Current understanding and the potential future of spinal fusion

Krishna Sharma[1]

[1]Consultant Neurosurgeon Annapurna Neurological Institute and Allied Sciences, Maitighar, Kathmandu, Nepal

Date of submission: 1st July 2023 Date of acceptance: 1st January 2023 Date of publication: 30th March 2023

Introduction

Trauma, infection, cancer, and congenital abnormalities are examples of spinal pathologies that can compromise structural stability. The spinal cord and nerve roots, which the spine is meant to safeguard, may become compressed and damaged as a result. To stop further damage in such cases, the spine needs to be decompressed, re-aligned, and fused. Spinal fusion is a normal bone-healing procedure that helps to regain structural stability. Although this unassisted process may accomplish alignment and strength, it may do so slowly and insufficiently, causing ongoing compression on neural structures.[1,2] Therefore, grafts and instrumentation may be required to supplement the natural process of spine fusion. Pharmacological agents, graft expanders, and graft enhancers may need to be added to the process in order to achieve sufficient and quicker fusion.

For Pott's spine, Albee published the first American account on assisted spinal fusion in 1911.[3,4] Since then, there has been a sharp rise in spinal fusion procedures. The increase in annual procedures done in the USA, from 174,223 in 1998 to 413,171 in 2008, is evidence of this.[5] Fusion is increasingly being included in all major spine surgeries. Time has also demonstrated the related effects and difficulties of spine fusion which could be reduced mobility, pseudoarthrosis, diseases of the neighboring segment, revision surgeries, rising costs, and other related morbidities. Continued study is necessary with an emphasis on appropriate case selection, risk reduction, fusion techniques, and postoperative spinal fusion optimization in order to maximize value and keep complications at a minimum level.

Hibbs treated a 9-year-old child with a kyphotic deformity at the turn of the 20th century by removing the spinous processes, repositioning them over the interspinous space to encourage fusion, and repairing the periosteum over the fusion mass.[4] During the same time frame, Albee suggested using bone grafts to improve spinal fusion in Pott's disease patients.[3, 6] Since then, the procedure for fusing the spine has progressed from fusing it alone to fusing it with instruments and the addition of medication.

Access this article online

Website: https://www.nepjol.info/index.php/NJN

DOI: https://doi.org/10.3126/njn.v20i1.51562

HOW TO CITE

Sharma K, Farrokhi F. Current understanding and future of spinal fusion. NJNS. 2023;20(1):2-21.

Address for correspondence:
Dr. Krishna Sharma MBBS, MS, DNB
Associate Professor
Consultant Neurosurgeon Annapurna Neurological Institute and Allied Sciences, Maitighar, Kathmandu, Nepal
E-mail: Krishnasharma@yahoo.com

ISSN: 1813-1948 (Print), 1813-1956 (Online)

Pathogenesis of fusion

Normal progression of spine fusion process includes inflammatory response, osteogenesis, angiogenesis, and remodelling. The spine does not fuse in the same way as the other bones, with minimal callus formation, for unknown causes. Bone fusion takes between three and six months. The oxygen tension, force application trajectory, and motion at the location of fusion all have a significant impact on bone fusion. In nearly a year, the bony callus matures, remodels in accordance with the strain applied[7], and completes the fusion process.

Factors influencing fusion

Co-morbidities of patients, major modifiable risk factors, surgical techniques, postoperative care, the use of grafts and implants, as well as the type of fusion carried out, are just a few of the many variables that can affect fusion.[8] To reach the ideal spinal fusion state, these variables should be recognized and optimized. They can be broadly separated into systemic and local variables. The specifics of each of these factors are outside the purview of this review and can be researched further using the references given.

Systematic factors

- Due to the reduced availability and delayed mobilization of growth factors, osteogenic factors, and anti-inflammatory factors in systemic diseases like metabolic bone diseases and immune compromised states like diabetes, renal failure, malignancy, and rheumatoid arthritis, the fusion process is slowed down. [9, 10]
- Osteogenesis, overall bone mass, and bone metabolism are all significantly influenced by hormones. Therefore, changes in hormone levels, particularly those of growth hormone, thyroid hormones, parathyroid hormone, leptin, adiponectin, angiotensin, cortisol, erythropoietin, insulin, oxytocin, and calcitriol, as well as estrogen and androgen, have a detrimental impact on osteogenesis. [11,12, 13]
- Low albumin levels, iron deficiency anemia, leucopenia and a negative nitrogen balance are indicators of poor nutritional condition.[14, 15, 16] These reduce healing process, and fusion. Patients who have hemoglobin A1c levels under 8% have a poor chance of fusion.[17]
- Osteoporosis and low bone mineral density (BMD), which is defined as a BMD 2.5 or more below the young adult mean or a T-score at or below -2.5, as well as a lack of nutrients like calcium, iron, and magnesium, all essential for bone formation, can delay fusion.[18, 19, 20, 21, 22, 23] If BMD is less than 0.3 g/cm^2, internal fixation devices ought to be avoided. [24]
- Drugs that inhibit bone development and healing include corticosteroids, methotrexate, adriamycin, H2 blockers, and NSAIDs. Additionally, these medications decrease bone fusion by causing mineral losses that are necessary for fusion.[25, 26, 27]
- Smoking decreases bone fusion by as much as 56% due to the effects of nicotine.[25, 28, 29, 30, 31]
- Alcohol intake on a regular basis slows down fusion as well.[17]
- Spinal fusion is delayed in obesity with greater body mass index (BMI).[32, 33]
- Lack of exercise hinders union.[34]
- Genetic factors: It has been demonstrated that alterations in the genes for the vitamin D receptor (VDR), the oestrogen receptor (ER), and collagen type I1 (COLIA1) affect bone fusion.[35, 36]

