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# NEWER APPROCHES IN THE TREATMENT OF BACK PAIN

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## Abstract:

Low Back Pain or ache in the lumbo-sacral area is precipitated by means of some mixture of overuse, muscle stress and harm to the muscles, ligaments, and disc that aid the spine. Low back pain (LBP) is a main reason of incapacity worldwide. Low back pain is the predominant reason of incapacity international and imposes a substantial medical and socioeconomic burden on society. The intervertebral disc, zyg-apophysical joint, and sacroiliac joint are believed to be frequent ache mills in axial lower back pain. Common sources of axial LBP consist of the intervertebral disc, side joint, sacroiliac joint, and paraspinal musculature, whereas frequent sources of radicular ache encompass a herniated intervertebral disc and spinal stenosis. The incidence of Chronic Low Back Pain (CLBP) is increasing. Treatment for the disease is advantageous in much less than 50% of sufferers after 1 year. This review gives the brief information about the newer approaches in the treatment of chronic low back pain. Conservative nonpharmacologic cure consists of bodily therapy, acupuncture, chiropractic manipulations, yoga, Tai Chi, cognitive behavioral therapy, and meditation.

## Keyword:

Chronic low back pain, Chemonucleolysis, Platelet-rich plasma injections, Artemin, Tanezumab, Stem cells Matrix metalloproteinases Ethanol, Collagenase

## Introduction:

LBP is the second most common cause of disability in adults in the United States1 and a leading cause of missed work days. Multiple studies using national and insurance claims data have found that individuals with chronic LBP are more likely to use spinal injections, surgery, and opioid medications as treatments. Medication prescriptions and visits to physicians, physical therapists, and chiropractors have also increased, according to studies. Because people with chronic LBP are more likely to seek care and use more health care services than people with acute LBP, chronic cases drive increases in health care use [2].

Back pain is extremely common, affecting nearly everyone at some point in their lives[3]. Low back pain (LBP) is the major leading cause of disability in all over world. In the absence of a pain syndrome classification system, classification of LBP as axial (pain generally localized to the low back) or radicular neuropathic (pain radiating to the lower extremities) is relevant to clinical practice because pain distribution is frequently a corollary of commonly occurring disease processes involving the lumbar spine[4].

## Anatomy and Pathophysiology:

CLBP (Chronic Low Back Pain) can be caused by a variety of factors, the most common of which are intervertebral disc degeneration and herniation (IVDs). A nucleus pulposus (NP) is surrounded by an annulus fibrosus in each intervertebral disc (AF). The nucleus pulposus is a gelatinous inner core that is made up of type II collagen, proteoglycans, and non-collagenous proteins[1,4]. Proteoglycans are linked to glycosaminoglycans and hyaluronic acid chains. The nucleus pulposus acts as a "shock absorber". It reduces internal friction by transmitting radial pressure onto the vertebral endplates[1,5]. Fibroblasts in the annulus fibrosus synthesize types I and II collagen into circumferential rings. This orientation allows it to provide tensile strength and resist anterior and posterior vertebral body sliding[5]. A thin layer of hyaline cartilage exists between the vertebral body and the IVD. Its function, also known as the endplate, is to distribute intradiscal pressures onto adjacent vertebrae in order to prevent the NP from bulging into the underlying trabecular bone [1,6].

