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Review Article

Degeneration of intravertebral disc and facet joints and promising strategies for regeneration: a review of literature

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Abstract: Vertebral fractures and facet joint degeneration are common among the elderly, and predominant in post-menopausal women. Lumbar spondylolisthesis is observed in the matured spine, with a maximum impact in the L4-5 region. A sagittal location of facet joints promotes deformity at L4-5, and increased angular orientation between the facet joint and transverse plane enhances fracture risk. Both cemented vertebroplasty and cementless fixation procedures are adopted to treat vertebral fractures. Polymethylmethacrylate cement provided respite from pain and prevented future bone disintegration. Injection with carbonated apatite served the same role, added to an increased biomechanical strength. However, these processes involved chances of cement leakage into the epidural disc, endplate cracks, vacuum cleft and contralateral space. Cement leakage following kyphoplasty and vertebroplasty showed unfavorable neurological symptoms and pulmonary embolism as well. Alternatively, lumbar disc arthroplasty using the Prodisc and Charité designs seemed favorable, involving keel-mediated anchorage on the osseus endplates. A cementless and durable fixation method, entailing flexible titanium mesh implants, offered significant pain reduction in thoracolumbar burst fractures. However, the functional impact failed to linger, and hence seemed non-advantageous compared to vertebroplasty. Additionally, an important bone regenerative method used tricalcium phosphate collagen implants in combination with osteoprotective growth factors. Nonetheless, this method required further studies for its thorough understanding. Overall, although several procedures for bone regeneration have emerged, a perfect long-term therapy for vertebral fractures is still unknown. On this basis, stem cell therapy appeared as a novel strategy, facilitating recovery from facet degeneration. However, targeted stem cell strategies await validation.

Keywords: Vertebral, fractures, recovery, vertebroplasty, cementless, growth factor implants

Introduction

Chronic low back pain (LBP) accounts for around 9% of global population, and has resulted in cases of acute disabilities in several countries, including USA [1, 2]. The occurrence is more common in women, and among the 40-80 year old age group [3]. Lower extremity pain is a key feature of LBP, prevalent in 25% of the affected population [2]. The symptoms mainly include muscle strain and musculoskeletal pain, fatigue and spasm, and are primarily detected in patients suffering from arthritis and lumbar compression [3, 4]. Osteoporotic patients are also a key target of LBP [3, 4]. LBP is a form of mechanical pain that may radiate into legs in severe conditions [5]. Of the various factors causing severe low back and leg pain, damages to intra and intervertebral discs and facet joints are key reasons [6]. Structural alterations at the facet joints and intravertebral discs lead to spinal instability, affecting gait and motion [7]. However, any modulation in the integrity of vertebral discs and facet joints may be effortlessly detected through easily available diagnostic tools and non-invasive imaging techniques [7]. In the current review article, we discussed the major causes of vertebral disc and facet joint degeneration. We highlighted the diagnosis and manifestations of vertebral damage. We also focused upon the regenerative mechanism for treating vertebral and facet joint degeneration.

Vertebral disc damage

Vertebral disc degeneration: causes and symptoms: Intervertebral and intravertebral instabilities are the two major causes of back pain, commonly observed in the geriatric population [8, 9]. The problem has gained prominence owing to increased longevity of the aging population [8]. While intravertebral damage involves degeneration of the vertebral body, intervertebral instability relates to the erosion of endplates and associated vertebral discs [8]. These two conditions are the leading causes of back pain, and the symptomatic remedies involve treatment with anti-inflammatory drugs, such as Cox-2 inhibitors, ibuprofen, etc., site specific steroid injections or by the conservative physiotherapy process and ultimately spine surgery [10]. Magnetic Resonance Imaging (MRI) analysis identified that patients with a vertebral disc collapse contain cracks and wear and tear in the thoracic spine vertebra and T1-T2 endplates within the intravertebral body surrounding the spine [8, 11]. MRI further revealed an extended protuberance from the posterior cortical region within the spinal canal in the degenerated vertebral disc [8, 11]. This ultimately resulted in relative immobility of the lower limbs [11]. Seepage of cement from the superior and inferior endplates to the intravertebral disc, associated with fluid accumulation in the inter-cement space has also been reported during vertebral disc degeneration [12]. Radiograph images showed prominent osteophytes from the Lumbar spine vertebra, L1-L3, which impeded motor functioning and coordination [8]. These symptoms appeared to be relatively common in hypothyroid and diabetic patients, and very prominent in situations of severe osteoporosis [13, 14]. Fractures in the vertebral discs led to a progressive and then an absolute collapse of the soft and brittle osteoporotic bones, triggering vertebral stiffness [8, 15]. Increased cementing at the discs and end plates alongside incident fractures caused a synergistic or additive adverse impact in the osteoporotic bones [8, 16].