Local factors

- During fusion, maintaining equilibrium is crucial, including sagittal balance. Sagittal balance problems result in deformity, pain, neurological compression and impairments, as well as a changed force distribution that slows the rate of fusion.[37, 38] Sagittal balance and normal spine biomechanics must be attained in order to improve fusion and re-establish mechanical stability.[37]
- The donor graft can fuse more quickly if there is sufficient compressive force applied to it, which encourages the ingrowth of vascular branches and proliferating mesenchymal cells from the cancellous host bone into the donor graft.[39]
- Multiple level fusion and junctional area involvement have a detrimental effect on fusion and increase the chance of non-union.[40]
- There are seven biological variables that affect fusion.[7]
    - Sufficient local blood flow, particularly in the union bed vascularity.
    - The use of grafts with good osteogenic potential and osteo-progenitor cell supply.
    - Proper receiver site setting, such as decortication, to enhance fusion.
    - If radiotherapy is administered within three weeks of operation, it slows fusion. [41]
- Diseases of the bone, such as tumors, fibrous dysplasia, and Paget's disease, inhibit union.[42,43]

Radiologically, instability that requires fusion is defined as having at least 4mm of anterio-posterior translation above the L1-L5 levels, 5mm of translation at the L5-S1 levels, or 11 degrees or more of end plate angular shift at a single level compared to an adjacent level.[17]

Standard radiography, dynamic radiography, radio-stereometric analysis (RSA), CT, and MRI can all be used to determine the fusion state. The most popular way to evaluate spinal fusion is with plain static spine radiographs, which look for bridging trabecular bone across the section.[44] The existence of deformity under physiologic load and graft resorption, implant subsidence or migration, implant integrity, and non-union, on the other hand, are signs of non-union.[45] However, there are some concerns about the accuracy of X-rays in identifying small voids connected to pseudoarthrosis, especially in the thoracic and lumbar spine. It was found that almost 25% of those who had been labelled as fused on plain radiographs had not actually fused.[46]

Fusion can be divided into three phases radiologically.[47] (Table 1)

With a specificity of 89% and a sensitivity of 91%, dynamic X-rays improve the efficiency of fusion detection. Pseudarthrosis has been identified on lateral dynamic radiographs by movement of more than 2 mm across fused segments between spinous processes and a Cobb angle greater than 2°. For pseudoarthrosis, a Cobb angle of at least 4° had a 100% positive predictive value (PPV). [48, 49]

Table 1

Classification of Interbody Fusion Success: Brantigan, Steffee, Fraser (BSF)

BSF-1: *Radiographical pseudarthrosis* is indicated by collapse of the construct, loss of the disk height, vertebral slip, broken screws, displacement of the carbon cage, or significant resorption of the bone graft, or lucency visible around the periphery of the graft or cage.

BSF-2: *Radiographical locked pseudarthrosis* is indicated by lucency visible in the middle of the cages with solid bone growing into the cage from each vertebral end plate.

BSF-3: *Radiographical fusion*: bone bridges at least half of the fusion area with at least the density originally achieved at surgery. Radiographical fusion through one cage (half of the fusion area) is considered to be mechanically solid fusion even if there is lucency on the opposite side.

Reproduced with permission from Fogel GR, Toohey JS, Neidre A, Brantigan JW: Fusion assessment of posterior lumbar interbody fusion using radiolucent cages: X-ray films and helical computed tomography scans compared with surgical exploration of fusion. *Spine J* 2008;8(4):570-577.

The ability of computed tomography (CT) to clearly display the bridging trabecular bone, a sign of arthrodesis, is a unique advantage. [50] An accurate CT scan can reliably show a posterolateral fusion 89% of the time.[51] A spinal segment's motion and stability are evaluated using quantitative motion analysis (QMA) software both before and after operation [52], as well as for real-time feedback during fusion and instrumentation. The combination of CT scans and dynamic radiograph QMA, which has a positive predictive value (PPV) of 100% and a negative predictive value of 73%, is fast becoming the gold standard of treatment.

