

# Topical Reviews

An overview of current research and practice in rheumatic disease



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## LOW BACK PAIN

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- **Low back pain is the most common musculoskeletal complaint, with potentially devastating consequences**
- **Accurate diagnostic tests are limited but imaging, particularly MRI, has made a substantial contribution to our understanding of back pain**
- **90% of patients with acute low back pain are better at 8 weeks**
- **In chronic low back pain, exercise and intensive multidisciplinary treatment programmes are beneficial in reducing pain and improving function**
- **Therapies to inhibit active metabolic processes in intervertebral disc degeneration may be developed in the future**
- **Percutaneous vertebroplasty and kyphoplasty are new therapies for painful osteoporotic collapse**
- **Anti-TNF $\alpha$  therapies are likely to become popular for severe ankylosing spondylitis**

### INTRODUCTION

Low back pain is not only the most common musculoskeletal complaint, but arguably is also the most common human illness with the exception of the common cold. The anatomy, biomechanics and aetiology of back pain are complex, and unsurprisingly the pathophysiology in many cases is still poorly understood. Technological advancements in the fields of imaging, molecular biology and immunology are providing insights into the aetiology of some specific complaints and potential new therapies. This review focuses on recent and ongoing developments in the field of back pain.

### EPIDEMIOLOGY

Low back pain has an annual incidence of 2–5% and a point prevalence of 15–25%, and affects 70–90% of the population at some stage in their lifetime.<sup>1</sup> The prevalence rises with increasing age until 65 years, then decreases thereafter. This decrease may relate to age and activity but could also be due to recall bias, differential mortality or a cohort effect.

Back pain accounts for 13% of health related absences from work in the UK. Most cases of back pain settle quickly, with 90% of patients showing some improvement by 8 weeks. The economic burden due to low back pain is enormous and furthermore is increasing, with both the number of back pain related sick days and the rate of lumbar spine surgery showing a significant increase over the last decade.<sup>2</sup>

The strongest risk factor for back pain is a previous history of back pain. Other strong risk factors that have been identified are poor job satisfaction, emotional

distress, manual jobs involving heavy lifting (particularly in those over 45 years of age), and prolonged sitting or standing. Working with vibration tools, smoking, obesity, and poor physical fitness have been identified as moderate risk factors.<sup>3,4</sup>

## FUNCTIONAL ANATOMY AND BIOMECHANICS

The structures of the vertebral column are designed to meet the significant demands placed upon it. These demands include maintaining upright posture while standing and ambulating, coping with compressive and torsional loads, providing smooth and often complex movements, and forming a stable base to which other structures (the ribs and numerous muscles) are attached. The basic anatomical and functional unit of the spine is the articular triad consisting of the fibrocartilaginous intervertebral joint and the two synovial facet joints. The intervertebral joints allow for most of the flexibility of the spine and act as load transmitters and shock absorbers.

Flexion and extension of the lumbar vertebrae occur around an axis, postero-inferior to the midpoint of the vertebrae. Location of the axis is influenced by forces acting upon it, including the weight of the trunk and resistance by the facet joints, surrounding soft tissues and muscles acting upon the spine. Displacement of the axis occurs in spinal pathologies and low back pain,<sup>5</sup> and forms part of the concept of spinal 'instability'.<sup>6,7</sup>

## DIAGNOSTICS

Back pain has many causes, although the vast majority of cases are due to structural or mechanical factors (Table 1). Evaluation of the patient addresses this wide differential diagnosis and the characteristics and expectations of the patient in order to develop an appropriate management strategy. Clinical assessment of back pain can be difficult and there are limitations in the accuracy of all clinical diagnostic tests.<sup>8</sup>

Several diagnostic approaches have been advocated to supplement the clinical examination in the patient with low back pain. Such tests require accurate determination of the abolition or reproduction of the patient's painful symptoms. Facet joint diagnostic blockade has been recommended to identify those individuals who may respond well to a facet denervation procedure, as the greatest specificity for a positive response is seen when the diagnosis is established via highly controlled anaesthetic blocks.<sup>9</sup>