Bone mineral density (BMD), vertebral strength and intravertebral damage: The vertebral strength and bone health are dependent on variability in intravertebral density and bone size, similarity or analogy in the spatial density dispersal along the vertebra and the strength of the surrounding intervertebral discs [17]. Vertebral strength and intravertebral density confer an ability to overcome the undesirable effects of vertebral fractures [18]. Bone Mineral Density (BMD) is considered as the key determinant for measuring the intensity or chances of vertebral fracture and osteoporosis within the trabecular centrum [17]. Few studies indicated that a lesser heterogeneity in the intra and intervertebral BMD and vertebral microstructure leads to increased bone strength [19, 20]. Likewise, it has been strongly proposed that increased variability in BMD may be beneficial, particularly when a congruity is maintained in the spatial distribution of bone density all along the vertebral structure [21, 22]. Microcomputed tomography (mCT) and quantitative computed tomography (QCT) revealed that vertebral bodies with greater variability in bone density showed higher vertebral strength and sturdiness even when exposed to axial compressive stress [17]. Supportively, it has been observed that the anterior end bears lower than half the overall vertebral density during straight spinal postures, which reduces with aging [21, 22]. A higher BMD at the posterior rather than the anterior vertebral region demonstrated a greater capability for load sharing [17, 23]. Additionally, intravertebral disc degeneration caused a shift in load towards the surface or outer areas, with elevated BMD values in the middle and innermost trabecular region [17, 23, 24]. However, an altered load distribution caused aberrant vertebral disc space narrowing [17, 25]. Because the bone adjusts to the BMD distribution along end plates, any change in this clustered sharing of bone density impaired the vertebral strength [26]. Most importantly, mCT and QCT analyses showed that the density and strength of adjacent intravertebral discs have a significant contribution to the distribution pattern of vertebral density and also regulate biomechanical pathways and processes of vertebral fractures [17].

Facet joint degeneration

Facet joint pain: causes and symptoms: The facet joint serves as a vital point in the lumbar spine that helps in the uniform distribution of lumbar load and in retaining a normal angle with the traverse plane, which helps sustaining lumbar disc stability [27-29]. The facet angle also determines bending and orientation, and

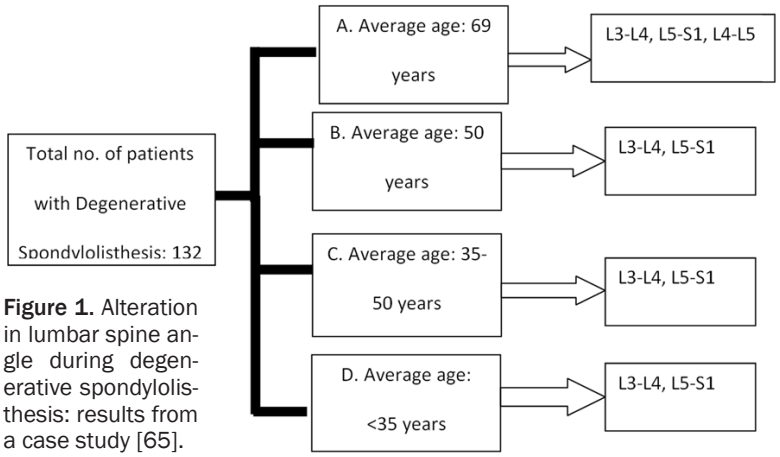

Figure 1. Alteration in lumbar spine angle during degenerative spondylolisthesis: results from a case study [65].