By converting two-dimensional data to three-dimensional data through radio-stereometric analysis, [53] it is possible to calculate the three-dimensional motions between grafts. The invasive nature of this methodology makes it largely unsuitable for regular clinical use. Similar to that, MRI is not the best technique for evaluating union. It is only applicable to instances where non-metallic cages have been used and inter-body fusion has been assessed. [54]

Indications of a spine fusion keep on evolving as we gain a better knowledge of natural history, spinal fusion biomechanics, pathophysiology, socioeconomic factors, patient factors, surgeon factors, resource availability, and regional beliefs and customs. The primary indication is the spinal instability, both static and dynamic. Other important indications include:

- Complex spinal canal stenosis, which is a stenosis of the spinal canal accompanied by grade II and III spondylolisthesis as well as serious, static, or progressive deformity and pain.[55,56,57]
- Recurrent disc herniation, typically with more than two recurrences and instability.[58, 59]
- Iatrogenic instability is a state of instability brought on directly by surgical and/or medical intervention. They are more likely to need revision surgery. [60,61,62]
- Progressive congenital spine deformities that result in instability and compression of the neural tissue
- Kyphotic flat back condition
- Laminectomy of more than three levels
- Osteoporotic vertebral fracture not responding to conservative therapy [63]

A scoring system has been developed by Kulkarni et al. to help determine who would most likely benefit from spinal fusion. Fusion surgery would be beneficial if the result is higher than 5.5. [64]

TABLE 1. The Scoring System

Factors	Score
Clinical factors	
Mechanical back pain (bothersome pain, present on loading the spine and decreasing on lying supine)	2
Age <70 y	1
High-demand activity	1
Radiologic factors	
Segmental kyphosis (change in angle from lordosis to kyphosis)	1.5
Segmental dynamic spondylolisthesis (>2 mm translation on lateral dynamic films)	1
Disk height (50% more than adjacent cephalad level)	1
Bilateral facet effusion (bilateral full facets on T2-weighted axial magnetic resonance imaging > 1 mm fluid)	1
Sagittal facets (measured by calculating the angle generated by connecting the 2 endpoints of each facet on a preoperative axial lumbar magnetic resonance imaging (midcut through the disk) and a line connecting the 2 ventral points of each facet joint. >50 degrees = sagittal facets)	1
Technical factor	
Feasibility to decompress (anatomy unfavorable for complete decompression via a laminotomy that is both facet and midline sparing)	1.5

Complications of fusion

Up to 25% of fusion surgeries can have complications.[65,66] The main complications are:

1. Adjacent segment disease (ASD)

Adjacent segment disease (ASD) is a significant issue following fusion surgeries, with a prevalence of nearly 25% within 10 years of the initial fusion and an incidence of symptomatic ASD of 2.9%. [67, 68, 69] Fusion modifies the

spine's biomechanics, increasing the mechanical load on the nearby disc space.[70] Fusion can result in rapid disc degeneration, pain, deformity, facet arthropathy, and increasing stenosis with neural compression. Taken together, these conditions lead to ASD. This risk has been greatly decreased by recent developments in taking into account and correcting sagittal balance as well as attention to limiting disruption of adjacent segment tissues.[71] The result of adjacent segment disease is progressive deformity, especially junctional kyphosis.[72]

2. Non-union or pseudoarthrosis

Pseudoarthrosis, also known as non-union, is a surgical fusion failure. It is the primary reason for revision surgery and has a prevalence between 5 and 42%.[73,74,75] Smoking, patient co-morbidities, multilevel arthrodesis[76,77], the use of medications that affect osteogenesis, and ineffective fusion techniques are a few of the many variables that delay fusion.

Other complications include

3. Mobility restrictions, primarily flexion and extension
4. Osteomyelitis of the fused section [78, 79, 80]
5. Vascular and neural compression associated with displacement for transplant [81, 82]
6. Biomechanical collapse [83]
7. Failed back condition and persistent pain syndrome.[84]

To minimize these complications, the following steps could be taken,

- Managing the patient's comorbid conditions, such as osteoporosis, diabetes, renal failures, cancer, etc., as well as addressing nutritional deficits and other issues.
- Preoperative analysis of clinical features and imaging and planning accordingly.
- Correcting and maintaining biomechanics like sagittal alignment [85,86] and lumbar lordosis (LL) in relation to a patient's-age-adjusted pelvic incidence (PI) [86, 87]
- Carefully choosing fusion levels[88, 89], preventing multilevel fusion, and excluding hypermobile adjacent segments[90] are important for maintaining motion segments.
- Avoid including adjacent degenerative levels.
- Use grafts that are of right sort, size, and shape.
- Interbody placement of the graft completes a circumferential (360°) fusion, lessens stress on the pedicle screws, and corrects lordosis, and thus may improve fusion rates from 83.3% to 95.9%.[91, 92, 93]
- The shortest plates and implants should be used.
- Multiple rods that decrease motion at L5-S1 have been shown to reduce lumbosacral junction stress.[94,95,96]
- Stiffer rods (cobalt-chromium or steel) can reduce rod motion and strain and thus improve strength and resistance to fatigue better than less stiff rods (titanium). However, proximal junctional kyphosis (PJK) may occur more commonly with a stiffer rod. [97]
- In-depth understandig of surgical technique, and preservation of critical structures like the adjacent annulus, cranial and caudal anterior longitudinal ligament (ALL), and longus coli muscle help to lessen fusion complications. [98, 99]
- Meticulous prior planning with the goal of eradicating all sources of infection and use of suitable and sufficient antibiotics when necessary.
- Supervised physical therapy before and after surgery, helps to keep the graft in position, prevent stiffness or contractures, maintain alignment, and gradually build up the associated muscle strength.