Lumbar discography for the diagnosis of discogenic pain is a controversial area and of unproven accuracy. In patients with sciatica, nerve root blockade, sciatic

**TABLE 1.** Causes of low back pain.

<b>Structural</b>
Mechanical/non-specific
Facet joint arthritis/dysfunction
Proapsed intervertebral disc
Annular tear
Spondylolysis/spondylolisthesis
Spinal stenosis
<b>Neoplasm</b>
Primary/secondary
<b>Inflammatory</b>
Spondyloarthropathies
Sacroiliitis/sacroiliac dysfunction
<b>Infection</b>
Discitis
Facet joint sepsis
Osteomyelitis
Paraspinal abscess
<b>Metabolic</b>
Osteoporotic vertebral collapse
Paget's disease
Osteomalacia
Hyperparathyroidism
<b>Referred pain to spine</b>
From major viscera, retroperitoneal structures, urogenital system, aorta, or hip

nerve block, posterior ramus block and subcutaneous injection are all used. The sensitivity of nerve root block is reportedly very high, but with only a moderate level of specificity.<sup>10</sup> In the case of diagnostic selective nerve blocks used for the evaluation of complex nerve compression, conflicting results are reported. Clearly there are inherent limitations in the accuracy of all diagnostic tests.<sup>10</sup>

## IMAGING

Advances in imaging of the lumbar spine have made a significant contribution to the diagnosis. Various imaging modalities are now available, each with its own merits and limitations. The use of conventional plain radiography, myelography and discography have receded in the light of advances in other imaging modalities. Three-dimensional imaging provides exciting opportunities in the evaluation of spinal complaints such as scoliosis and aids in operative planning and even in intraoperative management.<sup>11-14</sup>

Magnetic resonance imaging (MRI) in particular has made the most significant contribution. It has many advantages, including the use of non-ionising radiation and multiplanar imaging. It is now the investigation of choice in the majority of spinal complaints, following plain radiographs. It is particularly good in the imaging of discs, bone marrow, neural tissue, the spinal canal, ligaments, and paraspinal tissues. MRI is,

**TABLE 2.** An overview of MRI sequences in evaluation of the spine.

Sequence weighting	Pulse sequence parameters	Best imaging for tissues with:	Signal intensity			Structures
			High	Intermediate	Low	
T1	Short TR, short TE	Fat especially; also protein, subacute/chronic haemorrhage	Epidural fat	Nerve, spinal cord, nucleus pulposus, facet cartilage, bone marrow, cancellous bone	Muscles, thecal sac/CSF, annulus, ligaments, cortical bone, gas, blood vessels	Spinal cord, nerve roots, surrounding tissues and spaces
T2	Long TR, long TE	Water	Epidural fat, thecal sac/CSF, nucleus pulposus	Nerve, spinal cord, facet cartilage, bone marrow	Muscles, thecal sac/CSF, annulus, ligaments, cortical bone, gas, blood vessels	CSF, discs, fluid, oedema, necrotic tumours, infections, acute haemorrhage

CSF cerebrospinal fluid; TE echo time; TR repetition time

however, inferior to computerised tomography (CT) in the demonstration of spinal stenosis, bone tumours and fractures, and does not demonstrate gas, calcium deposits or osteophytes well.<sup>11-14</sup>

In addition to obtaining information from the standard T1 and T2 weighted imaging sequences, proton density sequences, involving long repetition time (TR) and short echo time (TE), reflect the number of mobile hydrogen ions in a tissue and are extremely useful in demonstrating the posterior annulus, ligamentum flavum, central and lateral canals, facet joints and posterior elements. Enhancement techniques and the use of contrast media have further increased the sensitivity of MRI with regard to the detection of many pathologies. Gadolinium diethylenetriamine-pentaacetic acid (DTPA) is the most commonly used agent and is used to increase the signal on T1 weighted images. It aids in the detection of inflammation, infection, tumours and infarctions. Gadolinium enhanced MRI is also the technique of choice for investigating recurrent symptoms following discectomy, since it allows differentiation between recurrent disc herniation and epidural fibrosis.<sup>15</sup> MRI has also proved useful in the detection of sepsis in facet joints.<sup>16</sup>