therefore, flexibility of the vertebral spine [30]. An alteration in the facet angle or a change in the facet orientation in comparison to the traverse plane is an important cause for degenerative spondylolisthesis (DS) [31]. The facet joints are located proximal to the nerve roots, and thus, any alteration in the intravertebral disc integrity may also trigger LBP, owing to the eroded facet joints [4]. Nerve blocks at the facet joints are considered important for LBP, as well as referred pain in legs [32, 33]. The nerves and nerve endings are rich in 'substance P' and also contain peptides similar to calcitonin, and any change in this constitutive composition contributes to facet joint pain [6]. In addition, inflammatory events or muscular trauma and injury are key events dysregulating the functioning of lumbar nerves [34]. Degenerated facet joints and damaged ligaments together can cause vertebral misalignment and debility, and an eventual tissue inflammation and enlargement [5]. Facet joint changes are also observed in DS, where fractures within the pars interarticularis of the vertebral arch cause spinal instability [5]. MRI and CT scanning revealed a muscle and ligament swelling, thinning of the spinal channel and a thrust of bony elements on posterior end of the spinal cord in DS. At a later stage,spinal cord compression (myelopathy) is also evident, due to reduced gap area and a loss in space along vertebral bone tissue and apophyseal facet joints.

Facet joint asymmetry: Narrowing of the spinal canal, particularly upon aging, is an important characteristic of DS [35]. Degeneration and abnormality in the sagittal alignment during DS occur within the L4-L5 regions, and have been reported to be more prominent for women [31, 36, 37]. Thus it is evident that hormonal factors may have an important role in DS [37-39]. A biomechanical link is also present between the lumbar spine and facet joint, and the firmness and flexibility of the two are interdependent [27]. The mutual sharing of load serves as a protective factor against stress and strain on the lumbar disc as well as facet joints [40]. Additionally, it has been observed that a sagittal location of facet joints, especially L4-5, makes the joint prone to DS [31, 41].

Facet joint asymmetry resulted in the generation of herniated disc, where the outer potion or the annulus fibrosus of the vertebral disc appeared wrenched, allowing the extrusion of the nuclear region along vertebral nerve fibers [42-44]. Herniation of the lumbar spine further induced irradiating pain in legs [44]. Hence, diseases within the lumbar spine have been found to be associated with facet joint degeneration [45].

Facet joint and DS: an important case study

A study on the facet joint asymmetry and its direct link with DS in 132 patients had been carried out for different age groups, including aged and young ones (**Figure 1**) [36]. The patients were classified as four groups, (A): Patients, aged between 65-70, who suffered from sciatica pain and a slip disc in between L4-5 region of the lumbar spine; (B): Patients with moderate sciatica and back pain, and without detected slip disc [36]. Patients of group B were around 50 years of age. In group C, the patients had the same symptoms as group B, but were in the age group of 35-50 years, and patients of group D were of age lower than 35. Axial MRI and CT scanning images revealed that irrespective of age, sagittal alignment of the facet joints with a un-uniformity and variation of above 10° angle was a major cause for DS. Though for adults, an abnormality of L4-5 was more prominent, for the young patients with DS, aberration was more at the

lumbosacral disc, L5-S1. Hence, it was proposed that these aberrations in the facet orientations may be an intricate and pre-existing problem, observed even in the young population. The degeneration was more evident in women, particularly post-menopausal ones, and at double the levels compared to men.It was also observed that sacralization at the fifth lumbar vertebra, when synergized with the pressure on L4-L5, resulted in olisthesis. However, congenital issues and late-life osteoarthritic degeneration appeared to participate less in DS. Rather, the altered facet joint angle has been presumed to result from osteoarthritic degeneration associated with undesired bony projection, cartilage damage and varied bone density at the subchondral layer [30]. This culminated in an abnormal enhancement in the facet volume and increased compression at bony ends, causing a tapering of both the anterior and posterior domains [46]. The study ultimately proved that sagittal degeneration at L4-5 was prominent in DS, and involved changes in the facet joint and vertebral angles. A pre-existing or congenital factor hardly played any role, rather bone remodeling with increased age, and more for women, contributed significantly [36].