Osteoporosis

Osteoporosis is a co-morbidity that remains a significant risk factor for unsuccessful outcome of assisted fusion surgery due to fusion construct failure**,** interbody cage subsidence, compression fractures and pseudoarthrosis [100, 101, 102]. The NIH Consensus Statement predicted that osteoporosis would affect 12% of the population overall, 4.2% of males, and 18.8% of women, particularly after the age of 50.[103, 20] Women have a 29% lifetime risk and males have a 14% lifetime risk of developing an osteoporotic spine fracture.[104] There is slowed osteogenesis and poor grip to hold the implants in place.[105, 106, 20, 21, 22, 107] One must identify those who have or at risk for osteoporosis by determining metabolic bone health panels (vitamin D, parathyroid hormone, thyroid-stimulating hormone, albumin, and pre-albumin levels) and dual-energy X-ray absorptiometry (DEXA) scans to evaluate bone mineral density and initiate medical optimization before surgery.[108, 109,110,111,22]

Pharmacotherapeutic approaches, such as the supplementation of calcium, vitamin D3[108, 112], anti-osteoporotic medications like bisphosphonates, hormonal therapy, calcitonin, and teriparatide, depending on the severity and therapeutic reaction, are beneficial during the perioperative phase. These have been demonstrated to lower the chance of bone-implant failure while increasing fusion mass and rates.[113, 114] The surgical approach must be modified to preserve the endplates,[115] use longer constructs, concurrently use more anchors, perform additional interbody fusion, do under-tapping the pedicle and use longer, bigger, cement-augmented and growth factor-coated screws.[116]

Assisted bone fusion

The natural fusing process is further aided and enhanced by assisted bone fusion, which also lessens complications. In order to accomplish a better, faster, and stronger union, bone graft substitutes, fusion enhancers, and implants are being used to assist fusion. Broadly, assisted bone fusion can be divided as either structural graft or fusion substrate.

1. During the process of fusion, structural grafts provide the spine with instant physical support. These include,
   a. Bone grafts
      i. Autologous bone grafts
      ii. Allograft
   b. Artificial Grafts

2. Fusion substrates are those that enhances the process of fusion itself. The fusion substrates can be
   a. Autograft
   b. Allograft
   c. BMP (Bone morphogenic protein)
   d. Other synthetic products

A. Bone grafts

Bone grafts, either on-lay or inlay, are used to achieve better fusion. The appropriateness of graft depends on its properties, namely osteo-induction, osteo-conduction, and osteogenesis. Among the bone grafts, autologous (autograft) bone graft is the time tested and gold standard living graft obtained directly from the index host. It has very high osteogenic, osteo-inductive and osteoconductive properties.[117] At no extra cost, it is readily available from adjacent exposed spinous processes or either anterior or posterior iliac crest. [118] These have up to 100% fusion in instrumented spinal fusion procedures.[119, 120, 121, 122] It became less popular due to donor site complications like pain, neurovascular injury, anterior–superior iliac spine avulsion fracture, hematoma, and infection.[123, 124, 125, 126] These limitations have led spine surgeons to look for other potential substitutes.

Allograft is a poplar commercially available substitute of autologous graft[125, 127 128] with fusion rate up to 94.3%[129] and similar clinical and radiologic out-comes.[130] It is a cadaveric bone, sterilized to remove infectious agents and processed to contain only inert material. They have only osteoconductive properties acting as a scaffold for the bone from adjacent bone to grow. Allografts take longer time to fuse but give an immediate additional structural support.[131] While available in large amounts, allograft carries a theoretical risk for disease transmission, including hepatitis B or C and HIV though the risk is extremely low: less than 1 in 1,000,000.[132, 127] Allograft also has the potential to incite a host immune reaction.[133] Allograft is available in a variety of forms, including cancellous bone, cortical bone, and demineralized bone matrix (DBM). With absent donor site morbidity, equivalent outcomes, and increased availability, allograft has become a popular choice for many surgeons.

Xenograft are the grafts obtained from other species and are not a popular source of bone graft.

