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Bony Stress and Its Association With Intervertebral Disc Degeneration in the Lumbar Spine: A Systematic Review of Clinical and Basic Science Studies

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Abstract

Study Design: Translational review encompassing basic science and clinical evidence.

Objectives: Multiple components of the lumbar spine interact during its normal and pathological function. Bony stress in the lumbar spine is recognized as a factor in the development of pars interarticularis defect and stress fractures, but its relationship with intervertebral disc (IVD) degeneration is not well understood. Therefore, we conducted a systematic review to examine the relationship between bony stress and IVD degeneration.

Methods: Online databases Scopus, PubMed and MEDLINE via OVID were searched for relevant studies published between January 1980-February 2020, using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines. Two authors independently analyzed the data, noting characteristics and biases in various studies.

Results: Thirty-two articles were included in the review: 8 clinical studies, 9 finite element modeling studies, 3 in-vivo biomechanical testing studies, and 12 in-vitro biomechanical testing studies. Of the 32 articles, 19 supported, 4 rejected and 9 made no conclusion on the hypothesis that there is a positive associative relationship between IVD degeneration and bony stress. However, sufficient evidence was not available to confirm or reject a causal relationship.

Conclusions: Most studies suggest that the prevalence of IVD degeneration increases in the presence of bony stress; whether a causal relationship exists is unclear. The literature recommends early diagnosis and clinical suspicion of IVD degeneration and bony stress. Longitudinal studies are required to explore causal relationships between IVD degeneration and bony stress.

Keywords

Bony stress, intervertebral disc degeneration, lumbar spine, clinical studies, cadaver testing, finite element analysis, in vivo testing

Background

Low back pain (LBP) is widespread, with a lifetime prevalence of 65-80% in the general population.[1] The prevalence of LBP is similar in adolescents and adults, with 70-80% of cases occurring by the age of 20.[2] Adolescents with LBP and familial history of LBP are more likely to experience LBP later in life.[3] As degenerative processes in the lumbar spine can begin in the first decade of life, adolescents present as interesting cases to study the interaction between the relatively stiff bony elements and the viscoelastic intervertebral disc (IVD) while avoiding potential age-related confounding factors.[4]

Bony stress refers to bony edema or a bony defect of the vertebrae, which includes a pars interarticularis defect and

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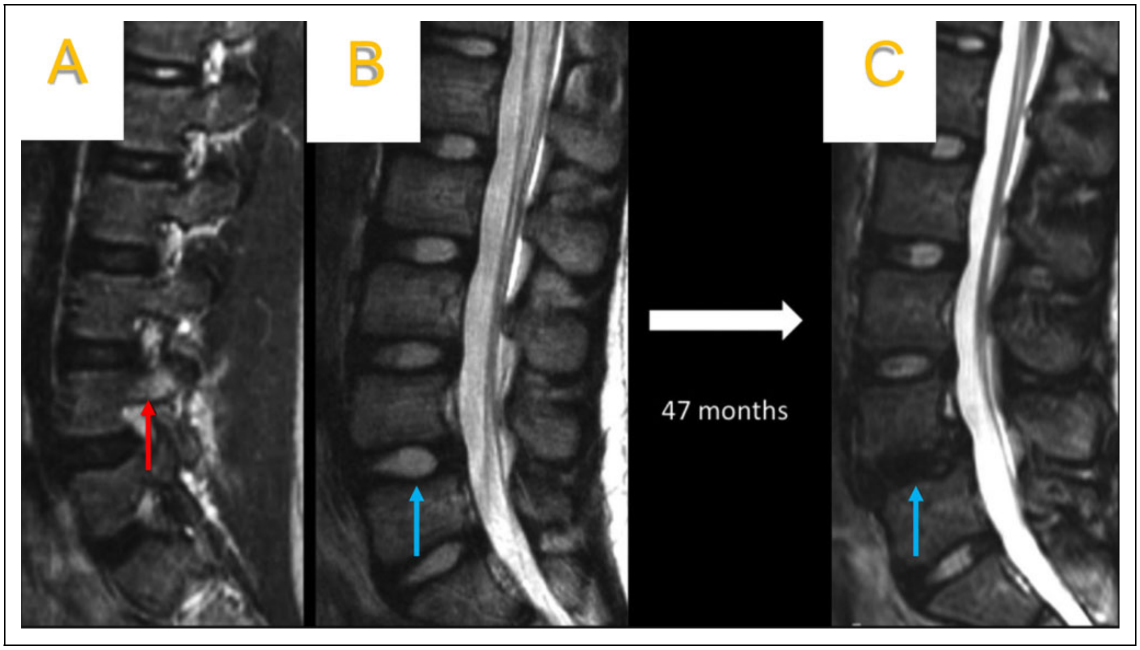

Figure 1. (A) T2 weighted mid-sagittal cut on magnetic resonance imaging (MRI) of a 12-year-old female patient showing edema in the L4 right pedicle (red arrow). MRI from initial presentation (B) and 47-month follow up (C) shows the progression of L4-L5 disc degeneration (blue arrows). Other discs in the lumbar spine, including the L5-S1 disc that normally experiences the greatest axial load, are spared from degeneration.[7] Image courtesy Sharma et al 2017.

spondylolysis. Abnormal load and stress distribution are believed to be precursors to a bony stress fracture and IVD degeneration.[5] Sharma et al (2014) defined bony stress on magnetic resonance imaging (MRI) of the lumbar spine (Figure 1) as "bony oedema or a bony defect involving either pars interarticularis or pedicles."[6] The authors recognized early phases of bony stress on MRI and concluded that early imaging assessment may prevent a complete fracture non-union from occurring. Bony stress is thought to either alter load transmission throughout the IVD or occur secondary to the altered load distribution following IVD degeneration.[7]

Whether IVD degeneration is a causative factor for discogenic LBP is unclear.[8-10] Discogenic LBP may arise from not only the structural failure of the IVD but also from nociceptive neurotransmitters, and neural and vascular ingrowth in the outer annulus fibrosus.[11] IVD degeneration has a variety of recognized risk factors and causes including genetic inheritance, age, lifting, loading or repetitive movement activities, nutritional factors, the anatomy of the lumbar spine, weight, gait and posture; but is usually multifactorial.[6,12] It remains unclear whether IVD degeneration alters vertebral loading patterns or segmental movements or both, in a manner that results in bony stress in the vertebrae adjacent to the disc.

