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REGENERATIVE STRATEGIES IN AVASCULAR NECROSIS: STEM CELLS, SCAFFOLDS, EXOSOMES, AND EMERGING THERAPIES

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ABSTRACT

Avascular necrosis (AVN) is a condition that affects bones due to reduced blood supply. This leads to the death of osteocytes, the weakening of bone structure, and eventually joint collapse, with the femoral head being the most commonly impacted area. Traditional treatments, including medications and surgical options like core decompression and total joint replacement, often do not effectively repair damaged bone and can lead to significant complications. As a result, regenerative medicine has emerged as a hopeful alternative that focuses on biological repair and restoring function to necrotic bone. This review examines recent progress in regenerative strategies for AVN, emphasizing therapies based on stem cells, scaffold-guided tissue engineering, and new acellular methods. Mesenchymal stem cells (MSCs) from bone marrow, adipose tissue, and umbilical cord have strong abilities to promote bone growth and blood vessel formation through both differentiation and signaling processes. Clinical studies show that implanting autologous MSCs in the early stages of AVN can decrease pain, promote bone healing, and slow the disease's progression. Improvements in biomaterial scaffolds, including natural, synthetic, and composite systems, have also enhanced cell survival, mechanical strength, and the controlled release of vital molecules. Additionally, growth factors, platelet-rich plasma, and exosomes from stem cells

are gaining interest as additional or alternative treatment options. Even with positive results, challenges like low cell survival, immune system reactions, regulatory hurdles, and high costs still exist. Future advancements that include gene-modified stem cells, smart materials, and large-scale clinical trials are expected to refine regenerative treatments and enhance their application in clinical settings.

KEYWORDS: Avascular necrosis; Osteonecrosis; Stem cells; Regenerative medicine; Bone regeneration; Biomaterial scaffolds; Angiogenesis; Exosomes.

INTRODUCTION

Avascular necrosis (AVN), also referred to as osteonecrosis, is a progressive skeletal disorder characterized by the death of bone cells due to compromised blood supply. The condition most commonly affects the femoral head but may also involve the knee, shoulder, and ankle joints. AVN predominantly occurs in young and middle-aged adults and is associated with risk factors such as corticosteroid use, alcohol abuse, trauma, hematological disorders, and metabolic diseases. If left untreated, AVN progresses to subchondral fracture, articular surface collapse, and secondary osteoarthritis, resulting in significant pain and functional disability.

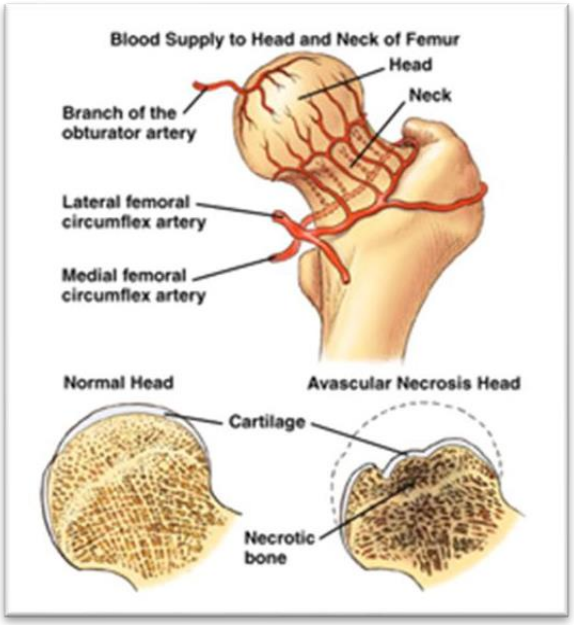
The pathophysiology of AVN involves vascular interruption leading to ischemia, hypoxia, and subsequent osteocyte apoptosis and necrosis. Impaired angiogenesis and disruption of the bone marrow microenvironment hinder natural repair mechanisms, limiting the capacity for bone regeneration. Conventional treatment options, including pharmacological agents (bisphosphonates, anticoagulants), physical therapies, and surgical interventions such as core decompression, bone grafting, and total joint arthroplasty, primarily aim to relieve symptoms or manage advanced disease stages. However, these approaches fail to address the underlying biological deficits and often provide limited long-term benefits, particularly in younger patients.