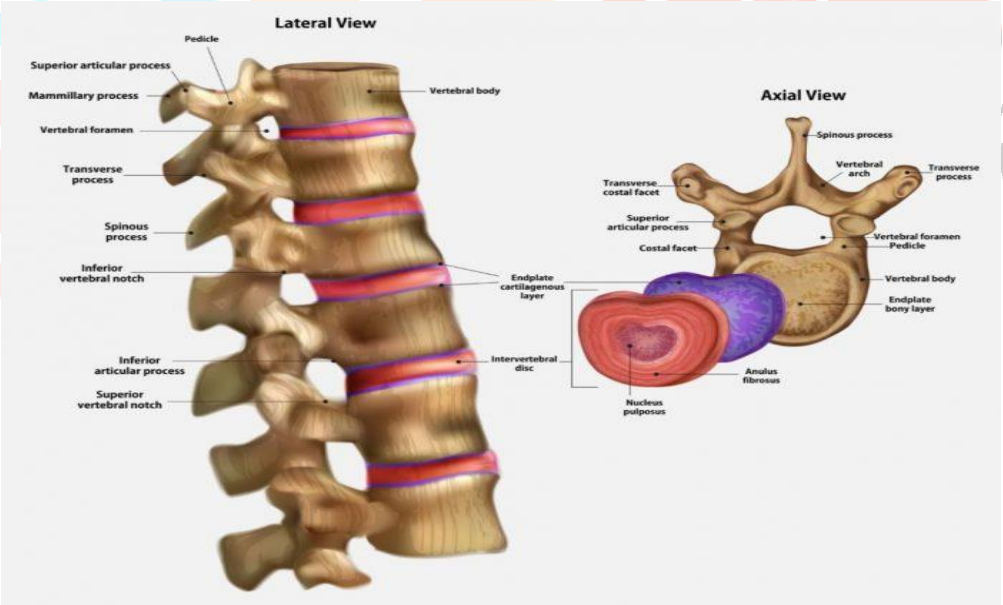


**Fig no.1:** Lateral and Axial View for intervertebral disc

Tissue synthesis and degradation are mainly balanced in a normal intervertebral disc. However, as nutrient supply and/or cellular demand decrease, degradation takes over and the disc loses its biomechanical function [1,7]. Avascular IVDs predominate [1,8]. As a result, nutrient supply becomes an issue. The AF is supplied with nutrients by nearby capillaries. Nutrient diffusion from capillaries off vertebral bodies that terminate near the endplates is essential for inner disc cells [1,9]. Growth factors and cytokines are expressed during periods of severe disc degeneration [1,10.] This increases the consumption of glucose and the production of lactic acid. Nutrient demand increases, but a cell may not be able to keep up with, which is resulting in more disc

degeneration[1,11]. Proteoglycans and glycosaminoglycans are lost as the balance shifts further, and type II collagen denatures [1,12]. The discs dehydrate and become more prone to herniation [1,13]. Furthermore, a decrease in disc height increases loading on nearby joints, leading to osteoarthritic changes and ligamentum flavum thickening [1,14].