The functional spinal unit is a 3-joint complex comprising an IVD and 2 posterior facet joint capsules. Suboptimal performance of one joint adversely affects the other 2, and this may result in their accelerated degeneration.[13] However, it is also believed that the articulations are closely linked to load distribution in the surrounding bony tissues and that the system involves more than just the 3 points of contact between 2 vertebrae.[14] It remains unclear whether altered mechanics consequent to the degenerative changes in the 3-joint-complex can lead to or are associated with bony stress in the lumbar vertebrae.

While IVD degeneration has a multitude of risk factors and causes, the relationship between IVD degeneration and bony stress in the lumbar spine is of interest. To present a comprehensive understanding of the pathophysiology of bony stress and its relationship with IVD degeneration, we conducted a systematic review of the basic science (in-vivo animal testing, computer modeling, and in-vitro biomechanical testing) and clinical data available in the published literature.

Methods

Eligibility Criteria

Only journal articles and book chapters in English, published between January 1980 and February 2020 were considered for this review. The inclusion criteria were:

1. Studies reporting clinical data on bony stress and IVD degeneration in the lumbar spine
2. Finite Element (FE) modeling studies making use of imaging data from living human subjects or human cadaveric material

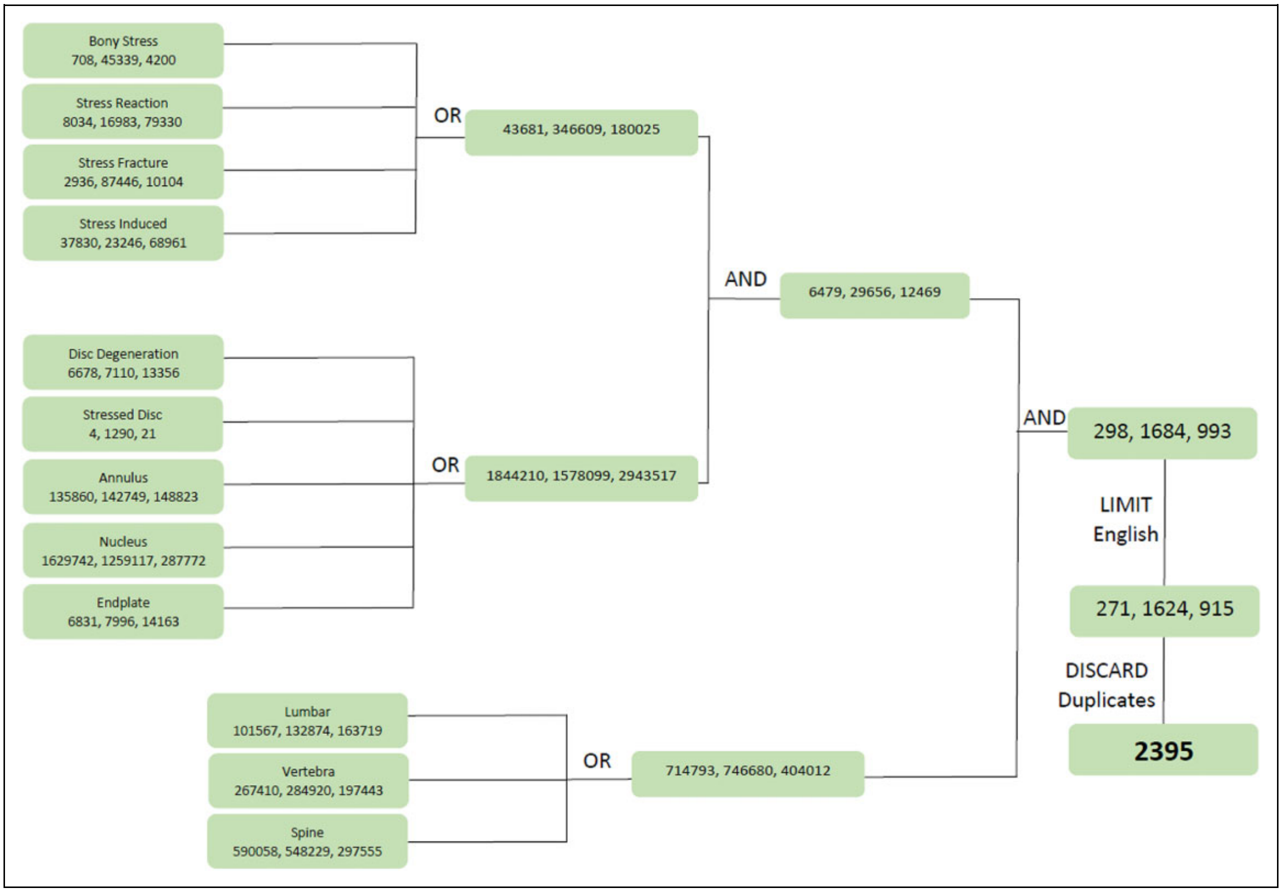

Figure 2. Database search strategy and keywords used in the systematic review. Numbers under each search term represent the number of results returned from MEDLINE via OVID, PubMed, and Scopus online databases, respectively. The actual search included the use of synonyms and truncation for high sensitivity and low specificity.

3. Biomechanical *in vitro* testing studies making use of human and non-human cadaveric material
4. *In vivo* animal studies reporting on the association between induced vertebral damage and IVD degeneration

The exclusion criteria were:

1. Studies reporting clinical data on the surgical treatment of bony stress fracture in the spine

Search Strategy

A review of the literature was undertaken following the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines.[15] Electronic databases Scopus, PubMed, and MEDLINE, were searched using relevant keywords for journal articles and book chapters in English, published between January 1980 and February 2020. The search strategy, as presented schematically in Figure 2, was intentionally designed to be of high sensitivity and low specificity to ensure that a minimum of potentially relevant studies was excluded based on poor keyword assignment or regional variations in terminology and spelling.

Study Selection

Abstract screening, full-text review for the eligibility criteria were used to include relevant studies. This process was conducted by 2 reviewers (DC and UC).