In recent years, regenerative medicine has gained significant attention as a promising strategy to restore bone viability and structural integrity in AVN. Regenerative approaches focus on enhancing osteogenesis, angiogenesis, and tissue remodeling through the use of stem cells, biomaterial scaffolds, growth factors, and biologically active molecules. Mesenchymal stem cells (MSCs), in particular, exhibit the ability to differentiate into osteoblasts and secrete paracrine factors that promote vascularization and bone repair. Advances in tissue engineering

and 3D bioprinting have further enabled the development of biomimetic scaffolds that provide mechanical support while facilitating targeted cell and drug delivery.

This review aims to provide a comprehensive overview of current regenerative strategies for AVN, including stem cell–based therapies, scaffold-guided tissue engineering, and emerging acellular modalities such as exosomes and platelet-rich plasma. Additionally, the challenges, clinical limitations, and future prospects of these approaches are discussed to highlight their potential in delaying disease progression and reducing the need for invasive surgical interventions.

Anatomy of Femoral Head Blood Supply and Development of Osteonecrosis



ETIOLOGY AND RISK FACTORS OF AVASCULAR NECROSIS (AVN)

- Traumatic Causes
- Fractures and Dislocations

Traumatic fractures and dislocations represent significant risk factors for the development of avascular necrosis (AVN), primarily due to their potential to disrupt the vascular supply to bone. Ischemia resulting from vascular injury is a central mechanism in post-traumatic AVN. Among these injuries, femoral neck fractures and traumatic hip dislocations are particularly well recognized for their strong association with AVN development. The risk is closely related to the severity of trauma, degree of displacement, and extent of vascular compromise. Fractures with marked displacement or prolonged joint dislocation substantially increase the likelihood

of avascular damage. Prompt and appropriate management is therefore critical. Early reduction, surgical fixation, and stabilization play a vital role in restoring anatomical alignment and re-establishing blood flow, thereby reducing the incidence of AVN. Evidence suggests that timely surgical intervention in displaced femoral neck fractures significantly lowers the risk of subsequent AVN. Additionally, structured rehabilitation programs emphasizing early mobilization and joint protection contribute to comprehensive prevention strategies.

JOINT TRAUMA

Direct joint injuries, including severe contusions and crush injuries, can significantly impair intra-articular and periarticular blood circulation. Such trauma may cause microvascular damage that compromises perfusion and initiates pathological processes leading to AVN. Given the vulnerability of joint structures to avascular changes, early detection and vigilant monitoring following joint trauma are essential. Advanced imaging modalities facilitate early assessment of vascular compromise and guide clinical decision-making. Initial management strategies may include joint aspiration to reduce intra-articular pressure, immobilization to limit mechanical stress, and pharmacological agents to control inflammation and pain. Multidisciplinary collaboration between orthopaedic surgeons and rehabilitation specialists is crucial to optimize outcomes and mitigate the risk of AVN following joint trauma.

NON-TRAUMATIC CAUSES

CORTICOSTEROID USE

Prolonged or high-dose corticosteroid therapy is one of the most established non-traumatic causes of AVN. Steroids contribute to AVN through mechanisms such as lipid microembolism, intravascular coagulation, and endothelial dysfunction, all of which impair bone perfusion. Patients receiving long-term corticosteroid therapy—particularly those with autoimmune diseases or post-organ transplantation—are at heightened risk. Clinicians must carefully balance therapeutic benefits against potential skeletal complications by monitoring cumulative steroid exposure, implementing dose-reduction strategies where possible, and considering alternative treatments to minimize AVN risk.

ALCOHOL ABUSE

Chronic alcohol consumption is a significant contributor to AVN, especially in weight-bearing joints such as the hip. Alcohol-induced AVN is multifactorial, involving vascular impairment, abnormal lipid metabolism, and disrupted bone remodeling. These effects collectively reduce blood supply to bone tissue, promoting necrosis. A thorough assessment of

alcohol use is essential in patients presenting with AVN, as identification of this modifiable risk factor allows for targeted interventions. Lifestyle modification and substance abuse counseling may help prevent disease progression and improve long-term outcomes.