Unilateral lateral mass-facet fractures (ULMFFs): Degeneration of the spinal cord and traumatic cervical spine injuries, often resulting from accidents, lead to situation termed as ULMFF [47, 48]. In ULMFF, the spinal cracks and fissures caused compression or excessive loosening and aberrant rotational movement of the spine towards superior and posterior facet joints, leading to severe instability and irregular bending of the spine [48, 49]. A strain or stress in ligaments at the anterior region, close to the spine, adds to the pain and tenderness during ULMFF, and the posterior ends showed a bent orientation [49, 50]. However, ULMFF is known to have little association with neurological damages [51]. Unilateral spondylolisthesis (US) is a distinctive category of ULMFF, marked by rotational instability, but devoid of facet joint dislodgement [49, 51]. Nonetheless, in rare situations, facet fractures with joint displacements are also observed for patients suffering from ULMFF [51]. Usually, during facet joint dislocation, aberrations close to 10° are detected between the axial rotatory angles and convex kyphotic angles. This is a typical situation categorized as Split (SP) in the medical language [52, 53]. An important feature of SP is a crack or fissure formation within the zygapophyses and postzygapophysis [53, 54]. In terms of detection, the most important three-dimensional detection tool for ULMFF is the high-speed spiral CT that gives a distinct 3-D measurement of the facet and its surrounding regions [12, 55, 56]. The treatments relied on surgical processes based on dynamic X-Ray and CT scan image diagnoses [51]. The extent of damage was dependent on the facet joint movements around the axis, and kyphosis and sagittal dislocations as well [51]. Facet joint dislocation or the loss in stability of the cervical spine could also be measured through MRI. MRI detected cracks and splits at the intervertebral discs and the adjacent ligaments. Based upon the degree or site of fractures, ULMFF could be classified into four types. The first type, i.e. 'US' though showed a consistency in linking the upper and lower facet joint, demonstrated fractures along the superior and inferior articular processes, causing a dislocation of the upper cervical spine. The second type, i.e. separation (SE) fractures exhibited a fracture within the lamina and pedicle, segregating the lateral mass from the vertebral structure. Thus, the double fracture lines had a marked adverse impact, causing alterations in the adjacent motion segments. The third type or combination (CO) type was more severe, marked by a series of cracks and fractures within the lateral mass, which often culminated in a bending or distortion at the coronal site. The split (SP) category of fracture demonstrated a vertical fissure within the plane dividing the dorsal and ventral parts, and thereby isolating the anterior and posterior domains and affecting the nearest caudal vertebra. The cervical spine and lateral mass fractures and fragmentations had two further sub-categories, termed as 'articular process fractures with dislocation (AFD)' or the AF, devoid of dislocation and dislodgement. The treatment procedures for mild spine and lateral mass damage necessitated an anatomic reinstatement, without involving a surgery. Medications for pain reduction appeared necessary. However, severe degeneration, proved through the X-ray, CT and MRI, essentially entailed a secondary surgery.

Regeneration of spinal stability

Stabilization techniques for ULMFF: It has been observed that surgical procedures are pre-