Data Extraction and Risk of Bias

Studies included in the final search were read, analyzed, and synthesized independently by 2 reviewers (DC and UC). A third reviewer (ADD) was available to resolve any disagreement between the 2 reviewers but was not needed. Due to the heterogeneity in the type of studies considered, the risk of bias was independently assessed for each study (instead of using a bias assessment tool). Data extracted from clinical studies varied depending on how the outcomes were reported and included specific details about the cohort, outcomes assessed, and results. The primary outcome of interest was the evidence of association (or lack thereof) between bony stress and IVD degeneration in the lumbar spine, defined as

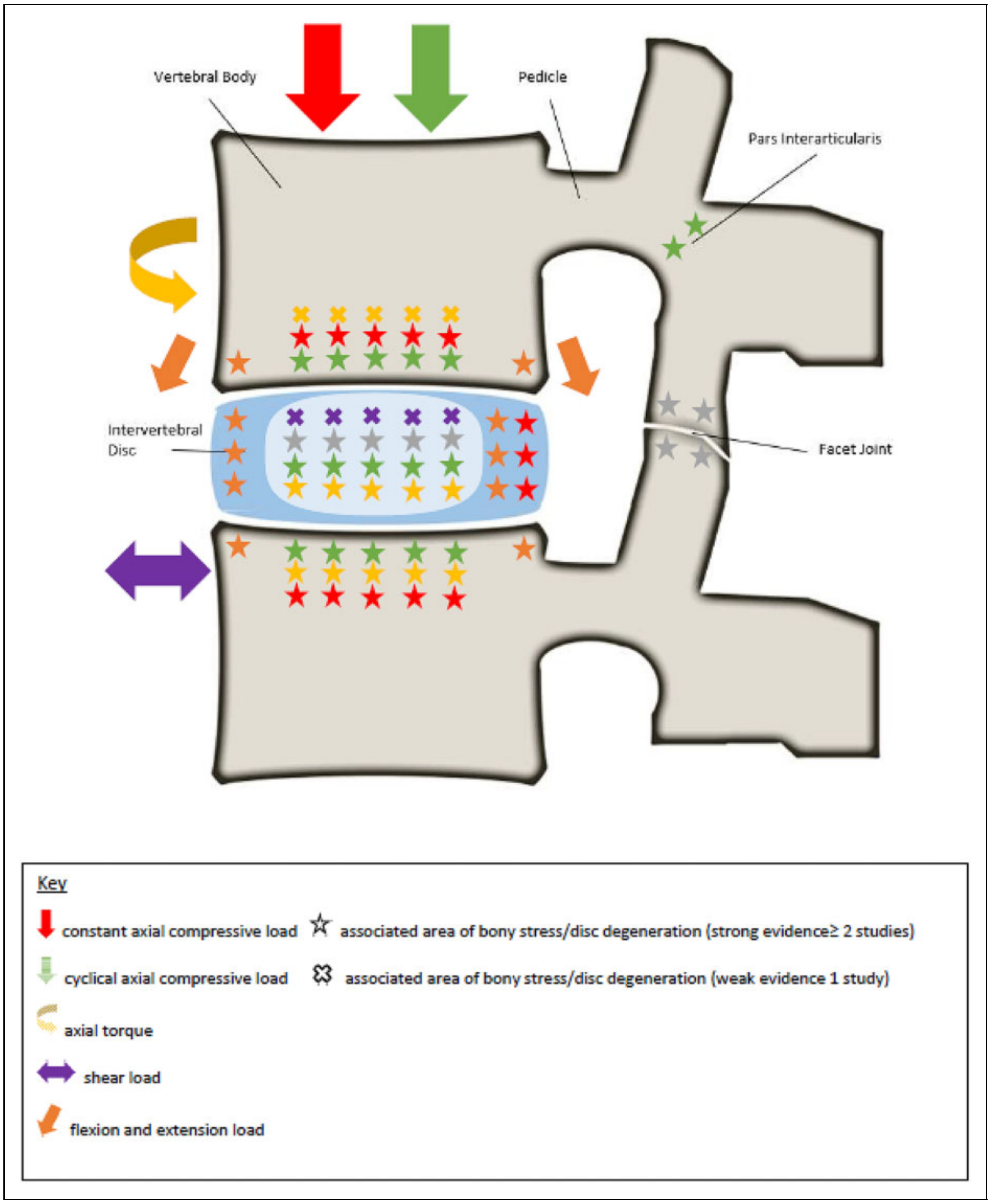

Figure 3. Color coordinated diagram showing positive associations between bony stress, intervertebral disc (IVD) degeneration and load in the lumbar spine segment as reported in various cadaveric, live animal, and finite element modeling studies. A color represents each loading force, and its corresponding region of positive association is shown with the same colored star or cross. A positive association was defined as an increased prevalence of bony stress with IVD degeneration or vice versa. The gray star has no corresponding load.

an increased (or unchanged) prevalence of bony stress with IVD degeneration.

Data Presentation

Due to heterogeneity in the type of studies included in the review and the outcomes reported, a meta-analysis of the data could not be undertaken. Therefore, data was collated into tables grouped by the type of study, and a narrative overview of the results was presented. Pictograms of the lumbar spine were used to present the synthesis of results from basic science and clinical studies separately (Figures 3 and 4).

Results

The search identified 2810 potential studies with 2395 studies remaining after duplicates were removed. Following a review of the titles and abstracts of all 2395 studies, 73 studies were identified for potential inclusion. On examination of the full texts against the inclusion criteria, 32 were included in the final review. Reference lists from these 32 studies were further