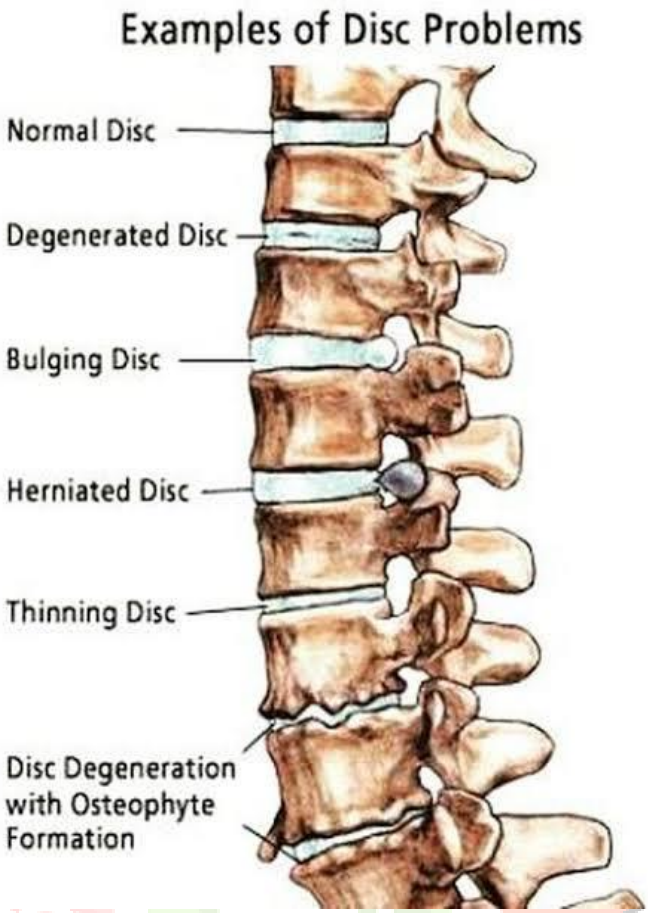


**Fig no.2:** Example of Disc Problem

## Current Treatment:

The American College of Physicians and the American Pain Society collaborated in 2007 to develop joint clinical practice guidelines for the diagnosis and treatment of low back pain. Physical therapy, acupuncture, chiropractic manipulations, yoga, Tai Chi, cognitive behavioral therapy, and meditation are examples of nonpharmacologic treatments[15]. Acetaminophen, nonsteroidal anti-inflammatory drugs, muscle relaxants, opioids, tramadol, and tricyclic antidepressants are examples of conservative pharmacologic treatment. Invasive treatment is considered if conservative treatment fails. This includes spinal cord stimulators, epidural steroid injections, and spine surgery [1].

## Chemonucleolysis:

Chemonucleolysis is a non-surgical treatment for a bulging disc that involves injecting an enzyme into the vertebral disc with the goal of dissolving the nucleus pulposus, the inner part of the disc. The most significant advantage of chemonucleolysis over surgery is the absence of epidural scarring and permanent postoperative anatomical changes. Patients may benefit from these advantages, but they must also be willing to accept the method's disadvantages [16]. Anaphylaxis, discitis, subarachnoid hemorrhage, paraplegia, and acute transverse myelitis are all possible side effects of chymopapain. As a result, chymopapain was removed from the market in the early 2000s [1].

## Collagenase:

Because of the potential risks, other enzymes with lower allergic potential, such as collagenase, have sparked interest. Collagenase is an enzyme that splits type II collagen fibers. Wittenberg and colleagues assessed the efficacy of chymopapain and collagenase for intradiscal injection over a 5-year clinical follow-up period in a prospective, randomized study. The researchers randomly assigned 100 patients to receive either 4000 IU of chymopapain or 400 ABC units of collagenase. Inclusion criteria included sciatic leg pain that was worse than back pain and a minimum of six weeks of unsuccessful conservative treatment. Neurologic deficits, pregnancy, allergy to injection substance, and surgery at the same segment were all exclusion criteria. Under general anesthesia, the disc injection was performed under fluoroscopic control.

Following discharge, the patients were seen after 2, 6, and 12 weeks, as well as at 1-, 3-, and 5-year intervals. Twelve percent of the patients in the chymopapain group had allergic reactions. One of these patients experienced an anaphylactic reaction. Patients rated their results as excellent, good, fair, or poor at each time interval. Those who were lost to follow-up or underwent surgery were rated as poor. At 5 years, 72 percent of the chymopapain group rated the results as excellent or good, compared to 52 percent of the collagenase group. Pain scales decreased from 8.5 to 0.7 in the chymopapain group and from 8.6 to 0.9 in the collagenase group. Patients in the chymopapain group returned to work in 8 weeks, while those in the collagenase group returned to work in 11 weeks. The authors concluded that the two substances are not significantly different. However, chymopapain is known to be relatively safe, whereas collagenase requires more research.

## Chondroitinase ABC:

Another enzyme that has been reported to be as effective as chymopapain is Chondroitinase ABC (C-ABC). However, no study examined intradiscal pressure changes caused by C-ABC in vivo. Sasaki and colleagues injected various doses of C-ABC into 11 sheep's intervertebral discs. In the control group, phosphate-buffered saline was injected. Intradiscal pressure was measured with a pressure transducer one week before injection and again one and four weeks later. At the same time intervals, roentgenograms were used to calculate the disc height index.