The main limitation of MRI is its sensitivity to degenerative changes in the intervertebral disc. Up to 50% of asymptomatic lumbar spines will demonstrate degenerative changes on MRI. Hence many of the challenges arise in relation to the interpretation of the findings in a clinical context. Accurate recognition of spine abnormalities on MRI and their reporting requires knowledge of normal anatomy and its variants. It is now well recognised that there are many additional pitfalls which may be the source of errors in interpretation and it is essential to recognise imaging artifacts that may be mistaken for true pathologies.<sup>17</sup>

The development of new imaging technologies has led to a vast increase in the costs of assessment of individuals with back pain. Although the use of MRI can aid the clinician in terms of diagnosis and treatment strategies, studies are needed to prove that these diagnostic and therapeutic impacts do lead to improved health.<sup>18</sup>

Although bone scintigraphy is still the standard approach to the investigation of possible inflammatory back pain, early diagnosis of sacroiliitis and other inflammatory lesions of the spine such as spondylitis and spondylodiscitis can be visualised early by MRI.<sup>19</sup> Spinal inflammation can be demonstrated by MRI using gadolinium DTPA enhancement or by use of the fat-saturating short tau inversion recovery (STIR) technique. This is especially useful in early and active disease, in young women and in children, and for the differential diagnosis of septic sacroiliitis.<sup>19</sup>

## MANAGEMENT OF LOW BACK PAIN: CLINICAL EVIDENCE

Fifty per cent of individuals with acute back pain have improved at 1 week and 90% at 8 weeks. The remainder continue to be symptomatic beyond 6 months.<sup>20</sup>

In acute low back pain, advice to stay active significantly increases the rate of recovery and reduces pain and disability. NSAIDs also increase the likelihood of improvement over the first week. Behavioural therapy and multidisciplinary treatment programmes are also likely to be beneficial. Other treatments are unproven.<sup>21-23</sup>

In chronic low back pain, exercise and intensive multidisciplinary treatment programmes are beneficial in reducing pain and improving function. Analgesics, NSAIDs, back schools, behavioural therapy, massage and trigger point injections may all provide some benefit. Other treatments are of unproven benefit.<sup>20,24-27</sup>

**TABLE 3.** The range of therapies and current evidence for effect.<sup>24-26</sup>

Beneficial	Likely to be beneficial	Unknown effectiveness	Unlikely to be beneficial	Likely to be ineffective or harmful
<b>Acute low back pain and sciatica</b>				
Staying active, NSAIDs	Behavioural therapy, intensive multidisciplinary treatment programmes	Acupuncture, analgesics, back schools, colchicine massage, epidural steroid injections, lumbar supports, spinal manipulation, TENS, heat, traction	Back exercises	Bed rest
<b>Chronic low back pain and sciatica</b>				
Intensive multidisciplinary treatment programmes, exercise	Back schools in occupational settings, behavioural therapy, massage, NSAIDs, trigger point and ligamentous injections, analgesics	Acupuncture, antidepressants, electromyographic feedback, epidural steroid injections, lumbar supports, muscle relaxants, spinal manipulation, TENS		Facet joint injections, traction
<b>Herniated lumbar disc</b>				
	Standard discectomy, microdiscectomy	Advice to stay active, automated percutaneous discectomy, bed rest, epidural steroid injections, heat/ice, massage, analgesics, laser discectomy, antidepressants, muscle relaxants	NSAIDs	

NSAIDs non-steroidal anti-inflammatory drugs; TENS transcutaneous electrical nerve stimulation