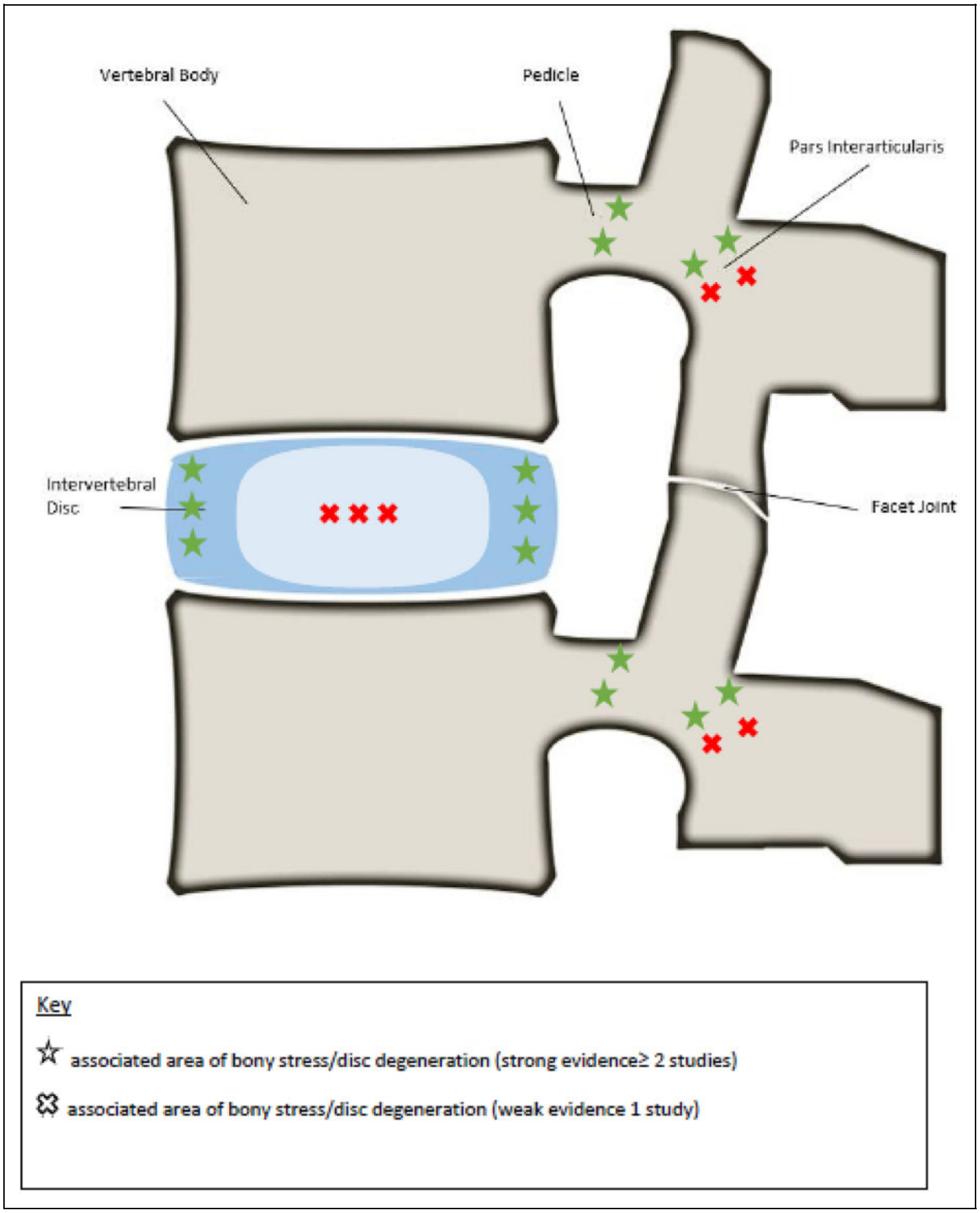

Figure 4. Color coordinated diagram showing positive associations between bony stress and intervertebral disc (IVD) degeneration in the lumbar motion segment based on data extracted from clinical studies. A positive association between nucleus pulposus degeneration and bony stress in the pars interarticularis is shown in red, and a positive association between annular degeneration and bony stress in the pars interarticularis and the pedicle is shown in green. A positive association was defined as an increased prevalence of bony stress with IVD degeneration.

reviewed for identifying relevant studies, but none were found. A flowchart of the selection process is presented in Figure 5.

The characteristics of each of the 32 studies are presented in Table 1. Eight clinical, 9 FE analysis, 3 in-vivo biomechanical testing, and 12 in-vitro biomechanical testing studies are presented in this review. In the clinical studies, cohort sizes ranged from n = 22 to 642. The studies included retrospective reviews, cross sectional studies and prospective follow-up studies. Basic science studies (FE analysis, in-vivo biomechanical testing and in-vitro biomechanical testing) were mostly cross-sectional. Cohort sizes ranged from n = 15 to 24 for the in-vivo biomechanical testing studies and n = 6 to 600 for the in-vitro biomechanical testing studies. All FE analysis studies based their model on data from one human subject.

Risk of bias was assessed in each study. Limitations included small cohort (or sample) sizes, observer bias, publication bias and selection bias, as well as bias from more recent publications using data from older publications. However, no