The authors discovered that low dose C-ABC (1 and 5 U) caused a small decrease in intradiscal pressure after 1 week and a larger decrease after 4 weeks. After one week, a high dose of C-ABC (50 U) had a statistically significant effect, with a greater decrease at four weeks. In the control group, there was no change in intradiscal pressure over time. The low-dose C-ABC group's disc height index decreased more than the high-dose groups. There was no correlation found between intradiscal pressure decrease and disc height index (r 5 0.339). As a result, evaluating chemonucleolysis using disc height as a surrogate for intradiscal pressure may be inaccurate.

## Matrix Metalloproteinases:

Matrix metalloproteinases (MMPs), also known as matrix metallopeptidases or matrixins, are calcium-dependent zinc-containing endopeptidases; a family of proteolytic enzymes involved in the degradation of matrix components such as glycoproteins, proteoglycans, and collagen [1]. MMP-3 degrades proteoglycan protein cores and small non-collagenous proteins. Matrix metalloproteinases are the primary enzymes responsible for collagen and other protein degradation in extracellular matrix (ECM) (MMPs). Collagen is the main structural component of connective tissue, and its degradation is a critical process in development, morphogenesis, tissue remodeling, and repair. MMPs typically have several distinct domains. MMPs are classified into six groups: collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs, and other unclassified MMPs [17].

MMPs and their inhibitors are being studied extensively as potential anticancer drugs. MMP inhibitors are classified into two types: synthetic and natural inhibitors. Selected synthetic inhibitors, such as synthetic peptides, non-peptidic molecules, chemically modified tetracyclines, and bisphosphonates, are in human clinical trials. Isoflavonoids and shark cartilage are the most common natural MMP inhibitors.

Haro and colleagues [18] conducted a large study in 2005 to investigate the role of MMPs in the treatment of herniated discs. Patients undergoing primary lumbar herniotomy had five-disc samples taken. The tissues were cultured without, with, and without recombinant human (rh) MMP-3, MMP-7, and chymopapain. They were then stained with safranin O, a marker of proteoglycan content. rh MMP-3, rh MMP-7, and chymopapain were also injected into healthy disc tissue of 5 Japanese white rabbits. After a week, disc samples were collected, fixed, and stained with safranin O.

In the final group, ten beagles with herniated discs were given rh MMP-7, chymopapain, or saline. To investigate morphologic changes, Safranin O staining was performed, as well as MRI and myelography. The authors discovered that culturing human surgical tissue with rh MMP-3, rh MMP-7, and chymopapain resulted in significant proteoglycan degradation. The healthy rabbit IVDs produced similar results. The degradation level was highest with rh MMP7 and chymopapain.

MRI and myelography revealed that injecting rh MMP-7 and chymopapain into canine herniated discs reduced protruded disc mass. Histologically, rh MMP-7 destroyed the NP while leaving an intact nucleus area and AF. Chymopapain, on the other hand, degraded through the NP and AF. In rh MMP-7–treated cells, this could allow disc chondrocytes to regenerate the NP, but not in chymopapain–treated cells. The authors came to the conclusion that rh MMP-7 holds the most promise for the treatment of herniated discs. Following the discussion of the findings, Haro and colleagues investigated the effects of rh MMP-7 on human herniated discs in vitro and dogs in vivo. Surgical samples of herniated discs were collected from patients undergoing primary lumbar herniotomy and incubated with or without rh MMP-7.

Before and after treatment, the wet weight and concentration of keratan sulphate were measured. Keratan sulphate is an IVD degradation product. Herniated disc wet weight decreased concentration-dependently, while keratan sulphate level increased. There was no correlation between the decrease in wet weight and any of these associated conditions when patient age, grade of herniation, and interval between onset of symptoms and surgery were all controlled for. As a result, rh MMP-7 may be used to treat a wide variety of patients with herniated discs.