COAGULATION DISORDERS

Hypercoagulable states, including inherited thrombophilia and acquired coagulation disorders, significantly increase susceptibility to AVN. These conditions promote microvascular thrombosis within bone, leading to impaired perfusion and ischemic necrosis. A detailed medical and family history, along with appropriate laboratory investigations, is essential in identifying coagulation abnormalities in at-risk patients. Early recognition and management of these disorders may reduce both the incidence and severity of AVN.

COMMON RISK FACTORS

AGE AND GENDER

AVN most commonly affects individuals between 30 and 50 years of age, with a higher prevalence observed in males. Hormonal influences, lifestyle factors, and age-related changes in bone metabolism may contribute to this demographic predilection. Understanding these associations assists clinicians in identifying high-risk populations and implementing early surveillance and preventive measures.

JOINT LOADING AND WEIGHT-BEARING

Mechanical stress plays a crucial role in the development of AVN, particularly in weight-bearing joints such as the hip and knee. Repetitive loading and excessive joint stress can impair microcirculation within subchondral bone. Obesity further exacerbates this risk by increasing mechanical load and metabolic demand, underscoring the importance of weight management in susceptible individuals. Preventive strategies should incorporate biomechanical optimization, activity modification, and lifestyle interventions to reduce cumulative joint stress.

PATHOGENESIS OF AVASCULAR NECROSIS

Avascular necrosis (AVN) occurs due to an interruption in the blood supply to the bone, resulting in reduced oxygen and nutrient delivery. This leads to bone ischemia and eventual death of osteocytes. Traumatic causes, such as fractures or dislocations, directly damage blood vessels supplying the bone. Non-traumatic factors, including prolonged corticosteroid use and excessive alcohol intake, contribute to intravascular coagulation, fat embolism, and increased

pressure within the bone. These factors reduce blood flow and impair normal bone repair mechanisms. As a result, the affected bone becomes weak and structurally unstable, leading to subchondral fracture, collapse of the articular surface, and joint dysfunction.

SYMPTOMS OF AVASCULAR NECROSIS

The symptoms of avascular necrosis develop gradually over time. In the early stages, patients experience mild or intermittent pain, especially during weight-bearing activities, which is relieved by rest. As the disease progresses, pain becomes persistent and may occur even at rest or during the night. Joint stiffness and reduced range of motion are commonly observed. In advanced stages, patients may develop limping, difficulty in standing, walking, or climbing stairs, particularly when the hip or knee joints are affected. These symptoms indicate progressive bone damage and structural collapse.

DIFFERENTIAL DIAGNOSIS

Differential Diagnosis for Avascular Necrosis

NO	Disease	Inclusion Criteria	Exclusion Criteria
1	Bone marrow oedema (Transient osteopenia)	Pain, stiffness, oedema of joints, and reduced range of motion (ROM).	Increased interstitial fluid within bone marrow.
2	Inflammatory synovitis	Joint pain, swelling, stiffness, and difficulty moving a joint.	The joint appears swollen and feels puffy or boggy to the touch.
3	Neoplastic bone.	Persistent bone pain that increases at night	Redness or inflammation over a bone associated with a lump.
4	4. Osteoarthritis..	Loss of flexibility, crepitus, pain, and stiffness	Presence of bone spurs
5	Osteomyelitis	Bone pain, local swelling, and night pain	Open wound with pus, fever, and chills.
6	Osteoporosis	Bones break easily; pain is caused by a collapsed bone.	Spinal malfunction with stooped or hunched posture.
7	Rheumatoid arthritis.	Pain, joint swelling, and reduced ROM	Morning stiffness, fever, and loss of appetite.
8	Septic arthritis	Swelling, reduced ROM, and joint stiffness.	fever, and Sudden onset of pain warmth over the joint.
9	Soft tissue trauma	Swelling, pain, and loss of power.	Bruising and sudden onset of pain.
10	Avascular necrosis	Intermittent pain that appears and eases when pressure is applied to the bone and then is relieved.	--

CONSERVATIVE TREATMENT APPROACHES FOR AVASCULAR NECROSIS (AVN)

1. REST AND ACTIVITY MODIFICATION

A) PROTECTED WEIGHT-BEARING

Protected weight-bearing is an important conservative treatment for AVN. The main aim is to reduce stress on the affected joint and allow healing of the damaged bone. Patients are advised to avoid putting full body weight on the affected joint. Assistive devices such as crutches or walkers are commonly used to reduce joint load during walking. This approach helps in reducing pain, preventing further bone damage, and supporting natural bone repair.