B. Artificial Bone graft

Bone graft substitutes or artificial bone grafts have been created to address the drawbacks of organic bone grafts. They can be resorbable or non-resorbable. It is necessary to take into account the unique mechanical, chemical, and immunological characteristics of each class of bone graft alternatives. Currently, there is no single substitute material that contains all the ideal properties for a bone graft substitute[134], i.e. a three-dimensional structure strong enough to mimic the mechanical and biological properties of natural bone, allowing osteo-induction by having surface proteins necessary for osteoblast attachment and containing cells and signalling factors to promote osteogenesis.[135] It is immunologically inert and prevents the formation of fibrous tissue, which can lead to aseptic loosening.[134] Bone graft substitutes can be supplemented with natural bone, bone marrow aspirate, bone graft expanders, bone growth factors, or stem cells to improve fusion and achieve a fusion rate that is similar to autogenous bone graft. There are no complications or morbidities at the donor location, a shorter operating time, less blood loss, and a quicker and more powerful fusion. With in-lay grafts, there is less sinking and the height of the intervertebral disc is maintained. [135] The various artificial graft replacements include:

1. Metalic structural grafts

Metals are powerful in both compression and strain. However, they can cause an unspecific immune reaction and do not offer a natural substrate for cell adhesion.[136] The surface is customized and made rougher with the introduction of additive fabrication. Computer design is used to manage the layering of three-dimensional structures. New surface properties are being developed in metals to enable improved osteointegration.[137] They are sprayed with bone growth factors and promote bone fusion in the metal-bone interface. Titanium metallic implants are the most frequently used.

2. Polyetheretherketone (PEEK) structural grafts

PEEK cages are made of plastic and have rigidity characteristics comparable to those of normal bones. It is possible for radiological fusion study because it is radio-opaque. When used alone, PEEK causes fibrosis and inflammation, which may lead to implant separation. It results in a similar fusion when impregnated with titanium and bone growth stimulators.[138, 139]

3. Ceramic structural grafts and bone graft substitutes

Ceramics are inert, calcium-derived materials and, one of the most widely studied groups of bone substitutes in spinal fusion. It includes bioactive glass, calcium phosphates, and corals. It is an attractive graft option as they demonstrate good biocompatibility and osteo-conduction.[136,137] It is biodegradable by osteoclast-mediated resorption. They have limited osteo-induction potential. These synthetic grafts are easily manufactured, have porous structure resembling cancellous bone that enhances ingrowth of bone while offering scaffolding with immediate and significant mechanical strength. They have limited immunogenicity and have no risk for disease transmission.[125,127,121] The implants have demonstrated satisfactory outcomes and good efficacy compared to autologous bone grafts.[140, 141] They have shown successful outcomes and high fusion rates even in multilevel and revision fusions.[142, 143]

4. β-tricalcium phosphate (TCP) bone graft substitutes

β-tricalcium phosphate (β-TCP) is one the most used and potent synthetic bone graft substitute. It is not only osteoconductive, but also osteo-inductive. These properties, combined with its cell-mediated resorption, allow full bone defects regeneration. They can be moulded or cut, allowing great versatility in surgery, and can act as carriers for demineralized bone matrix (DBM) or other growth factors. β-TCP has shown fusion rates up to 85% when used alone or up to 96% when used in conjunction with iliac crest bone graft (ICBG).[140, 144]

One unique subset of ceramic bone substitutes is silicate substituted calcium phosphate, which have both osteoconductive and osteoinductive properties. Its osteoinductive ability originates from silicate's negative charge, which attracts osteoblasts to the ceramic implant.[145] Despite their cost-effectiveness and fusion efficacy, ceramics are brittle and have poor resistance to tensile forces, making them susceptible to fracture. Additionally, ceramic resorption rates vary widely, with β-TCP absorbed over a period of months, while hydroxyapatite may remain latent in the body for up to a decade.[127,146] Tricalcium phosphate has been associated with soft tissue inflammation[147] and calcium sulphate has been associated with serous drainage.[148]

5. Polymers

Polymers include a vast array of materials, ranging from natural (collagen, chitosan, silk, hyaluronic acid, and peptides) to synthetic compounds (polyglycolic acid and polylactic acid). Naturally derived polymer scaffolds, such as collagen or chitosan, have the ability to resorb and also contain signalling factors for cell migration. They lack the ideal mechanical properties of bone and have to be integrated with other harder materials.[136]

6. Peptide hydrogels

Peptide hydrogels are a new bone graft substitute that have shown promise in the regeneration of tissues, with some reparative potential of cartilaginous, neuronal, and cardiac tissues.[149] Hydrogels are synthesized from the molecular self-assembly of amphiphilic peptides into an entangled nanofiber structure, which is similar to the extracellular matrix of native tissues.[150] Moreover, they can be engineered to contain epitopes such as the α5β1 integrin receptor that promote cell migration and adhesion.[151, 136] Hydrogel materials can be combined with osteogenic cells and assembled into a matrix that allows osteoid formation and can be tuned to degrade at an appropriate time.[136, 152] Hydrogels can also act as a delivery system that maintains and releases rhBMP-2 from microporous tri-calciumphosphate in controlled fashion at the surgical site while preventing systemic diffusion.[153] Thus, they represent a new horizon in bone grafting, offering the panacea of osteoinductive, osteoconductive, and osteogenic properties.