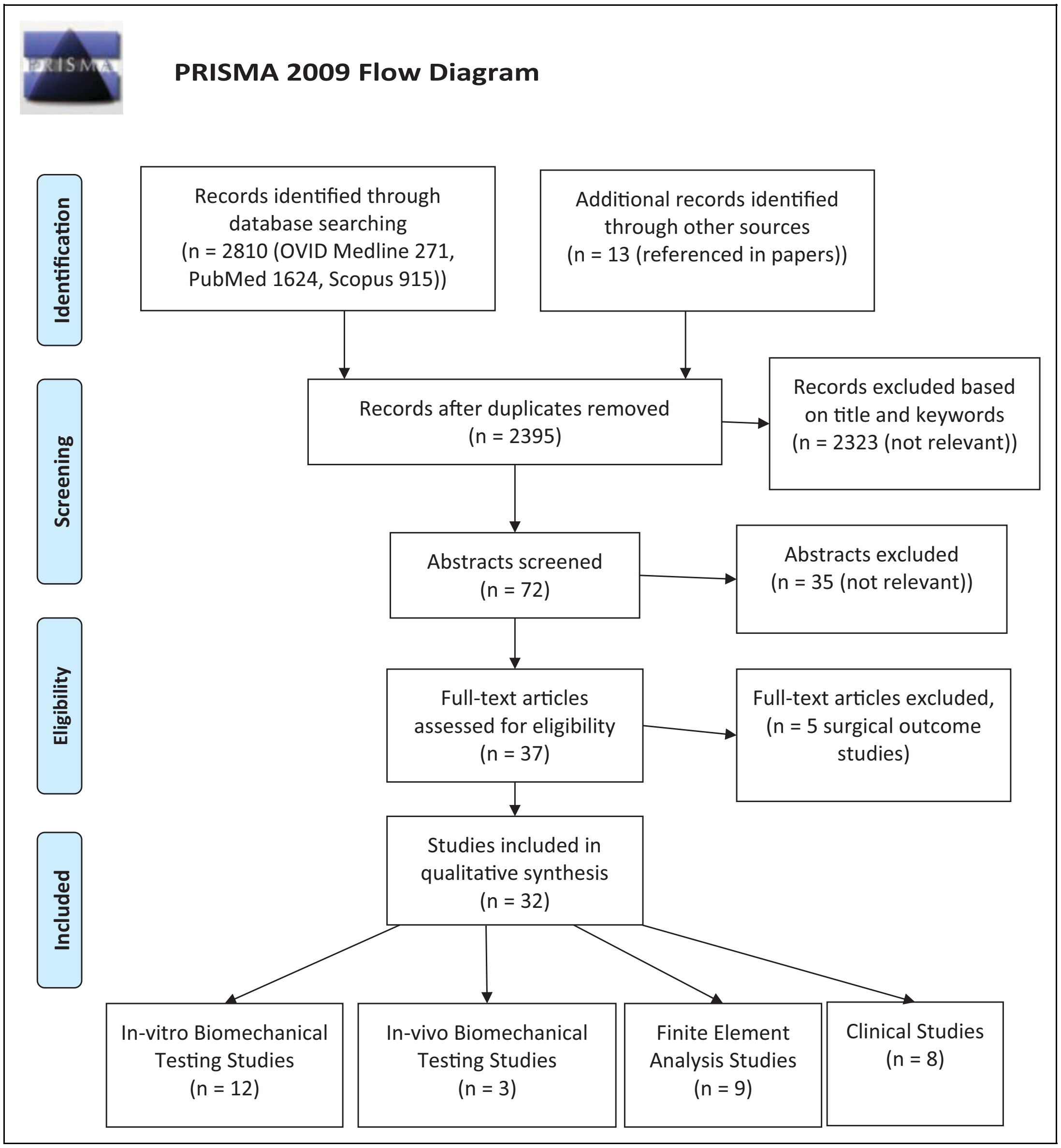

Figure 5. Schematic representation of the results from the literature search of 3 online databases following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15]

study was excluded based on the risk of bias. The majority of studies (59%) reported positive associations between bony stress and IVD degeneration; 13% reported a negative association and 28% did not conclude. The majority (63%) of human studies reported a positive association, none reported a negative association, and 37% did not conclude. The majority (56%) of FE modeling studies reported a positive association; 22% reported a negative association, and 22% did not conclude. None of the in-vivo biomechanical testing studies reported a positive association; 33% reported a negative association, and 67% did not conclude. The majority (75%) of in-vitro biomechanical testing studies reported a positive association; 8% reported a negative association, and 17% did not conclude.

The data from basic science and clinical studies was synthesized separately and presented spatially using pictograms of the lumbar spine (Figure 3 and 4).

Discussion

This translational review aimed to examine the relationship between bony stress and IVD degeneration in the lumbar spine by analyzing evidence from the published literature. A total of 32 studies met the inclusion criteria for this review. Of those 32 studies, 19 reported evidence supporting a positive association and 4 reported evidence supporting a negative association or no association between bony stress and IVD degeneration. Nine studies did not provide any evidence on the nature of the

Table 1. Characteristics of Studies Included in the Review.

Clinical studies							
Author and year	Objective	Cohort	Age and sex	Follow-up	Results	Supports IVD & Bony stress associative relationship	Limitations & bias
Hollenberg et al (2002)[16]	To examine the reliability of MRI grading system for bony stress in pars interarticularis	55 athletes with LBP and suspected stress injury to pars interarticularis	Female age 14.7 ± 2.6 (8-22 years); male age 18.9 ± 4.5 (14-31 years). 28 females and 27 males	Retrospective study	23 of 55 patients had bony stress or spondylolysis visible on MRI. Interobserver reliability for the 3 radiologists was sufficient (Kappa coefficients ranged from 0.71 to 1.00 (95% CI, 0.55-0.86))	N/A	N/A
Congeni et al (1997)[17]	To investigate the treatment regimen and radiological healing of bony stress and fracture	40 athletes with LBP and evidence of spondylolysis by nuclear medicine study	Average age of 14.5 years (range 12-20); 31 males and 9 females	Prospective study, follow-up of 6 months	Hyperextension avoidance for 6-8 weeks, physical therapy and guided return to play sport was useful in 47% of acute fractures	N/A	N/A
Maurer et al (2011)[18]	To compare MRI findings between rowers and inactive controls	22 asymptomatic rowers and 22 controls	Rowers' age 16.0 ± 1.63 years, controls' age 16.27 ± 1.31 years. 44 males	Cross sectional study	Seven rowers had IVD degeneration and 6 had bony stress; 3 controls had IVD degeneration and none had bony stress	Yes	Small cohort size, a specific patient group—findings may be less relevant to a broader population
Ranson et al (2010)[19]	To study changes in MRI of lumbar spine and incidence of stress fracture captured over 2 years	28 fast bowlers	Average age of 19 years (range 16-24); 28 males	Prospective study; follow-up of 2 years	12 bowlers had stress fractures. Fifteen bowlers had bony stress; 11 of these had a partial or complete stress fracture within a mean of 10 weeks; the relationship was highly significant (Fisher's exact text, $P <$ 0.001). Three bowlers had IVD degeneration	Yes	Small cohort size, a specific patient group—findings may be less relevant to a broader population
Sharma et al (2014)[6]	To investigate the prevalence and pattern of IVD degeneration in lumbar segments with and without bony stress	87 patients under 25 years diagnosed with bony stress or stress fracture	Average age of 15.3 ± 3.3 (range 5-25); 55 males and 32 females	Retrospective study	Burden (per disc basis, e.g. if AF tear in 1 of 2 stressed IVDs, burden is 0.5) of AF tears 0.6 in stressed IVDs compared to 0.28 in controls. NP degeneration burden was 0.13 in stressed IVDs and 0.02 in control IVDs	Yes	N/A
Sharma et al (2017)[7]	To study the pattern of IVD degeneration in lumbar segments with and without bony stress	42 patients under 25 years diagnosed with bony stress or stress fracture and presenting with LBP without acute injury	Average age of 16.0 ± 3.7 (range 7-25 years); 22 males and 20 females	Retrospective study; follow-up of >6 months	Burden (per disc basis, e.g. if AF tear in 1 of 2 stressed IVDs, burden is 0.5) of AF fissures, radial fissures and herniation was more in bony stress segments	Yes	N/A

(continued)

Table 1. (continued)