B) ACTIVITY MODIFICATION

Activity modification involves changing daily activities to minimize stress on the affected joint. Patients are advised to avoid prolonged standing, sitting, or repetitive joint movements that can worsen symptoms. Lifestyle and occupational changes are planned according to the severity and location of AVN. Orthopaedic doctors and physiotherapists guide patients in making suitable adjustments to daily routines, which helps in pain control and protects long-term joint function.

2. PHARMACOLOGICAL INTERVENTIONS

A) NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

NSAIDs such as ibuprofen and naproxen are commonly used to reduce pain and inflammation in AVN. These drugs work by inhibiting inflammatory mediators, thereby providing symptomatic relief. However, long-term use may cause gastrointestinal and cardiovascular side effects. Therefore, patients using NSAIDs should be carefully monitored by clinicians.

B) BISPHOSPHONATES

Bisphosphonates like alendronate and pamidronate help prevent bone loss by inhibiting bone resorption. In AVN, these drugs may slow disease progression and help preserve bone structure, potentially delaying surgical intervention. Their use in AVN is still under research, and possible side effects must be considered. Regular follow-up is essential to evaluate treatment benefits and risks.

3. PHYSICAL THERAPY

A) RANGE OF MOTION EXERCISES

Range of motion exercises help maintain joint flexibility and prevent stiffness. These gentle movements allow the joint to move through its normal range and reduce the risk of contractures. Physical therapists design individualized exercise programs based on patient condition and tolerance.

B) STRENGTHENING EXERCISES

Strengthening exercises focus on improving the strength of muscles around the affected joint. Strong muscles provide better joint support and reduce stress on the damaged bone. Exercises are gradually progressed to improve stability and functional ability without causing excessive strain.

C) PAIN MANAGEMENT MODALITIES

Physiotherapists use various modalities such as heat therapy, cold therapy, ultrasound, and electrical stimulation to reduce pain and promote healing. Heat improves blood circulation and muscle relaxation, while cold reduces inflammation. Ultrasound and electrical stimulation help relieve pain and support tissue repair.

D) FUNCTIONAL TRAINING

Functional training helps patients perform daily activities more efficiently and safely. It includes practicing movements such as walking, lifting, and reaching with correct posture and joint protection techniques. This training improves independence, quality of life, and long-term joint health in patients with AVN.

A. SURGICAL TREATMENT OPTIONS IN AVASCULAR NECROSIS (AVN)

Surgical interventions play a crucial role in the management of avascular necrosis (AVN), particularly when conservative treatment fails to prevent disease progression. The choice of surgical procedure depends on several factors, including the stage of AVN, extent of bone involvement, affected joint, and overall health of the patient. The primary objectives of surgical management are pain relief, restoration of blood supply, preservation of joint integrity, and improvement of functional outcomes.

1. CORE DECOMPRESSION

Core decompression is one of the most commonly employed surgical procedures for early-

stage AVN, particularly involving the femoral head. The procedure involves making a small surgical incision over the affected joint and drilling or removing a cylindrical core of necrotic bone from the ischemic area. This removal creates a channel within the bone, which serves to reduce intraosseous pressure and remove dead tissue.

The created channel facilitates the ingrowth of new blood vessels, thereby improving vascular supply to the affected bone. Restoration of blood flow is essential for bone repair and regeneration. Core decompression may be performed alone or combined with adjunctive procedures such as bone grafting or biological agents to enhance healing.

OUTCOME

Clinically, core decompression has shown favorable results in relieving pain and slowing disease progression when performed in the early stages of AVN. The success of the procedure largely depends on the stage of disease, lesion size, and patient-related factors. Although outcomes vary, early intervention significantly increases the likelihood of preserving joint structure and function. Combination therapies, including bone grafting, may further improve success rates.

2. VASCULARIZED BONE GRAFTING

Vascularized bone grafting is a more advanced surgical option, typically reserved for patients with progressive AVN and extensive bone damage. In this procedure, a segment of bone along with its intact blood supply is harvested from a donor site (commonly the fibula) and transplanted into the necrotic area.