Twenty male beagles were anaesthetized and injected with rh MMP-7 into lumbar IVDs to study its effect in vivo. After one week, the injected discs were harvested and stained to look at the proteoglycan content and keratan sulphate concentration. The keratan sulphate concentration increased while the proteoglycan content decreased in a dose-dependent manner. rhMMP-7 [125I]-labeled injected into canine lumbar IVDs revealed radioactivity in the NP and AF but not in muscle or surrounding tissue. There were no changes in clinical signs, body weight, food consumption, or necropsy findings that suggested systemic effects from rh MMP-7.

## Ethanol

Another possible treatment for CLBP is chemonucleolysis with ethanol. Bellini and colleagues [19] enrolled 90 patients with herniated lumbar or cervical discs. They were given radiopaque gelified ethanol intradiscal injections. Dehydration of the NP caused by radiopaque gelified ethanol results in disc herniation retraction. Inclusion criteria included MRI or computed tomography assessment of disc herniation contained, without complete annulus tear, and not contained, with posterior longitudinal ligament integrity and no free

fragments. Previous symptomatic surgery, a high degree of disc degeneration, spinal stenosis, and asymptomatic disc bulging were all exclusion criteria.

The VAS and Oswestry Disability Index were used to assess pain immediately after treatment and again three months later. Eighty-five percent of lumbar disc herniation patients and 83 percent of cervical disc herniation patients experienced significant symptom improvement. The VAS score dropped by 4 points, and the Oswestry Disability Index dropped by 40%. In 19 patients, radiopaque gelified ethanol leaked into surrounding tissue with no clinical side effects. In patients who had failed conservative treatment, Touraine and colleagues [20] discovered similar results with percutaneous chemonucleolysis using ethanol gel. After one month, pain intensity decreased by 44%, and by 62% after three months (P 5 .007). The VAS score dropped from 7 at the start to 3.8 after one month and 2.6 after three months.

## Platelet-Rich Plasma Injections

Platelet-rich plasma (PRP) is made by centrifuging platelets and other blood components from an autologous blood sample. Platelets, growth factors, and cytokines in the concentrate boost collagen content, hasten endothelial regeneration, and promote angiogenesis [21]. Levi and colleagues [22] injected intradiscal PRP into 22 patients with discogenic pain defined as positive discography, clinical features suggestive of discogenic pain, and discogenic pain on MRI.

The VAS was evaluated before treatment, as well as 1, 2, and 6 months later. At 6 months, 9 of 19 patients had a 50% improvement in symptoms and a 50% decrease in VAS. In 2016, a prospective, double-blind, randomized, controlled study was conducted to see if PRP injections improved pain and function in patients with symptomatic degenerative IVDs [23]. The study included 58 patients who fulfilled the trial criteria.

There were 36 patients in the treatment group and 22 in the control group. The patients were tracked for a year using various metrics such as the Functional Rating Index, Numeric Rating Scale, 36-Item Short Form Health Survey, and patient satisfaction (North American Spine Society Outcome Questionnaire). There were statistically significant improvements in the Numeric Rating Scale (P 5.20), Functional Rating Index (P 5.03), and North American Spine Society Outcome Questionnaire over the first 8 weeks (P 5 .10). This thing was maintained during the one-year follow-up period. There were no complications reported in either study following the intradiscal injection of PRP.

## Artemin

Artemin is a ligand in the glial cell line-derived neurotrophic factor family [24]. It binds to the RET receptor tyrosine kinase's GFRa3 receptor [25]. This receptor is expressed following axonal injury [26]. Artemin helps sensory, sympathetic, and central neurons survive. Artemin has been shown in animal studies to prevent histochemical changes in the dorsal root ganglion, maintain C-fiber function, and restore sensory neuron function following nerve injury [27]. A study by Rolan and colleagues [28] included subjects with unilateral sciatica for at least 6 weeks and a pain rating of 40 mm or greater on a 100-mm VAS. The participants were divided into 11 groups: placebo, intravenous artemin, and subcutaneous artemin.