## INTERVERTEBRAL DISC DISEASE

The intervertebral disc is composed of the inner nucleus pulposus and the outer annulus fibrosus. The nucleus consists of a core of proteoglycan matrix with a high water content, surrounded by fibrocartilage. The annulus fibrosus forms a capsule around the nucleus and is a collagenous structure composed of concentric lamellae. The outer lamellae are attached to the ring apophyses of the associated vertebrae. The inner lamellae blend with the vertebral endplates such that the otherwise hyaline endplate becomes partly fibrocartilaginous. Within each lamella the collagen fibres run at an angle of approximately 55° to the vertical, with the direction alternating between successive layers.<sup>28</sup>

Disc cells rely on nutrients that diffuse through vertebral endplates. Scoliosis is associated with decreased endplate permeability, a factor that may influence subsequent disc degeneration.<sup>29</sup> The health of an intervertebral disc is based on a complicated interplay between physiology and biomechanics. The nucleus pulposus must remain well hydrated and the surrounding annulus fibrosus must be competent in order for the disc to function properly.

Causes and risk factors for degenerative lumbar disc disease, the most common identifiable pathological cause of back pain, have been identified. Lifting heavy loads, torsional stresses and driving have been highlighted as environmental risk factors. Family and twin studies have indicated that two collagen IX alleles are associated with sciatica and disc degeneration. Disc degeneration has also been related to an aggrecan gene polymorphism, a vitamin D receptor and matrix metalloproteinase-3 gene alleles.<sup>30,31</sup>

The process of 'degeneration' is in fact an active process; physical, cellular and metabolic, genetic, nutritional and age-related factors contribute to disc degeneration and subsequent herniation.<sup>32,33</sup> The interplay between metalloproteinases and mechanical forces is an area of great significance.<sup>33</sup> It is clear that extracellular matrix degrading enzymes, matrix metalloproteinases (MMPs), exert particularly important effects. Such effects may be direct, as there is a high correlation of MMP expression with the formation of disc clefts and tears. Indirect effects of MMPs on the disc are also apparent, through the promotion of neovascularisation. The production of these enzymes is dependent on a number of cytokines and on the cell changes they

induce. This complex effect acts both on disc matrix degeneration and on the pain generated by contact between the protruding disc and the nerve roots. However, it can have a favourable effect by promoting resorption of the herniated disc which appears to be related to the infiltration of peripheral blood mononuclear cells and MMP production.<sup>33-35</sup>

The finding that the degenerative process is a biologically active process raises the possibility in the future of therapies involving inhibition of such metabolic changes using targeted therapy.<sup>36</sup> In addition, the genetic associations that have been identified in disc disease have implications for new gene therapies in the future.<sup>37</sup>

The clinical course of disc herniation varies, although the majority of patients will heal spontaneously without interventions such as surgery or chemonucleolysis. Common surgical approaches to the degenerative disc are discectomy or fusion of the affected vertebrae. The extent of annular deficiency and the type of herniation appear to influence clinical outcome after lumbar discectomy.<sup>38</sup> Post-operatively, intensive exercise programmes (at least if started about 4–6 weeks post-operative) lead to significantly improved functional status and faster return to work.<sup>39</sup>

Although these treatments can be effective, they also have their limitations.<sup>40</sup> Newer techniques such as intradiscal electrothermal therapy have been proposed for chronic discogenic low back pain, but there is no evidence base to support their use.<sup>41</sup> Bioengineering techniques may offer the possibility of repairing the damaged disc if an engineered tissue with the appropriate functional properties can be generated to augment the ailing disc.<sup>42</sup> The development of prosthetic nuclei pulposi has also been reported.<sup>43</sup>

## **OSTEOPOROTIC VERTEBRAL COMPRESSION FRACTURES**

Osteoporotic vertebral compression fractures of both the lumbar and the thoracic spine are a common cause of morbidity in older people. Patients who have persistent pain despite conservative treatment require investigation to exclude other pathological causes of fracture. Standard approaches to pain management have focused upon pharmacological approaches. Intravenous pamidronate is of significant therapeutic benefit in providing pain relief.<sup>44</sup> Percutaneous vertebroplasty and kyphoplasty are new techniques that offer some promise in the treatment of these elderly patients.<sup>45,46</sup>