ferred for restoring the facet and spinal stability during ULMFF, especially under a condition associated with severe ligament injuries [51]. Both anterior and posterior stabilization methods had been adopted for the surgical procedures, where the latter seemed theoretically better in biomechanical terms [57-59]. The anterior stabilization procedure involved cervical arthrodesis, joining selected bones of the anterior domain with the joints [51, 55, 60, 61]. An autologous iliac bone transplantation and cruciate substituting prostheses at the anterior region helped in the joining process [51]. The combination of anterior and posterior approaches seemed encouraging, particularly when anterior arthrodesis failed to cause recovery in situations of facet displacement. A two-level stability of the anterior and posterior arthrodesis emerged most beneficial to bring marked stability and firmness for ULMFF. Both dynamic and firm surgical plating brought stability following cervical spine injuries, and the latter proved favorable in severe conditions. However, for ULMFF, the dynamic plating also worked, providing sufficient stiffness and involving lesser post-surgical trouble compared to the rigid or static implantation [62]. Apart from a few exceptions, the surgical techniques generally demonstrated no complications just after surgery on in the long-term follow-ups, until an average of around 18 months [51]. The time to achieve complete recovery of the cervical spine through anterior stabilization procedure required an average of around 5-6 months. The surgery also provided improvements in neurological symptoms. Nonetheless, posterior stabilization had the disadvantages of a late deformity, characterized by the inability to inhibit undesired rotation of facet joints [49, 57, 63]. Autografting from the region of the iliac crest bone proved important for treating cervical spine injuries in osteoporotic patients. Even so, the autograft process showed graft disintegration and incongruity, and stiffness at the donor-site had also been reported [64]. Most importantly, an improper setting and fusion with the graft, and infection at the damaged site were common features of autografting [51].

Bony healing of fractures in the aging population: A reduced velocity-trauma in the aging population caused marked increase in the vertebral compression fractures (VCF) [65]. VCF is a recurring event, with a fracture followed by degeneration in the osteoporotic spine within a span of a year [65]. Along with pain and discomfort, a significant increase in morbidity with kyphosis worsens quality of life. A trauma at a young age also forms one of the key reasons for VCF later. X-Rays, MRI and advanced CT-Scan procedures are diagnostic tools for VCF resulting from minor or major trauma.Fractures at a young age, especially the unstable fractures, are generally healed through a cementing and internal fixing procedure involving vertebroplasty and kyphoplasty [66]. However, the leakage of this cement into the intermediate disc gap causes harmful effects in the adjacent neurovascular units [67, 68]. Inserting fixatives failed to solve the problems, particularly the fractures of the dorsal wall and in the elderly population [69]. Hence, the only treatment method included vertebroplasty and kyphoplasty, in association with coverage of the dorsal wall damage [69, 70]. The most prominent advantage of this method is that it involves a single step, and requires least invasive procedures [65]. The major problems with the multi-stepped healing procedures in the aged are infections at the site of screw insertion and internal tissue non-alignment [71]. Multilevel fixations, however, bear certain risks in the elderly, like soft tissue complications, infection and pedicle screw cut-out [72]. A two staged insertion of expandable screws, together with flexible titanium mesh cages, not only reinstates the vertebral structure, but also mimics the cementing procedure in attenuating pain and morbidity in the elderly. This is termed as a good method for treating vertebral bone cracks and fractures, particularly in and around the thoracolumbar spine [65]. The combination of the expandable screw and titanium mesh cage is not only less invasive, but also a perfect fixation procedure that attenuates pain and morbidity and offers a uniform fixing [70].

A population based study had been carried out that involved sixteen patients, with a mean age of seven, and suffering from severe osteoporosis that adversely affected the integrity of about 7 of lumbar and 2 of the thoracic vertebrae (**Figure 2**) [65]. Combination of X-ray, MRI and CT scan demonstrated incomplete burst fractures in the patient population [65]. These patients had all undergone treatments with bisphosphonates and other anti-osteoporotic

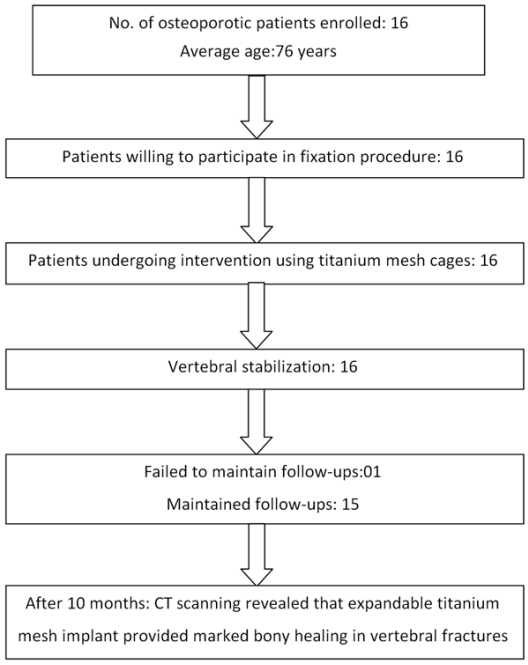

Figure 2. Flow chart for cementless fixation following osteoporotic fractures [36].