C. Bone graft enhancers

Bone graft enhancers can be used in conjunction with bone grafts and bone graft substitutes, to help with bone fusion. Most of these bone graft enhancers are still in trial form and need more experience before a firm commitment can be made for clinical use. The popular ones are:

1. Growth Factors and Gene Therapy

The common available growth factors include transforming growth factor beta (TGF-β) and platelet-derived growth factor (PDGF). These are signalling proteins that induce cellular division and/or differentiation and bone matrix synthesis thus allowing bone growth. The growth factors being used are mainly derived from platelet rich plasma.[136]

Transforming growth factor beta (TGF-β)

The most widely researched member of TGF- β is Bone Morphogenetic Protein (BMP).[154, 155] BMP was first extracted by Marshall Urist in 1980 from demineralized rabbit bone and were shown to be able to induce bone morphogenesis across species.[156] It contains many crucial factors in bone formation[125,127,155] Molecularly, they function by binding to a cell surface serine–threonine kinase receptor, which then transduces the signal through SMAD and ras/raf proteins to activate the gene expression necessary for bone production.[157] BMPs also potentiate cell differentiation, causing mesenchymal cells to become osteoblasts and stimulate osteo-induction.[157] At lower concentrations, BMPs induce endochondral ossification[158]

and at higher concentrations, through trans-membranous bone formation, it directly forms bone without a cartilage intermediary. BMPs have been shown to be safe and effective promoters of local bone healing in multiple animal studies[159, 160, 161, 162] BMP has been shown in humans to increase the rate of fusion, especially in cases of refractory non-union.[7]

BMP is incorporated in carrier material like collagen sponge or ceramic, such as calcium phosphate, and delivered to the fusion site to enhance fusion. This vehicle both serves as an osteoconductive agent for bone and also improves the tissue retention of BMP. Clinical trials involving BMP showed improvement in Oswestry Disability Index (ODI) scores at 24 months compared with iliac crest harvest, as well as a 12% higher fusion rate.[163] There are two preparations of BMPs available for clinical use: recombinant human BMP-2 (rhBMP-2) and rhBMP-7.[164] rhBMP-2 is genetically produced with recombinant technology, and is highly osteo-inductive, inducing bone formation by stimulating the differentiation of mesenchymal cells into chondroblasts and osteoblasts.[165,166] It has the ability to stimulate patient's own cells to make more bone and has been suggested as an innovative material to increase the fusion rate. rhBMP-2 helps with accelerated bone formation to achieve fusion.[92] Several prospective trials have demonstrated equivalent fusion rates between[167, 168] 60 to 100%, in instrumented fusion.[169] It provides a strong protective effect against pseudarthrosis and is safe and effective for grafting, with no significant complications other than radiculitis.[170, 171] RhBMP-2 has action on both osteoclast and osteoblast function, thus it enhances bone growth and it also induces transient bone resorption.[172] It is associated with complications like postoperative edema, dysphagia, cancer.[173, 174] ectopic bone formation, heterotopic ossification, end-plate resorption[175] retrograde ejaculation, osteolysis, post-operative radiculitis, and seroma formation[176, 177] especially in cervical spine.[178,179,180, 181,182, 183,184] rhBMP-2 is expensive.[185] However, studies evaluating costs have shown that the cost at 2 years post-operatively is actually less with BMP than ICBG due to decreased revision surgeries.[186] BMP is available in several forms, including putty, sheets, and within a glycerol carrier.

Mesenchymal stem cells (MSCs)

Regenerative medicine has investigated the role of mesenchymal stem cells (MSCs), a renewable population of undifferentiated multipotent cells, derived from bone marrow or bone marrow aspirate. It can give rise to the various types of mature cells like muscle, bone, tendons, fat, and other stromal tissues.[187] It was first described by Friedenstein.[188] Bone can be derived from mesenchymal tissues, and therefore MSCs are clinically useful in the context of bone healing and bone formation. They can be harvested from the host with minimal morbidity and even be modified to secrete osteo-inductive factors, which are implanted on an osteoconductive scaffold.[189] They have high potential of both osteogenic and osteoinductive properties within the fusion bed. Both local bone and distant site autologous bone grafts can serve as a source of stem cells at the fusion site, and many surgeons incorporate MSCs directly into grafting material with hopes of improving fusion rates.