The defining feature of this technique is the preservation and reconnection of blood vessels, ensuring immediate and sustained blood flow to the grafted bone. Microsurgical expertise is required to anastomose the graft vessels with recipient site vessels, promoting optimal vascularization and graft integration.

OUTCOME

Vascularized bone grafting has demonstrated good outcomes in advanced AVN cases by restoring blood supply and providing mechanical support to weakened bone. Although technically demanding and more invasive than core decompression, it offers significant benefits in preserving joint function and delaying or avoiding joint replacement. This technique is especially valuable in younger patients where joint preservation is critical.

3. TOTAL JOINT REPLACEMENT (ARTHROPLASTY)

Total joint replacement is indicated in end-stage AVN characterized by severe joint destruction, persistent pain, and significant functional limitation. It is most commonly performed in weight-bearing joints such as the hip and knee when other treatment modalities fail. The primary aim is to relieve pain, restore mobility, and improve quality of life.

OUTCOME

Total joint replacement has proven to be highly effective in patients with advanced AVN. Modern prosthetic designs and improved surgical techniques have resulted in durable implants with excellent functional outcomes. Postoperative rehabilitation plays a vital role in recovery. While the procedure offers substantial pain relief and improved mobility, outcomes depend on patient factors such as age, activity level, and comorbidities.

4. ARTHROPLASTY TECHNIQUES

A. HEMIARTHROPLASTY

Hemiarthroplasty involves replacing only the damaged portion of the joint, commonly the femoral head, while preserving the remaining healthy joint structures. This procedure is indicated when AVN is localized and the acetabulum remains unaffected. By conserving native bone, hemiarthroplasty offers pain relief and functional improvement with reduced surgical trauma.

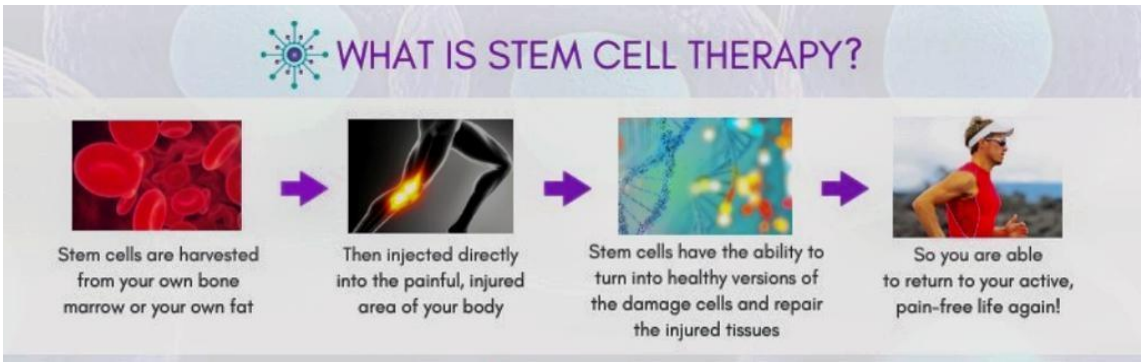
B. RESURFACING ARTHROPLASTY

Resurfacing arthroplasty replaces only the diseased joint surfaces while preserving most of the native bone. In hip AVN, the femoral head is reshaped and capped with a prosthesis rather than completely replaced. This technique closely mimics natural joint biomechanics and is particularly suitable for younger, active patients, as it preserves bone stock for potential future revisions.

C. REVISION ARTHROPLASTY

Revision arthroplasty is performed to correct or replace failed joint prostheses due to complications such as loosening, wear, instability, or disease progression. In AVN patients, revision surgery may be required following earlier joint replacement procedures. This complex intervention involves removal and replacement of prosthetic components and requires meticulous planning and surgical expertise to restore joint function.