Clinical studies							
Author and year	Objective	Cohort	Age and sex	Follow-up	Results	Supports IVD & Bony stress associative relationship	Limitations & bias
					compared to the control segments (0.76 ± 0.35, 0.59 ± 0.43, 0.07 ± 0.20, compared to 0.37 ± 0.48, 0.17 ± 0.38, 0.00 ± 0.00 respectively)		
Celtikci et al (2018)[20]	To investigate the prevalence of spondylolysis and IVD degeneration in different types of military roles and payload weights	642 military personnel with LBP; CT or MRI scans available	Average age of 22.9 years; 642 males	Retrospective study	14.6% had spondylolysis; higher prevalence of spondylolysis (34.2%) in the group with increased payload (increased axial load on the spine); 27.2% of spondylolysis had disc degeneration, 72.7% did not	N/A	follow up scans not available, did not provide results of IVD degeneration in non-spondylolytic group
Chepurin et al (2019)[21]	To investigate the prevalence of bony stress and IVD degeneration	55 patients with bony stress; 75 patients without bony stress on MRI	Average age 18.2 years; 73 males and 57 females	Retrospective study	Bony stress segments had over 2-fold (odds ratio 2.3 (95%CI 1.1-4.8)) higher likelihood of having IVD degeneration than the normal segments	Yes	N/A
Finite Element Modeling Studies							
Author and Year	Objective	Model Characteristics	Segment Tested	Load	Results	Supports IVD and Bony Stress Associative Relationship	Limitations and Bias
Kim et al (2013)[22]	To study the biomechanical influence of facet orientation and facet tropism on stress in the corresponding segment	CT data from a 46-year-old male	L2-3	Flexion, extension, lateral bending, torsion, anterior shear	Facet orientation did not alter IVD stress or facet joint stress at the corresponding level	N/A	Hyperelastic properties of IVD tissues not considered
Qasim et al (2014)[23]	To investigate the initiation and progression of structural damage in the annulus based on continuum damage mechanics methodology	Modeling IVD degeneration to mimic Thompson Grade III and IV degenerative changes, fatigue analyses based on damage accumulation	L4-5	Flexion, extension, axial rotation, lateral bending	Increased stress in posterior AF and central EP in disc degenerated model when compared to the healthy model	Yes	Hyperelastic properties of IVD tissues not considered. Changes in material properties due to fluid flow not considered in fatigue analysis

(continued)

Table 1. (continued)

Finite Element Modeling Studies							
Author and Year	Objective	Model Characteristics	Segment Tested	Load	Results	Supports IVD and Bony Stress Associative Relationship	Limitations and Bias
Guo and Fan (2017)[24]	To investigate the effect of single-level disc degeneration on the dynamic response of whole lumbar spine to vibration	CT data from female spine, motion segment with IVD degeneration at L4-5	L1-S1	Follower compressive (400 N) with vibrations ($\pm$40 N)	Decreased IVD bulge and AF stress and increased NP stress in IVD degeneration model compared with the intact model	N/A	A simplistic model of IVD degeneration based on 16.5% and 33% disc height loss and change in material properties
Du et al (2014)[25]	To investigate how sitting posture affects the response of thoracolumbar spine in ejection systems	Dynamic multi-body model, and an FE model of spine based on a 35 years old healthy male	T9-S1	Axial compressive	Ejection impact contributed to axial compression and anterior flexion of the spine, more so in the relaxed posture than the normal sitting posture	Yes	N/A
Huang et al (2014)[26]	To investigate the influence of NP removal on biomechanical response of lumbar motion segment	CT data from an adult male	L4-5	Axial compressive, flexion, extension, lateral bending, axial rotation	Increased stress in AF and facet joints	Yes	Complete NP removal not a clinically relevant scenario, single segment model—did not study adjacent segment changes
Galbusera et al (2011)[27]	To study the effects of degenerative morphological changes in IVD on lumbar spine biomechanics	CT based poroelastic model	L4-5	Axial compressive, flexion and extension	Axial displacement, facet force decreased when IVD height is decreased. Axial displacement, facet force and fluid loss reduced when water content is decreased. EP sclerosis had no significant findings.	No	Artificial IVD height, EP sclerosis, water content and IVD permeability model not comprehensively validated, sclerosis modeling approach arbitrary
Chosa et al (2004)[28]	To evaluate stress in the lumbar pars interarticularis region	CT data from a 29-year-old male	L4-5	Axial compressive, flexion, extension, lateral bending, rotation	Stress located principally in pars interarticularis. Axial compression caused stress in whole vertebra, compression and flexion caused stress in anterior vertebra and posterior pars, compression and extension caused stress in posterior vertebra and pars, compression and right lateral bending caused stress in right vertebra and pars, compression and left rotation caused stress in whole vertebra and pars	Yes	Hyperelastic properties of IVD tissues not considered; single motion segment modeled,

(continued)

Table 1. (continued)

Finite Element Modeling Studies							
Author and Year	Objective	Model Characteristics	Segment Tested	Load	Results	Supports IVD and Bony Stress Associative Relationship	Limitations and Bias
Yu et al (2015)[29]	To compare stress distribution between normal and degenerated IVD models	CT model, one segment with IVD degeneration	L4-5	Axial compressive, flexion, extension, lateral bending, axial rotation	Similar stress distribution between normal and IVD degenerated segment. Stress increased most under flexion loads	No	IVD degeneration artificial, hyperelastic properties of IVD tissues not considered, lack of model validation
Zahari et al (2017)[30]	To study the effects of body weight on intradiscal pressure and AF stress	CT data from a 21-year-old male, no deformities	L1-5	Axial compressive, flexion, extension	Maximum Iintradiscal pressure at L12 in flexion; greatest increase in pressure with weight observed at L45 ($\sim$30%). Intradiscal pressure decreased with increasing weight in extension loading	Yes	Lack of model validation

In-vivo Biomechanical Testing Studies							
Author and Year	Objective	Cohort	Intervention	Follow-Up	Results	Supports IVD and Bony Stress Associative Relationship	Limitations and Bias
Sairyo et al (2004)[31]	To understand the pathomechanism of slippage in immature spines	20 Wistar rats	L5 laminectomy, and L56 bilateral facetectomy	1, 3, 5, 7 days	None had IVD degeneration; slippage observed on Day 7, growth plate injury of the vertebral body	N/A	Spinal loading and anatomy different in rats compared with humans; IVD degeneration may have a more extended gestation period
Baranto et al (2005)[32]	To study injury patterns in the adolescent porcine spines with induced IVD degeneration	24 pigs	Hole drilled through cranial EP; animals sacrificed 2 months later functional spinal units harvested and exposed to compression load until failure	2 months	IVD degenerated segments were able to tolerate more compressive load compared with the non-degenerated ones	No	Method to induce IVD degeneration is not directly relevant to naturally occurring degeneration in humans.