medicines, but to no effect. The inclusion criteria comprised patients who suffered low-velocity vertebral injury leading to severe back ache and spine dorsal wall cracks. The exclusion criteria for the study included sensory damage, injuries beyond the specified vertebral fracture, senility and misplaced clinical and preliminary treatment records. For intravertebral regeneration of burst fractures within the dorsal wall, the thoracolumbar spine underwent operation, and then treatment. The two-stepped healing method involved insertion of two titanium mesh cages that reduced the vertebral height, in association with the steady fixing of posterior spinal region using flexible and lengthy polyaxial screws. The process was a cementless one and required a modest invasion surgery [65, 70]. The patients underwent regular checking for 10-11 months, and only one patient died owing to unrelated cardiac problems, and the rest survived the surgery. The patients also went through CT scanning and radiotherapy for periodic assessments, including pre-operative, intermediate and even post-operative, throughout the follow-up stages. Spine X-Ray revealed the extent of bone healing and regeneration. Radiography of saggital area mainly included the anterior, middle and the posterior region of the damaged dorsal spine vertebra. The sagittal index, kyphotic angle and the Cobb angle were diagnostic features measured as a follow-up to the surgery. Expert orthopedic surgeons and radiologists were deputed for thorough check-ups that included proper titanium cage positioning and alignment, devoid of the pathological destruction or disappearance of bone tissue [65].

Vertebroplasty

Intravertebral fracture is predominant as an aging feature, prevalent in more than 20% of the above-70 year old population, and strongly evident in the post-menopausal women [73]. Intravertebral fractures are generally treated using calcium, vitamin D, estrogen and bisphosphonate drugs [74]. Surgical treatments were relatively rare, and more so for severe degeneration involving significant osteoporotic bone distortion [74]. However, the processes had post-surgical complications that were often irreparable for the elderly [73]. Hence, alternatives to the procedure appeared very essential [74]. Vertebroplasty has been used as an important surgical procedure for treating or reducing osteoporotic fractures, and has shown considerable respite from severe pain and morbidity [75, 76]. Mild, modest and strong vertebral deformities underwent surgery, with a shift in vertebral angle in the range of 15°-30°, in association with a proportionate bone height reduction compared to normal ones for the same age group and sex [73, 74]. Being a painful process by itself, localized anesthesia accompanied vertebroplasty within the vertebral tract and with prior treatment of the patients with sedatives [74]. Hardened polymethylmethacrylate bone cement, at a polymer to the monomer ratio of 2:1 ratio, seemed suitable for vertebroplasty [73, 74]. Moreover, implantation technique appeared important [74, 77, 78]. The procedure caused significant pain relief and also helped regaining mobility [73]. The fractured region of the vertebra appeared to be the site for incorporating the cemented mixture, particularly along the central or side of the vertebral pedicle, using a suitable injector that could traverse through the cleft space as well [73, 74]. However, usage of secured corkscrews preventing cement leakage beyond the vertebra had been the precautionary measure [73]. Fluoroscopy and radiography helped visualizing the needle movement

along its point and area of insertion [73, 79, 80]. Intermittently, the damaged area underwent more than one injection of polymethylmethacrylate using several needles, particularly at the contralateral pedicle [73, 79]. This enabled uniform filling of cement along the vertebral tract to prevent its saturation at the lateral side [73, 80]. However, during follow-up, a repeated fluoroscopy, radiography and CT scanning indicated chances of undesired cement seepage into the clefts between the intravertebral discs [73, 80].