B.RATIONALE FOR STEM CELL THERAPY IN HIP OSTEONECROSIS



1. BONE MARROW CHANGES IN OSTEONECROSIS

- MRI shows abnormal bone marrow signals in hip osteonecrosis
- Increase in fatty marrow in the proximal femur
- Reduction in normal bone-forming activity

2. EFFECT OF STEROIDS ON BONE MARROW

- Steroids increase fat cell formation (adipogenesis)
- Decrease in osteogenic stem cells
- Reduced blood supply inside bone (intramedullary ischemia)
- Leads to osteocyte death and poor bone repair

3. DEFICIENCY OF OSTEOGENIC STEM CELLS

- Reduced mesenchymal stem cells (MSCs) in femoral head
- Poor bone remodeling and creeping substitution
- Inadequate repair after osteonecrosis
- Even after core decompression, repair is incomplete

4. NEED FOR STEM CELL THERAPY

- Autologous bone marrow grafting increases osteogenic cells
- Improves bone regeneration and repair
- Enhances healing in osteonecrosis of the hip

MECHANISM OF ACTION OF STEM CELLS

1. OSTEOGENIC EFFECT

- Stem cells differentiate into osteoblasts
- Help in new bone formation

2. ANGIOGENIC EFFECT

- MSCs secrete angiogenic cytokines
- Promote formation of new blood vessels
- Improve blood supply to necrotic bone

3. VASCULOGENESIS AND NEOANGIOGENESIS

- Endothelial progenitor cells form new vessels
- Repair damaged capillaries
- Enhance bone healing

4. PARACRINE (TROPHIC) EFFECTS

- Anti-inflammatory
- Anti-apoptotic
- Immunomodulatory effects

MESENCHYMAL STEM CELLS (MSCs)

CHARACTERISTICS

- Positive markers: STRO-1, CD73, CD146, CD106
- Negative markers: CD11b, CD45, CD34, CD31

FUNCTIONS

- Secretion of growth factors
- Coordination of tissue repair
- Support regeneration and healing

TECHNIQUE FOR TREATMENT OF HIP OSTEONECROSIS WITH MSCs

1. BONE MARROW ASPIRATION

- Bone marrow aspirated from iliac crest
- Small volume aspiration increases stem cell yield
- Aspirate collected in heparinized syringes

2. CELL PROCESSING

- Filtration removes fat and debris
- Mononuclear cell fraction isolated
- Contains MSCs and progenitor cells

3. CORE DECOMPRESSION

- Performed using a small trocar
- Reduces intraosseous pressure
- Creates space for cell injection

4. INTRAOSSEOUS INJECTION

- MSCs injected directly into necrotic femoral head
- Promotes bone repair and revascularization

ROLE OF MSC NUMBER IN BONE REPAIR:

- Normal femoral head contains ~35,000 MSCs
- Bone marrow graft supplies progenitor cells
- Stem cells proliferate and form new trabecular bone
- About 5 cm^3 of new bone formed in repaired area

CHALLENGES IN STEM CELL THERAPY:

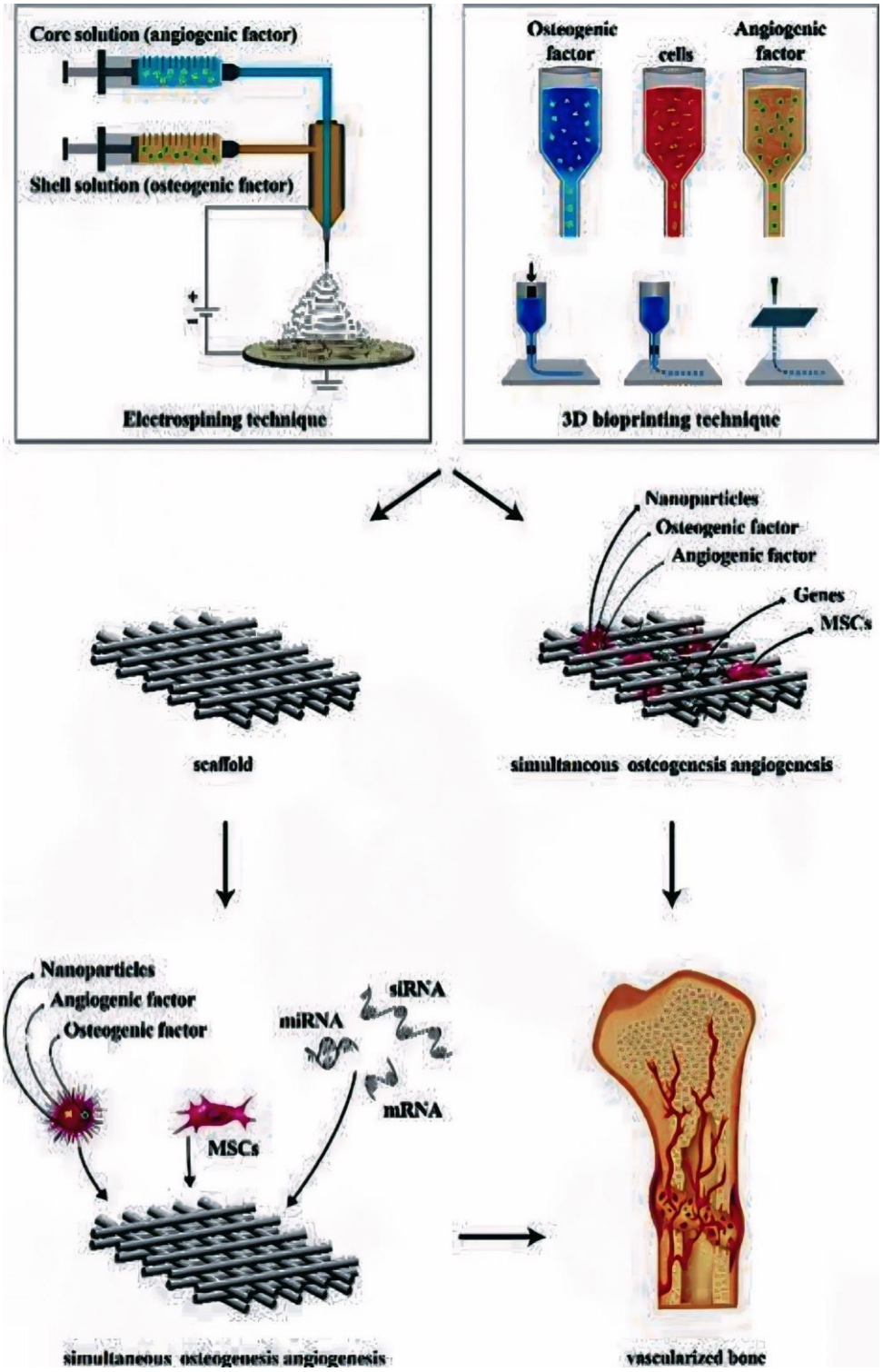
1. VARIATION IN MSC COUNT

- Reduced in steroid use, alcohol abuse, smoking
- Decreases with age

2. LIMITATIONS OF AUTOLOGOUS THERAPY

- Time-consuming
- Expensive
- Requires specialized facilities.

C.MNOX-BASED OSTEO-ANGIOGENIC SCAFFOLD THERAPY FOR AVASCULAR NECROSIS



PREPARATION OF MNOX NANOPARTICLES AND 3D-PRINTED SCAFFOLDS

MnOx nanoparticles (NPs) were synthesized using a modified bovine serum albumin (BSA)–assisted method. Briefly, BSA was dissolved in deionized water and homogenized by stirring,

followed by the addition of potassium permanganate. After continuous stirring at room temperature, the solution was dialyzed against deionized water and freeze-dried to obtain MnOx NPs.

FABRICATION OF 3D-PRINTED MNOX-DOPED PLGA SCAFFOLDS

Three-dimensional printed scaffolds were fabricated using a fused deposition modeling (FDM) technique. PLGA was dissolved in dichloromethane, and different amounts of MnOx NPs were added to form homogeneous mixtures. After solvent evaporation and freeze-drying, the composites were extruded into filaments and printed into cylindrical scaffolds with uniform pore spacing. Pure PLGA scaffolds without MnOx served as controls.

CHARACTERIZATION AND ENZYME-LIKE ACTIVITY

The morphology, size, and elemental composition of MnOx NPs and scaffolds were characterized using TEM, SEM, EDS, XRD, and XPS. Mechanical strength and degradation behavior were evaluated. The enzyme-like activity of MnOx was assessed through hydrogen peroxide decomposition, oxygen generation, antioxidant capacity, and free radical scavenging assays.

IN VITRO BIOCOMPATIBILITY AND OSTEO-ANGIOGENIC EVALUATION

Cytotoxicity, hemocompatibility, cell adhesion, proliferation, and apoptosis were evaluated using BMSCs and HUVECs. Osteogenic differentiation was analyzed by ALP activity, gene expression, and mineralization staining. Angiogenic potential was assessed using tube formation, migration, scratch assays, and immunofluorescence staining.

