accommodation [15, 50, 75, 79], the evidence of similar histopathology across sites with differences in weightbearing, shape, mobility, and other factors indicates that mucoid degeneration represents senescence (programmed biological degradation) rather than a response to events in the local environment [1]. This is important for at least two reasons. First, our conceptualization of the pathology of collagenous soft tissue structures as representing a form of injury may be inaccurate. Given that theories implicating injury or activity reinforce unhelpful thoughts about painful activity associated with greater discomfort and incapability [63, 76, 78], it seems prudent to rethink our conceptualization of structural soft tissue diseases. Second, if these changes represent a form of senescence (programmed biological deterioration with age), then patients and surgeons can expect a notable and increasing base rate of symptomatic and asymptomatic changes to these structures. There is evidence from studies of imaging, operative visualization, and postmortem examinations that most of us experience these conditions as we age [1, 32, 50]. Given the propensity of humans to misinterpret new symptoms as new diseases [35, 82], and often as injury [18, 35, 38], combined with the potential for symptoms to be inappropriately ascribed to imaging findings, there is a notable potential for misdiagnosis, overdiagnosis, and overtreatment of these conditions [5, 63].

Differences by Anatomic Structure

The observation that mucoid degeneration was consistent, inflammation uncommon, and vascularity imprecise and not clearly abnormal suggests a common underlying pathophysiologic process that may not be related to injury, use, or attrition. In conflict with this interpretation of the findings, a recent systematic review of the histologic and molecular aspects of rotator cuff tissue obtained at the time of defect closure interpreted molecular markers as indicating inflammation and angiogenesis [14], but we do not know the expected prevalence of these markers in mucoid degeneration. Studies addressing the hypothesis that

tendinopathy or enthesopathy is degenerative—such as one study in this systematic review of the histopathology of 80 rotator cuff tendon stumps obtained during surgery to close a rotator cuff defect [22]—have found all tendons have elements of mucoid degeneration [1, 46]. Reviews of the histopathology of Achilles tendinopathy and patellar tendinopathy also found mucoid degeneration [28, 44]. The structures studied (tendon, enthesis, labrum, and disc) have different roles and shapes but similar structural properties. The observation that mucoid degeneration is similar in these structures suggests a senescent process is present. In other words, the common pathophysiology is most likely because of deterioration with age rather than activity or injury. This is a notable finding, given the prevalence of theories of injury or overuse in patients with these conditions [2, 43, 77]. We know that new pains from gradual-onset conditions are often misinterpreted as injury [12, 15, 20, 22]; additionally, the thought that painful movement is harmful increases pain intensity and the magnitude of incapability [13, 23, 51]. That is, the concepts of injury, inflammation, and overuse can arise from human thoughts and emotions in response to symptoms and they can make people more ill [10, 45, 51]. The prevalence of mucoid degeneration at these sites suggests we can develop more accurate concepts and tell a healthier story about these diseases.

Conclusion

Our systematic review of the histopathology of structural, collagenous soft tissue diseases identified universal mucoid degeneration, very limited inflammation, and equivocal interpretation of vascularity. These findings indicate the need for greater rigor in evaluating the histopathology of these structures and indicate a noninflammatory, nonactivity-related etiology. Combined with epidemiologic data, we interpret these data as indicating senescence, or programmed deterioration with age, rather than response to injury or activity. Surgeons and patients might misinterpret painful activities as activities that cause or worsen pathophysiology. Misconceptions such as these may have contributed to inaccurate theories of etiology and pathogenesis related to injury or activity causing inflammation or damage [35, 38]. Given that conceptualization of these conditions as related to activity or injury might cause harm by reinforcing common unhelpful thoughts known to be associated with greater pain intensity and magnitude of incapability, it seems prudent to err toward a concept of no association with use and no evidence of damage. Furthermore, given the prevalence of age-related myxoid degeneration of structural soft tissue structures, the prevalence of imaging findings in asymptomatic individuals, and the absence of evidence of injury or repair, we are better off assuming that changes consistent with mucoid degeneration likely have a relatively limited relationship with symptoms in order to limit the potential for overdiagnosis and overtreatment.

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