(continued)

Table 1. (continued)

In-vivo Biomechanical Testing Studies							
Author and Year	Objective	Cohort	Intervention	Follow-Up	Results	Supports IVD and Bony Stress Associative Relationship	Limitations and Bias
Kim et al (2012)[33]	To investigate if the sustained application of shear force causes IVD degeneration	15 male Sprague–Dawley rats	Implantable loading device creating a shear force	One, 2 weeks	All 12 shear loaded rats had IVD degeneration, 0 in the control group	N/A	Artificially induced shear stress may be different in magnitude, application, duration from naturally occurring shear stress in human IVDs
In-vitro Biomechanical Testing Studies							
Author and Year	Objective	Sample Size	Sex	Load	Results	Supports IVD and Bony Stress Associative Relationship	Limitations and Bias
Ryan et al (2008)[34]	To understand the interdependence of IVD and subdiscal trabecular bone properties.	Lumbar spine segments from 10 sacrificed pigs	Complex axial loading of segments	N/A	Compressive load resulted in uniform stress distribution in the IVD. Asymmetric load resulted in increased peripheral IVD and adjacent bone stress	Yes	Anatomical differences between pigs and human spines, and therefore results not directly translatable
Veres et al (2010)[35]	To investigate whether torsion in combination with flexion affects the failure mechanics of IVD	30 motion segments from 10 sacrificed sheep	Axial rotation and flexion	N/A	17 vertebral failure and 8 IVD failure; IVD failure mostly occurring in mature motion segments	Yes	Morphological and stiffness characteristics different between ovine and human discs
Wade et al (2014)[36]	To study IVD herniation under compression and flexion	72 motion segments from sheep	Axial compressive load and flexion	N/A	IVD failure required 18% less force than vertebral fracture	N/A	Morphological and stiffness characteristics different between ovine and human discs
Berger-Roscher et al (2017)[37]	To investigate how loading combinations influence IVD failure	30 lumbar spinal segments from 9 sacrificed sheep	Combination of axial compressive, bending and torsion loads, 1000 cycles at 2 Hz loading of segments	N/A	13 segments experienced large endplate failures, 4 experienced sole annulus failures	Yes	Morphological and stiffness characteristics different between ovine and human discs

(continued)

Table 1. (continued)

In-vitro Biomechanical Testing Studies							
Author and Year	Objective	Sample Size	Sex	Load	Results	Supports IVD and Bony Stress Associative Relationship	Limitations and Bias
Sapiee et al (2019)[38]	To investigate the risk of IVD failure due to increased sacral slope and shear stresses	35 ovine lumbar spinal segments	Axial compressive load (9 in the horizontal position, 26 in slopping posture)	N/A	All 9 horizontal segments had endplate failure; none had a pars fracture. Of 26 slopping, 9 had pars fracture observed with or directly after IVD failure	Yes	Morphological and stiffness characteristics different between ovine and human discs
Hansson et al (1987)[39]	To study the effect of cyclic loading on IVD degeneration and failure types	17 thoracolumbar segments	N/A	Cyclic axial compressive	8 normal, 2 slightly degenerated, 7 moderately degenerated, zero severely degenerated	Yes	Small sample size, bending and torsional loads not employed
Hansson et al (1987)[40]	To compare the degree of IVD degeneration with compressive strengths of underlying trabecular bone	12 lumbar spinal segments	N/A	Cyclic axial compressive	Trabecular bone specimens from slightly degenerated IVDs were 24% stronger and 16% stiffer than those from severely degenerated IVDs	Yes	All samples were obtained from only 3 human spines.
Miller et al (1988)[41]	To correlate IVD degeneration with age, sex, and spinal level	600 lumbar IVDs from 273 cadavers	363 males and 237 females	N/A	Male discs more degenerated than female discs at all ages. By age 50, 97% of IVDs exhibited degeneration. L3-4 and L4-5 are usually most degenerated	N/A	N/A
Duncan and Ahmed (1991)[14]	To understand the relevance of axial rotation in IVD degeneration and facet asymmetry in injury mechanisms	35 L23 and 35 L45 specimens	25 males and 10 females	Cyclic axial torsion	No significant effect from different facet joints on the motion of segment or IVD degeneration	No	N/A
Kasra et al (1992)[42]	Experimental and finite element modeling study to measure the impact of vibration on spinal discs and vertebrae	One T12-L1 and 6 lumbar motion segments	Spinal segments were extracted from 4 males and 2 females	Cyclic axial compression	Fracture of bone adjacent to NP was most common and associated with IVD degeneration, AF not vulnerable to rupture under pure axial vibrations	Yes	Small sample size

(continued)

Table 1. (continued)

In-vitro Biomechanical Testing Studies							
Author and Year	Objective	Sample Size	Sex	Load	Results	Supports IVD and Bony Stress Associative Relationship	Limitations and Bias
Adams et al (1993)[43]	To investigate abnormal IVD stress concentration after vertebral body damage	23 lumbar motion segments	17 males and 6 females	Constant axial compression	Testing in the damage induced samples, stress levels in NP and anterior AF fell 30%, while stress increased in posterior AF.	Yes	Only 4 samples <25 years of age, response to torsional and bending loads not examined
Adams et al (2000)[44]	To investigate if minor damage to vertebral bodies can lead to progressive IVD disruption	38 lumbar motion segments	N/A	Compression and Bending	EP damage caused 25% ($\pm$ 27%)reduction in NP pressure and 16%($\pm$ 49%) increased pressure in posterior AF.	Yes	Torsional loads not examined, cyclic loading of the ligamentous lumbar spine gives unreliable results beyond 2000 cycles[45]

KEY: Colors in the first column indicate clinical studies shown in blue, finite element analysis studies shown in red, in-vivo biomechanical testing studies shown in green and in-vitro biomechanical testing studies shown in yellow**;** LBP: low back pain; MRI: magnetic resonance imaging; IVD: intervertebral disc; CT: computed tomography; AF: annulus fibrosus; NP: nucleus pulposus; EP: endplate.
Thirty-two studies were included in total: 8 clinical, 9 finite element analysis, 3 in-vivo biomechanical testing and 12 in-vitro biomechanical testing studies. Due to heterogeneity in the studies, data extracted differed between study categories, and therefore bias is reported in a narrative format.

relationship between IVD degeneration and bony stress. Nonetheless, the results were synthesized and included for the completeness of the literature review. The presence of various biases in the studies included in this review, however, limits the interpretation of the results.