Assessments were performed at baseline and then at 15 minutes, 1 hour, 6 hours, 24 hours, 72 hours, and 28 days after treatment. The VAS and Likert scales were used to assess pain. The VAS or Likert scale showed no dose-dependent trends. Heat intolerance, pruritus, headache, and rash were among the side effects. At doses of 100 mg/kg or higher, the incidence was higher. There were no significant dose-dependent trends in vital signs, laboratory parameters, intraepidermal nerve fiber density, or quantitative sensory testing.

Artemin antibodies were detected in two subjects in the treatment group, but both tested negative in a subsequent neutralizing antibody assay. The authors believe there was no trend in efficacy because it was

not the primary outcome of the study, the patients were receiving concurrent analgesic therapy, and the sample size was small. Because the medication is safe and tolerable, the researchers believe it should be studied further for the treatment of neuropathic pain.

## Tanezumab:

Neurotrophin nerve growth factor (NGF) is a key mediator of pain signal generation and potentiation in tissue injury. Increased NGF levels have been linked to increased pain perception in a variety of chronic pain conditions [29]. Tanezumab is a monoclonal antibody with a high affinity for NGF. It inhibits the binding of NGF to tropomyosin-related kinase A and p75 [30]. It has been shown to alleviate osteoarthritis, CLBP, and interstitial cystitis pain [31-33]. Kivitz and colleagues [34] confirmed and expanded on those findings studied tanezumab's efficacy and safety.

The study enrolled 1347 patients, according to the researchers. Inclusion criteria included CLBP for three months or longer that required short-acting analgesic medications, an average low back pain intensity (LBPI) score of four or higher, and a Patient Global Assessment of the low back of fair, poor, or very poor. Back surgery within the previous 6 months; significant cardiac, neurologic, or other pain; psychological conditions; and long-acting opioids within the previous 3 months were all exclusion criteria. The subjects were randomly assigned to one of three groups: placebo, naproxen (500 mg twice daily by mouth), or tanezumab (5 mg, 10 mg, or 20 mg) given intravenously every 8 weeks. Pain levels were measured at weeks 2, 4, 8, 12, 16, and 24.

The LBPI score, Roland-Morris Disability Questionnaire score, and Patient Global Assessment were used to assess efficacy. The 20-mg tanezumab group had a mean LBPI change from baseline of 2.18 at 16 weeks, compared to 0.93 in the placebo group (P.001) and 0.5 in the naproxen group (P 5 .006). Tanezumab 10 mg produced a comparable mean change from baseline. However, when compared to placebo or naproxen, tanezumab 5 mg did not reach statistical significance. A similar pattern was seen when the Roland Morris Disability Questionnaire was performed.

Tanezumab 20 mg, 10 mg, and 5 mg had a statistically significant difference between treatment and placebo using the Patient Global Assessment. The greatest reduction in LBPI score was seen at 4 weeks and was maintained throughout the study. Paresthesia, arthralgia, pain in extremity, headache, hyperesthesia, dysesthesia, and osteonecrosis were common adverse events in the treatment group.

## Stem Cell Therapy:

Over the last decade, regenerative cellular therapy has been a major focus of research. It has the potential to increase proteoglycan and type II collagen synthesis for IVD rebuilding. Mesenchymal stem cells (MSCs), embryonic stem cells, induced pluripotent stem cells, human umbilical cord MSCs, and NP cells are all cell types that can differentiate into chondrocyte-like cells. In vitro and in vivo, MSCs have been differentiated into chondrocyte-like cells [35].

MSC transplantation in animal degenerated IVD models resulted in the survival of chondrocyte-like cells. These cells were capable of producing aggrecan, which resulted in an increase in IVD height [36]. In humans, injection of MSCs into the NP of an affected segment increased the water content of the NP. The subjects' pain and functional status improved quickly. Anatomically, studies have shown an increase in IVD height and disc height index in MSC transplant groups [37]. Transplantation reduces degeneration grading scale values histologically. Furthermore, MRI shows that the water content of the treated NP increases. MSC-treated NPs have a higher level of type II collagen messenger RNA [38].