A study on about 66 patients with vertebroplasty demonstrated 40% to be suffering from cement leakage, particularly at the cleavage within or beneath the vertebral junction, close to the endplates [73]. Few patients also showed signs of severe blood vessel rupture and bleeding, especially at the sites of needle insertion [73, 80]. Cement seepage and bleeding following vertebroplasty had several deleterious effects on the overall health of patients [73, 80-82]. A penetration of cementing material into the veins, particularly the epidural veins and inferior vena cava, induced cascade of toxic events, which led to breathlessness and lung collapse as well [73]. Quite often the cement entered the vascular channels and cracked endplates [73, 81, 82]. Inadvertent excess penetration and an altered insertion angle of the needle in relation to the endplate proved to be the major underlying reasons for cement leakage [80, 81]. Additionally, an aberrant merging of the vertebral cleft with endplates, particularly due to a surplus polymethylmethacrylate injection, appeared to be the major cause of the leakage [83, 84]. The cementing material had certain adverse effects, owing to its heat generating properties [73]. Most importantly, the cement got ingrained in the system, with little chances of its removal or flushing out [73, 80]. An altered polymeric and monomeric ratio of the cementing materials that changed the consistency and uniformity of the filler also appeared as a key factor determining cement penetration and spill [73, 85]. Certain precautionary measures during vertebroplasty prevented the undesired cement leakage and vertebral cleft penetration. Of these, surgical care seemed essential in maintaining a gap between the vacuum cleft and the vertebral disc [73]. The point of needle insertion could also preferably lie within a distance from the fracture or vertebral crack [77].

Osteoconductive and osteoinductive materials that could overcome the damaging impact of polyrnethylmethacrylate have been proposed for vertebroplasty [74-76]. Carbonated apatite seemed good for bone remodeling during intravertebral degeneration and osteoporosis [74]. A major advantage of carbonated apatite as a fixative material was its extensive chemical similarity with bone composition, and secondly its ability to restrain from heat generation within the system. Carbonated apatite injection lied between the T2 and T4 vertebra. The vertebra showed higher mechanical strength and elasticity. When injected in osteoporotic spines, the cementing material prevented the trabecular bone collapse, even after acute fractures, by maintaining the bone energy dynamics, and also restrained imminent spine fractures by promoting new bone generation.

Total disc arthroplasty (TDA)

Lumbar total disc arthroplasty (TDA) has been considered as a regenerative implant for vertebral split fractures [86]. The method involves a sufficient shift of load to the adjoining vertebra causing anchorage on the osseus endplates [87]. This docking onto the osseus vertebral endplates involves two varied methods [86]. The Prodisc or Mverich process involves the generation of a precut slit within the endplate and deep penetration of a keel into the slit [87, 88]. The second design, i.e. Charité or the active L induces stability to the vertebral endplate using tiny spikes and ridges before placing the keel [88, 89]. The Charités primarily have un-uniform load sharing, and the use of the keel-induced anchorage through TDA implants were essential [88].

Case reports on women with lumbar disc degeneration showed restored bone formation and fracture healing due to TDA and keel implantation at the L4/5 facet joints [87, 90]. Radiography and MRI revealed that prior to surgery, the patients suffered from disc height shortening, disc dehydration, inward *lordotic* curvature at different lumbar segments and signs of osteochondritis dissecans within the endplates [87]. Distinct Modic changes type-1, at the L4/L5 anterior position, also formed important characteristics of degeneration [87]. The patients suffered from pain emanating at the facet joint L1, and the discomfort trailed along S1 [87]. The patient underwent surgery