Percutaneous vertebroplasty involves the injection of surgical polymethylmethacrylate into a vertebral body

via a large bore needle under imaging guidance. This technique provides increased strength and pain relief in vertebral compression fractures due to osteoporosis, myeloma, metastases and aggressive vertebral haemangioma. Potential side effects include leakage of cement, which may result in spinal cord compression. Contraindications include bleeding disorder, unstable fracture and lack of definable vertebral collapse.<sup>45</sup>

Kyphoplasty involves the inflation of a balloon tamp prior to the injection of opacified acrylic bone cement in an attempt to restore vertebral body height and reduce the associated kyphotic deformity. Significant pain relief is reported in some patients; whether restoration of vertebral height is achieved has not yet been established.<sup>46</sup>

Open surgery may still be required where there is significant neurologic compromise. Various spinal approaches including anterior or posterior decompression combined with a variety of stabilisation techniques have been reported in the literature. Rehabilitation is often required to improve physical function.<sup>47</sup>

## **INFLAMMATORY BACK PAIN**

Ankylosing spondylitis (AS) represents the most common inflammatory arthritis involving the whole spine.<sup>48</sup> It has a broad spectrum of clinical features and several disease subsets are apparent. The pathology involves an initial inflammatory erosive process involving the enthesis followed by healing and new bone formation. Involvement of the anterolateral portion of the outer annulus is commonly seen in the spine followed by new bone formation and syndesmophyte formation with potential ankylosis of adjacent vertebrae. Destructive lesions of the vertebral endplate – which may involve the whole disc-bone junction, unlike more localised lesions – appear to be unique to AS and occur in more advanced spinal disease.

The association between ankylosing spondylitis and human leukocyte antigen (HLA) B27 is well established and holds in all populations. Although the evidence strongly supports a direct role for HLA-B27 in genetic susceptibility to AS and related spondyloarthropathies, the underlying molecular basis has yet to be identified.<sup>49</sup> The incidence in Caucasians is 0.5–1%, with a male:female ratio of 5:1. In whites of northern European extraction, HLA-B27 is highly sensitive (92%) and specific (92%).

HLA-B27 itself is a serologic specificity that encompasses 26 different alleles that encode 24 different subtypes, HLA-B\*2701-B\*2725 with the exclusion of B\*2722.<sup>49</sup> The 24 HLA-B27 alleles (subtypes) originate from the most widespread subtype, B\*2705. No particular all-

ele appears to confer susceptibility to AS. Importantly, most HLA-B27 positive individuals do not develop AS. HLA-B27 homozygotic individuals do not show more aggressive disease than heterozygous individuals and HLA-B27 is not a useful prognostic indicator.

The major histocompatibility complex (MHC) genes (including HLA-B27) account for about half of the genetic susceptibility for AS, while HLA-B27 contributes only 16% of the total genetic risk for the disease in those of European descent. This implies that additional disease-predisposing genes in the MHC region of chromosome 6 exist. Research to date indicates potential areas of other chromosomes that may contain additional disease predisposing genes.<sup>49</sup> Much of the variability in disease severity in AS remains unexplained. Genetic factors in addition to HLA-B27 appear to influence the disease susceptibility and phenotypic expression of the disease and may have a greater influence than environmental factors on radiological progression and disability in AS. It may, however, be possible to improve long-term functional outcome in AS by targeting high-risk individuals early in the disease course with more aggressive management strategies.<sup>50</sup>

The standard current therapy for AS involves physical therapy, non-steroidal anti-inflammatory drugs (NSAIDs) and anti-rheumatic disease-modifying drugs (DMARDs).<sup>51</sup> More recently, biologic agents targeting tumor necrosis factor alpha (TNF $\alpha$ ) are proving to be highly effective and are providing new hope in patients with disease at the severe end of the spectrum. Etanercept and infliximab are effective and well tolerated for both axial and peripheral joint disease in AS.<sup>52</sup>