MSCs have anti-inflammatory properties and can reverse fibrosis through cytokine and MMP secretion. Orozco and colleagues injected autologous expanded bone marrow MSCs into the NPs of ten patients suffering from chronic back pain caused by lumbar disc degeneration. The VAS, Oswestry Disability Index, and 36-Item Short Form Health Survey were used to assess the patients over a one-year period. MRI scans of the disc height and fluid content were also performed. At 3 months, there was a rapid improvement in pain and disability, followed by modest additional improvements at 12 months. The water content increased, but the disc height did not. There were no significant side effects observed. Risks associated with injectate extravasation include discitis, tumorigenesis, osteophytes, and spinal stenosis.

Subhan and colleagues investigated carriers for stem cell extravasation. MSCs in HyStem (hyaluronan-based hydrogel), HyStem alone, and no intervention were given to rabbits with iatrogenic disc damage. Histologic analysis and an MRI were performed after 8 weeks. The T2-weighted signal intensity of HyStem hydrogel with MSCs was high, indicating increased disc water content, a high height index, a low degenerative index, and more type II collagen and aggrecan staining. Although many studies are preliminary, more research is being conducted because regenerative cellular therapy has the potential to have a significant impact on the future treatment of damaged IVDs

**Common Causes**

Low back pain is not always related to an underlying condition. It may be caused by:

- Lifting heavy objects
- Sudden jerks in a motor vehicle
- Excessive strain on the muscle due to prolonged sitting or wrong positioning while sleeping
- Prolonged use of high heel shoes
- Also common during pregnancy, before/during menstruation