Gene therapy is an additional endeavour to enhance fusion. When BMP gene is delivered to a host cell by a vector, it has been shown in animal models to induce fusion even in non-osteoid tissue[190,191]. When compared with locally delivered BMP, the gene therapy has shown to increase the bioavailability of BMP by producing ongoing osteogenic expression locally[192] Vectors to deliver the BMP gene range from viral (adenovirus or herpes virus) to nonviral (liposomes, electroporation) media. Delivery to a host may be either ex vivo (implantation of transfected cells into the host) or in vivo (injection of genes directly into host cells).[191] Riew et al. were able to show that ex vivo BMP-transfected bone marrow cells, replanted in rabbits, were able to produce spinal fusion.[193] Currently, gene therapy is limited by the massive immune response against viral vectors.[194]

2. Electrical stimulation

Electrical stimulation is one of the therapies available to enhance spinal fusion. This therapy has been used for more than 30 years [195,196,197]. Normally, when bone is mechanically strained, electrical potentials are generated; electronegative potentials are found in areas of compression and electropositive potentials in areas of tension. Bone is formed in the electro-negative regions and resorbed in the electro-positive regions. These electric fields may form the basis by which bone remodels in response to mechanical stimuli (Wolff's Law).[198] Three types of electrical stimulation are available clinically: direct current (DC), capacitive coupling (CC), and inductive coupling (IC) such as pulsed electromagnetic fields (PEMF) and combined magnetic fields (CMF). The mechanisms of action of each of the three electrical stimulation therapies differ. Broadly, they upregulate mRNA for growth factors[199,200,201, 202,203,204] like BMP-2, -4, -6, -7, FGF-2, and VEGF[199, 200], resulting into upregulation of several synergistic growth factors and promote bone healing [205] Various electrical stimulation devices have been designed to deliver these fields to enhance bone formation.[7, 205] The DC technology requires surgical implantation of the device whereas IC and CC technologies are non-invasive methods of producing electric fields at the fusion site. All of these technologies can also be utilized as adjuncts to surgical procedures using bone grafts. Treatment usually lasts for a minimum of 6 months post-implantation, after which the procedure can

be discontinued at the discretion of the surgeon. A large multicentre randomized double-blind clinical studies by Ken WJ[206], using the above mentioned methodologies of electrical stimulation to enhance radiographic and clinical spinal fusions showed a statistically significant higher success rate of 85 to 91.5% compared to 65 to 80.5% in the control groups. Electrical stimulation has been accepted as an established cost effective adjunct to spinal surgery, improving the outcomes of spinal fusion[207] typically in high risk patients with factures such as uncontrolled diabetes, untreated osteoporosis or continued nicotine use.

D. Instrumentation and implants

Spinal instrumentation has become an integral part of spinal fusion as it allows to achieve immediate stability, enhance fusion, allow early mobility, correct deformities and maintain alignment till fusion occurs. The role of postoperative external arthrosis is lessening. The chemical composition, hydrophilicity, topographical nature and overall roughness of the surface of an implant play role in bony fusion.[208,209,210,211]

After placement of an implant in patients, the surface of the implant is coated with proteins from the blood and serum. This protein layer facilitates the migration of mesenchymal progenitor cells into the implant surface via the α2β1 integrin receptor, a major collagen type 1 receptor.[209] These cells then differentiate into an osteoblastic lineage to form new bone. The roughness of implants is important for osteoblastic differentiation[212] as more progenitor cells can get attached to the surface to induce bone fusion.[213]

The latest achievements in implant development are:

1. Nanoscale surface technology

Application of nanoscale surface technology in the implant and instrumentation produces roughened titanium and generates an osteoblastic environment.[209,210,214,215] The increase in surface area and roughness of the implant surface allows host cells to attach on a molecular level via cellular membrane receptors. This interaction can trigger osteoblastic-lineage differentiation and improve fusion results.[216] There are two primary types of manufacturing of Nanoscale surface technology in the production of spine implants, additive and subtractive. In the subtractive manufacturing, surface features are generated through the removal of material. Acid etching and grit blasting are two forms of subtractive manufacturing.[217] Although subtractive manufacturing is much more commonly used, these techniques waste material substrate, and the physical process itself limits the types of designs that can be created. Interbody grafts are produced from treated pieces of titanium, and subtractive technologies are used to produce submicron surface textures.[215] Nano-roughened titanium surfaces induce greater differentiation of osteoblasts from mesenchymal stem cells, as compared with PEEK-treated surfaces. Roughened titanium also increases osteoblast maturation and produce an osteogenic environment that contains bone morphogenetic proteins (BMPs), as compared with smooth titanium and PEEK. Similar studies have shown that nanoengineered implants increase stimulation of local growth factors, including BMPs, VEGF, and TGF-β.[215]