through Prodisc-L-keel method, where the two adjacent TDA-implants had been positioned at the L4/5 disc spaces [12, 91]. For perfect fitting, the disc-spaces first underwent over-distraction [87]. X-Ray imaging during a mid-term follow-up revealed healing and generation of new trabecula bone, particularly at the L4 [87, 90]. Radiography further showed marked healing at the sagittal contour that was close to the L4/5 implant and in the S1 [87, 92]. At the sixth year after procedure, i.e. at a long-term follow up, axial CT-scan demonstrated a new bridge-like dense structure that held together the keels of two adjacent TDA implants [87]. Interestingly, the morphology and apparent visual density and trabecular bone orientation seemed identical to the bones of that particular region. Additionally, CT scan reconstruction showed that alongside the new bones generated between the two keels, trabecular bone formation also occurred in certain areas and slightly at the sacral promontory as well [87]. Overall, the TDA-implant procedure caused a significant change and recovery of the flattened curvature within the degenerated lumbar spine to a perfect lordosis. Specifically, the scanning and radiography analyses revealed an overall enhancement in the lordosis angle from 10-55° for L1-S1 and 10-33° in between S1 to L4. This led to a transfer in the vertebral load from the anterior towards the posterior region, causing a shift in the plumbline and generating a stronger sagittal balance. Positioning of the plumbline served as a key decisive factor in distribution and load transfer. The anterior positioning of plumbline promoted load transfer along the vertical spine bodies, while posterior plumbline loading shifted the load towards the posterior sides that mainly included the facet joints.The TDA implant design had a significant role in deciding the plumbline transfer [87]. The implant characteristics also regulated the vertical load transfer towards the keel and bony endplates [53, 91, 92]. These facts indicated that the TDA implants may have an adverse impact on the vertebral bodies, by particularly creating pressure at the keel and endplate sites [88, 89, 91]. This appeared to result in loosening of the implant and reduced fixation of the bony surface [87]. Thus, it has been proposed that the design of the TDA implants requires special attention, and further frequent follow-ups following TDA-implantation may be suggested to overcome these unfavorable effects of surgery [87, 93].

Growth factors and vertebral regeneration

Growth factor application promotes bone formation and facilitates the curing of osteochondral defects [94, 95]. A double-layered implant comprised of a collagen type I/II along with b-tricalcium phosphate (TCP) and growth factors that mend the damaged cartilage layers in osteochondral degeneration [96]. Additionally, the TCP also helped regenerating and repairing the degenerated subchondral bones [96-99]. TCP in association with osteo- and chondrogenic growth factor mixture (GFM) augmented the recovery process [100]. The GFM was a combination of a range of bone morphogenic proteins, tumor growth factor-beta, fibroblast growth factor, osteocalcin and osteonectin [100-102]. Based upon the observations of stimulated chondrogenesis and osteogenesis in the murine and bone marrow stems cells, *in vivo* studies started using the TCP implant and GFM [103]. Randomized studies on Gottingen minipig models showed osteochondral defects at the femoropatellar grooves [104]. The study included a set that had a TCP implant insert, and another in which the animals had undergone treatment with GFM following TCP implantation [100]. In the follow-up studies, following perpendicular incisions from the TCP implants, subchondral bone regeneration underwent assessment.

Orientation of the facet joints is an important factor governing the direction of lumbar discs, and a slight change in the facet angle leads to instability in the lumbar spine, culminating in severe DS. The main function of a facet joint angle is to maintain the normal distribution of load during compression and expansion and thereby prevent shear and stress that may lead to the development of DS. The trabecular mineralization appeared to be close to the TCP surface at 6-weeks post implantation. Microradiography revealed that after 12 weeks of TCP implantation osseus regeneration started taking place, with nominal signs of mineralization and trabecular bone growth along the defective region. At this time, the TCP underwent significant resorption. It took around 50-55 weeks for prominent mineralization of

the trabecular meshwork and damage repairing along the bone surface. Only minute remains of TCP appeared at the damage core, and the surrounding looked absolutely healed with new trabecular bone formation. Truly, within 52-55 weeks of implantation, a complete trabecular reconstruction had happened. Nonetheless, treatment with GFM accelerated the whole process, and within a span of 6-weeks, signs of trabecular regeneration surfaced. Twelve weeks post implantation, bone regeneration in areas adjacent to TCP implants appeared, and after 52 weeks, the TCP remains had almost vanished. The reconstructed bony structure with GFM supplementation exactly matched the orientation and structural design of the normal trabecular bones [100].

Conclusions

Overall, studies indicate that aberrant remodelling of the bony joints played a significant role in intra and intervertebral fractures and facet joint degeneration. The use of growth factors, at their perfect ratios, in combination with the stem cell therapy may be recommended as a good alternative as well.

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Disclosure of conflict of interest

None.

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