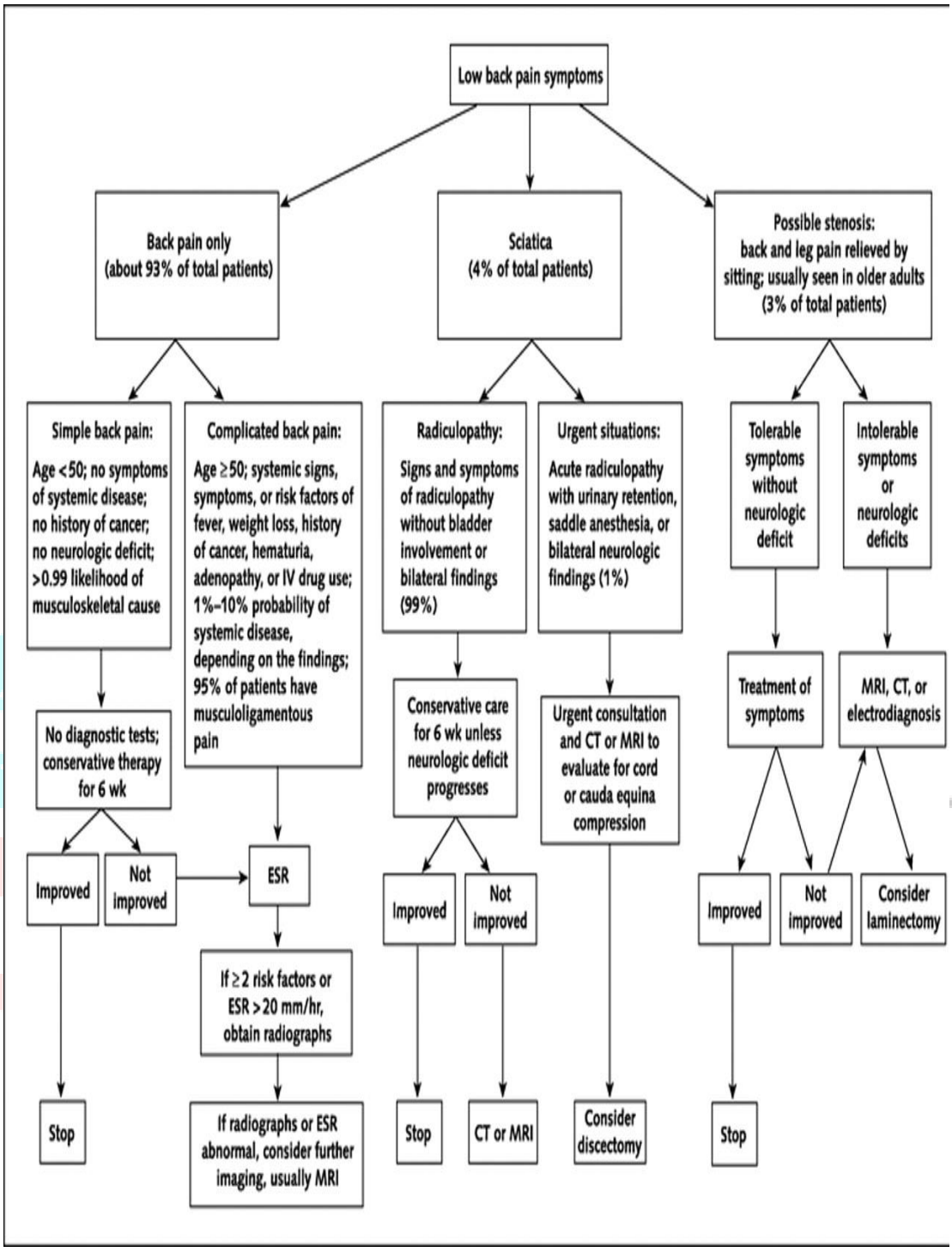


**Fig no 3:** Flow chart showing the Low back pain Symptoms

## Conclusion:

The IVD has a limited vascular supply, making it an unsuitable environment for herniation or degeneration healing. CLBP symptomatology has improved with chemonucleolysis using collagenase, C-ABC, MMP, and ethanol gel. More research is being done with MMP-7 and ethanol gel. PRP, artemin, and tanezumab have all shown varying degrees of CLBP improvement. More research is needed to determine their safety and clinical efficacy. Stem cell therapy has shown significant improvement in pain and disability scores. More clinical trials are being conducted to assess the safety and efficacy of the drug.

## Discussion:

Low back pain is caused by a muscle (strain) or ligament injury (sprain). Improper lifting, poor posture, a lack of regular exercise, a fracture, a ruptured disc, or arthritis are all common causes. Physical therapy, acupuncture, chiropractic manipulations, yoga, Tai Chi, cognitive behavioral therapy, and meditation are examples of nonpharmacologic treatments. Chemonucleolysis is a non-surgical treatment for a bulging disc that involves injecting an enzyme into the vertebral disc with the goal of dissolving the nucleus pulposus, the inner part of the disc. Because of the potential risks, other enzymes with lower allergic potential, such as collagenase, have sparked interest.

Another enzyme that has been reported to be as effective as chymopapain is Chondroitinase ABC (C-ABC). Matrix metalloproteinases (MMPs), also known as matrix metallopeptidases or matrixins, are calcium-dependent zinc-containing endopeptidases; a family of proteolytic enzymes involved in the degradation of matrix components such as glycoproteins, proteoglycans, and collagen.

Another possible treatment for CLBP is chemonucleolysis with ethanol. Platelet-rich plasma (PRP) is made by centrifuging platelets and other blood components from an autologous blood sample. Artemin is the ligand in the glial cell line which is derived from neurotrophic factor family. It binds to the RET receptor tyrosine kinase's GFRa3 receptor. Neurotrophin nerve growth factor (NGF) is a key mediator of pain signal generation and potentiation in tissue injury. Over the last decade, regenerative cellular therapy has been a major focus of research.

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