Hardware infection can be a life-threatening sequela of spinal fusion surgery.[218] Nanotechnology is also used to fight infection by coating the implants with bactericidal antibiotics or chemical like silver. Bacteria adhere to implants via the formation of a complex glycocalyx that protects them from antibiotics, making eradication very difficult.[219] The surface features of an implant can decrease bacterial adhesion.[220] Nano-roughened surfaces have been shown to significantly decrease rates of bacterial adhesion, specifically of Staphylococcus aureus, S. epidermidis, and Pseudomonas aeruginosa.[221] Moreover, silver nano-particles have been shown to have a bactericidal effect while still being biocompatible with bone. They achieve this through the release of silver ions from soluble complexes, which then generate reactive oxygen species that break down bacterial components. Silver nanoparticles can be applied to an implant via silver plasma ion immersion or by vapor deposition. Nanoparticles have also been shown to inhibit bacterial biofilm formation in animal studies. In particular, titanium pedicle screws coated in silver-based nanoparticles have been shown to be bactericidal in rabbits because of their release of silver ions.[222,223, 219]

2. Three-dimensional (3D) printing

Additive manufacturing, known as three-dimensional (3D) printing[224] involves customised layer-by-layer construction of complex 3D objects **u**sing computer-aided design software or the deposition of a material coating on the implant itself.[217] These provide more surface area for adhesions of macrophages and growth factors, thus enhancing fusion and strong bone-implant interface fusion.

Use of PEEK in implants is common, primarily because of its radiolucency and modulus of elasticity that closely resembles that of native bone. However, it produces fibrous encapsulation because of its induction of an inflammatory environment, and this can result in nonunion.[211] Porous surface may also be applied to PEEK by extruding it through a bed of sodium chloride crystals, which has been shown to improve osteoconductivity but only in the presence of osteogenic mediators.[225,226] To overcome this limitation, PEEK implants are sprayed with titanium spray (post-processing) which improves the surface properties of PEEK, but this method has been associated with increased generation of wear debris.

3. Bio-absorbable implants

Bioabsorbable interbody fusion is a new addition in the science of fusion where the graft is resorbed over time and replaced by host bone. The issue is the ability to preserve and maintain postoperative distraction, biomechanical stability and histological characteristics of intervertebral bone matrix formation. These implants create the extracellular matrix of bone.[227] They generate an inflammatory response and have poor osteo-conductivity.[228] To improve the osteo-conductivity, nano-sized β-tricalcium phosphate (β-TCP) has been incorporated into PLA cages.[229] Poly (D,L-Lactide-co-Glycolide) (PLDLLA) Cage and Polymer Calcium phosphate-composite (PCC) Cage have been used in animal models as absorbable intervertebral implants and have given promising results.[230]

4. Self-Assembly of Peptide Amphiphiles

This is a new addition of bio-nanotechnology where peptide amphiphiles, a class of molecules that combine the structural features of amphiphilic surfactants with the functions of bioactive peptides, assemble into a variety of nanostructures. A specific type of peptide amphiphiles are known to self-assemble into one-dimensional (1D) nanostructures under physiological conditions, predominantly nanofibers with a cylindrical geometry. The resultant nanostructures could be highly bioactive and are of great interest in many biomedical applications, including tissue engineering, regenerative medicine and drug delivery.[He B 2014] Reversible intramolecular disulfide bonds allow for cross-linking of nanofibers, resulting in a robust network that directs the mineralization of hydroxyapatite. The alignment of hydroxyapatite in the resulting composite material was found to be identical to the alignment observed between hydroxyapatite crystals and collagen fibrils in bone.[231] Using this foundation, phosphorylated serine segments within the PA molecules were incorporated, which allows for the generation of a self-supporting, bioactive gel matrix that mimics bone sialoprotein, further augmenting mineralization.[151]

5. Artificial intelligence (AI) and machine learning (ML)

Access to big, high fidelity clinical databases and the development of machine learning algorithms are making analysis and prediction a reality today. New technology using the newest advancements in machine learning and predictive analytics may offer significant clinical advantages in determining unique goals of correction to reduce the rates of pseudarthrosis, revision surgery, and proximal junctional failure.[232] Development of a validated computer-based preoperative predictive model for pseudarthrosis with 91% accuracy in adult spinal deformity is a step forward to decrease non-union. Clinical oversight of "black box" algorithms to determine real-world practical application and interpretations in clinical settings is one of the limitations of machine learning. These tools hold the potential of aiding with improved diagnosis, surgical planning and risk optimization.

Conclusions

Spinal fusion has become an integral part of spine surgery. The evolution of fusion over the last 100 years has dramatically increased the safety and efficacy of this treatment. Much of this was driven by the advancement in instrumented and assisted fusion. Improvements in fusion rates, faster recovery times and reduction in complications are also due to better patient selection and peri-operative optimization of modifiable risk factors. Advances in material and design of fixation instrumentations, nanoscale surface technologies of structural grafts as well as use of biological agents for supporting and accelerating fusion are contributing to highly reliable rates of arthrodesis. All these advancement has made bone fusion almost a guaranteed event with very low complication rates. Artificial intelligence and machine learning aims to make fusion a more predictive procedure with a better prognosis helping patients to get a better quality of life.[233] These technological advancement and results come with a huge financial burden to the community and the patients, and it is the surgeons' added responsibility to strike a good balance.

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