Data from FE analysis and in-vitro biomechanical testing studies suggest that bony stress and IVD degeneration are positively correlated. A wide range of experiments investigating the forces transmitting through the lumbar spine in human and animal cadaveric and FE models have been conducted across the 21 basic science studies included in this review. Most reported a specific load placed onto the lumbar spine that led to both bony stress and IVD degeneration (shown in Figure 3).[14,22-25,28-30,34-40,42-44] Cyclical axial load was found to positively correlate with increased NP stress and stress in the pars interarticularis.[24,38-40,42] These findings suggest that abnormal cyclical loading may lead to increased stress in the NP and redistribution of stress in the pars interarticularis region, which may eventually progress to a spondylolytic defect. Using a FE model of lumbar spine subjected to axial loads, Du et al (2014) reported an increase in stress in the cephalad vertebral body, caudal pedicle, posterior IVD and the endplates.[25] Whether an increased load is associated with bony stress and/or microtrabecular injury is not fully understood.

However, data from in-vivo biomechanical testing studies suggest that bony stress and IVD degeneration are negatively correlated. Animal studies allow for in-vivo examination of spine models, which introduces important concepts of bone remodeling and use of muscles and ligaments.[46] Ryan et al (2008) found that applying an asymmetrical load to pig spinal segments resulted in increased stress in the annulus fibrosus (AF) and vertebral bone adjacent to the AF when compared to a symmetrical load.[34] Baranto et al (2005) found that pigs with induced IVD degeneration (hole drilled through the endplate) were able to bear more compressive load and had altered stress distribution in the bone compared to those without IVD degeneration.[32] The results suggest a negative correlation between bony stress and IVD degeneration, where bony stress does not occur in the presence of IVD degeneration, but rather bone remodeling occurs as a protective mechanism for the IVD. However, cohort sizes in the in-vivo studies ranged from 15 to 24; and with different animal models used the degree to which results may be compared across studies and are translatable to clinical settings remains unclear.[31-33]

The majority of the clinical studies provided evidence for a positive correlation between bony stress and IVD degeneration (shown in Figure 4); none supported a negative correlation. Outcomes were consistent throughout the clinical studies that showed a positive correlation, with all studies using MRI to diagnose bony stress and IVD degeneration.[6,7,18-21] Chepurin et al (2019) found that in a group of 55 patients with bony stress, 38 (69%) had IVD degeneration; whereas in a control group of 75 patients without bony stress, 37 (49%) had IVD degeneration.[21] Sharma et al (2014) compared IVDs adjacent to segments with bony stress with non-adjacent IVDs and found an increased burden of AF tears (0.6 versus 0.28) and NP degeneration (13% versus 2%) in IVDs adjacent to the stressed segments.[6] Sharma et al (2017) conducted a follow-up study of bony stress patients for a minimum of 6 months and found that AF fissures, radial fissures and IVD herniations are more prevalent in bony stress segments compared to the control segments.[7] Progressive IVD degeneration was observed in stressed IVDs irrespective of bone healing,[7] which may suggest the importance of diagnosing early signs of bony stress even if the healing occurs in subsequent follow-up scans. Bony stress may also be a contributing factor to the non-specific LBP, due to its association with IVD degeneration or due to the microtrabecular injury alone or both. However, this hypothesis needs further clinical investigation.

This review noted several gaps in the literature on the association between bony stress and lumbar IVD degeneration. There is not enough evidence to suggest that IVD degeneration is a cause of bony stress in the lumbar spine or vice versa. Whether one is a pathological sequela of the other, or whether the 2 constitute a protective mechanism to mitigate further degenerative changes in the lumbar spine is unknown. Reliability of the results may also be limited in some studies due to small sample sizes *and specific population inclusion criteria (some studied athletes only),* and difficulty replicating lumbar spinal loading. Hence it is difficult to generalize the results to broader patient populations. There is evidence of potential sources of bias throughout the literature, including observer bias and publication bias regarding the non-significant association. The small number of clinical studies, lack of high-quality evidence cohort studies, and heterogeneity in the outcome measures for the included studies are limitations that should be taken into account when interpreting results discussed in this review. While basic science studies help elucidate the relationship between bony stress and IVD degeneration, animal and numerical models used in such studies have different biomechanical and physiological characteristics compared with humans. Therefore, results from such studies must be viewed in light of those differences. Most of the studies examined bony stress in the pars interarticularis, but not in other regions of the lumbar spine. It is unclear if this is because the pars interarticularis has historically been studied more, or it is easier to visualize and diagnose bony stress in the pars interarticularis. The results of these studies may differ if bony stress in other regions were also assessed.

To our knowledge, this is the first review of the literature examining the relationship between bony stress and IVD degeneration in the lumbar spine. This review combines evidence from basic science (FE analysis, in-vivo biomechanical testing and in-vitro biomechanical testing studies) and clinical studies. Studies utilizing FE analysis can control various parameters and attempt to understand the influence of just one parameter on the outcomes. Cadaveric studies utilize human or animal spinal tissues for in-vitro testing to examine altered biomechanics in specimens with induced defects. In-vivo animal studies simulate pathological conditions or interventions to understand the biological and biomechanical response in somewhat more realistic conditions. This translational review was designed to be inclusive of different types of studies to synthesize all available evidence to understand better the pathophysiology of bony stress in the lumbar spine and its relationship with IVD degeneration.

Conclusion

As evident from the majority of clinical and basic science studies, this translational review suggests that there is a positive associative relationship between bony stress and IVD degeneration in the lumbar spine. Bony stress in the lumbar spine may cause LBP due to its association with IVD degeneration, microtrabecular injury/inflammation or both. The prevalence of IVD degeneration increases with bony stress in the lumbar spine. In adolescents, bony stress in the lumbar vertebra may heal with time; however, the prevalence of IVD degeneration is higher in such individuals even after bony stress has resolved. We, therefore, recommend a careful diagnosis of bony stress in younger patients presenting with or without IVD degeneration, so that the increased likelihood of early IVD degeneration in such patients can be effectively managed. However, there is insufficient evidence to suggest whether IVD degeneration is the cause or the consequence of bony stress in the lumbar spine. This review has identified a need for further basic science and clinical research to elucidate the role of bony stress in causing degenerative changes in the lumbar spine and LBP.

Abbreviations

LBP: Low Back Pain; MRI: Magnetic Resonance Imaging; IVD: Intervertebral Disc; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta Analyses; FE: Finite Element; NP: Nucleus Pulposus; AF: Annulus Fibrosus; EP: Endplate

Authors' Note

DC, UC and ADD were all involved in the conception and planning of the methods of this study. DC conducted the literature search. DC and UC independently extracted data from the selected studies. DC wrote the original manuscript and designed the figures. DC and UC were both involved in editing the manuscript. DC, UC and ADD edited the finalized version of the manuscript. All authors have read and approved the final manuscript. The datasets used in this study are available from the corresponding author on reasonable request.

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