The place of anti-TNF therapies in the treatment armory for AS differs from that for rheumatoid arthritis (RA) in that effective disease-modifying agents for the management of severe spinal disease appear to be lacking in AS. Thus TNF blockers might even be considered first-line immunosuppressive treatment in patients with active AS for whom NSAIDs are not a sufficiently effective treatment.<sup>53</sup>

The mechanism of action is not entirely clear. Infliximab has been shown to down-regulate both interferon gamma (IFN $\gamma$ ) and TNF $\alpha$  secreted by T-cells but does not induce a change in cytokines produced by monocytes during 3 months of treatment. This is likely to be a relevant mechanism for the clinical efficacy of this therapy.<sup>54</sup>

On the basis that bisphosphonates inhibit the development of delayed type hypersensitivity chronic inflammation and suppress inflammation and cartilage/bone erosion in murine models, intravenous pamidronate therapy has been utilised in the management of AS.

Dose-dependent therapeutic effects have been demonstrated with respect to pain, function and stiffness. This approach may be indicated for the symptomatic management of NSAID refractory disease.<sup>55</sup>

## OTHER CAUSES OF BACK PAIN

The clinician needs to maintain a high degree of suspicion of possible sinister causes of back pain. The 'red flags' are well described and are listed in Table 4. Patterns of pain also help to identify the cause. Localised unilateral back pain that is worsened by extension and rotation in a young sports person is typical of a spondylolysis. Single photon emission CT (SPECT) is currently the most popular mode of diagnostic imaging in this respect, although it is likely that MRI will supercede this. Spondylolisthesis (anterior vertebral slippage) may result from bilateral spondylolyses or may be congenital. Not all are symptomatic but pain and/or neurological compressive symptoms can occur. Pain usually responds to relative rest and where necessary bracing, but fusion may be necessary in the minority of those with persisting pain or neurological dysfunction.

**TABLE 4.** Red flags in the patient with low back pain.

- Weight loss, fever, night sweats
- Nocturnal pain
- History of malignancy
- Acute onset in the elderly
- Constant or progressive pain
- Bilateral or alternating symptoms
- Neurological disturbance
- Sphincter disturbance
- Morning stiffness
- Immunosuppression
- Infection (current/recent)
- Claudication or signs of peripheral ischaemia
- Pain that is not improved with lying prone (with the stomach supported) or in the foetal position

Infections can affect the spine in the form of osteomyelitis or discitis. In 40% of cases of osteomyelitis there is haematogenous spread from an identifiable extraosseous source, most commonly genitourinary, respiratory or skin. In 60% of these cases staphylococcus aureus is the causative organism. Gram negative bacteria are more commonly seen in the elderly (*E coli*) and parenteral drug users (*Pseudomonas*). Discitis is seen in particular after lumbar disc surgery (up to 3% of cases).

Malignancies predominantly affect the anterior elements. Multiple myeloma is the most common primary malignancy affecting the spine, representing 27% of

biopsied bone tumours; and low back pain is the presenting symptom in 35% of patients with this disease.

Spinal stenosis is a common spinal disorder in the elderly, presenting with pseudoclaudication, sciatica and neurological dysfunction of the cauda equine. Physiotherapy and bracing may result in significant improvement in symptoms. In those in whom decompressive surgery is necessary the outcome is better in those with a higher degree of stenosis, and predictors of poorer outcome include significant comorbidities, single level decompression and coexisting depression. Postoperative complications include bone regrowth spondylolisthesis in approximately 20% of cases.

## CONCLUSION

Low back pain is a major cause of morbidity and poses a significant socioeconomic burden upon the community. Although the anatomy, biomechanics and aetiology of back pain are complex, inroads are being made in the understanding of specific complaints. The clinician's priority is to identify the underlying source of pain where possible and to use the best available evidence in devising a management programme.

The modern medical age has seen the development of imaging technologies and advances in immunology and genetics that will continue to dramatically improve the understanding of spinal pain. New approaches to the management of specific spinal complaints are fast developing and doubtless will include gene therapies in the years to come. Recent advances in our understanding of the pathophysiology of pain are likely to lead to improved invasive and non-invasive approaches to the management of diffuse spinal pain.

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