In Vivo Bone Repair and Mechanistic Analysis

An osteonecrosis of the femoral head (ONFH) rabbit model was established, followed by scaffold implantation after core decompression. Bone regeneration was evaluated using micro-CT and histological analysis. Transcriptome sequencing and protein expression studies revealed activation of osteogenic and angiogenic signaling pathways.

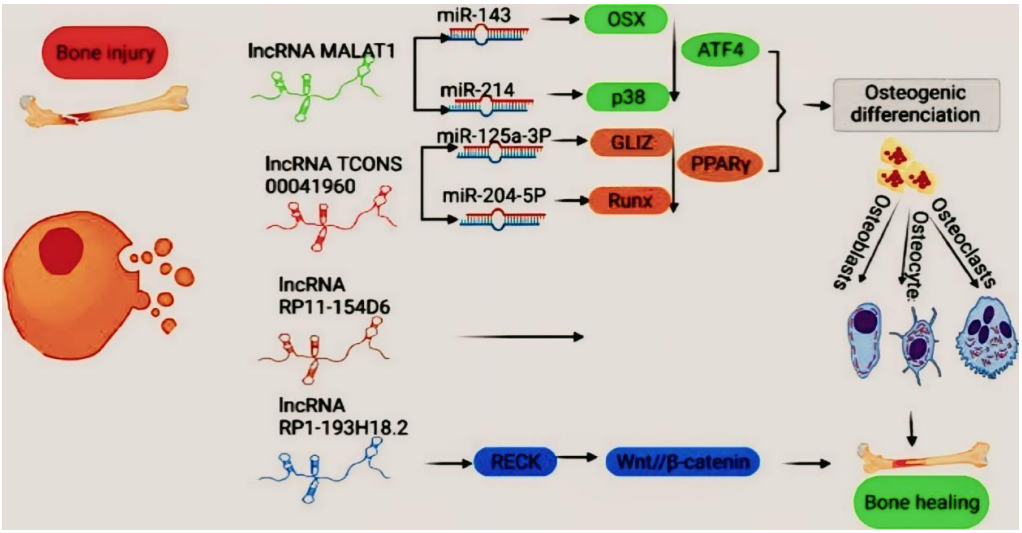
D. Growth Factors and Exosome Therapy

Role of Growth Factors in Bone Regeneration:

Growth factors play a critical role in bone regeneration and angiogenesis, making them promising therapeutic agents for avascular necrosis (AVN). Bone morphogenetic proteins (BMPs), particularly BMP-2 and BMP-7, are potent osteoinductive molecules that stimulate

mesenchymal stem cell (MSC) differentiation into osteoblasts and promote new bone formation. Vascular endothelial growth factor (VEGF) is essential for angiogenesis, facilitating neovascularization in ischemic bone tissue and restoring oxygen and nutrient supply. Transforming growth factor-β (TGF-β) regulates extracellular matrix synthesis, osteoblast proliferation, and bone remodeling, contributing to structural integrity and repair of necrotic bone.

ROLE OF EXOSOMES IN BONE AND JOINT DISEASE METABOLISM



Limitations and Controlled Delivery of Growth Factors

Despite their regenerative potential, the clinical application of growth factors is limited by their short biological half-life, rapid enzymatic degradation, and potential adverse effects following systemic administration. High local concentrations may also lead to ectopic bone formation or inflammatory responses. To overcome these limitations, advanced controlled delivery systems, including nanoparticles, injectable hydrogels, and scaffold-based release platforms, have been developed. These systems enable sustained, localized release of growth factors at the necrotic site, enhancing therapeutic efficacy while minimizing systemic toxicity.

Exosome Therapy as an Acellular Regenerative Approach

Exosome therapy has emerged as a promising acellular alternative to stem cell transplantation in AVN management. Exosomes are nano-sized extracellular vesicles secreted by stem cells that carry bioactive molecules such as microRNAs, proteins, and lipids. These vesicles replicate the paracrine effects of stem cells by promoting osteogenesis, angiogenesis, and immunomodulation, without the risks associated with poor cell survival, immune rejection, or tumorigenicity.

Mechanisms and Therapeutic Potential of Exosomes

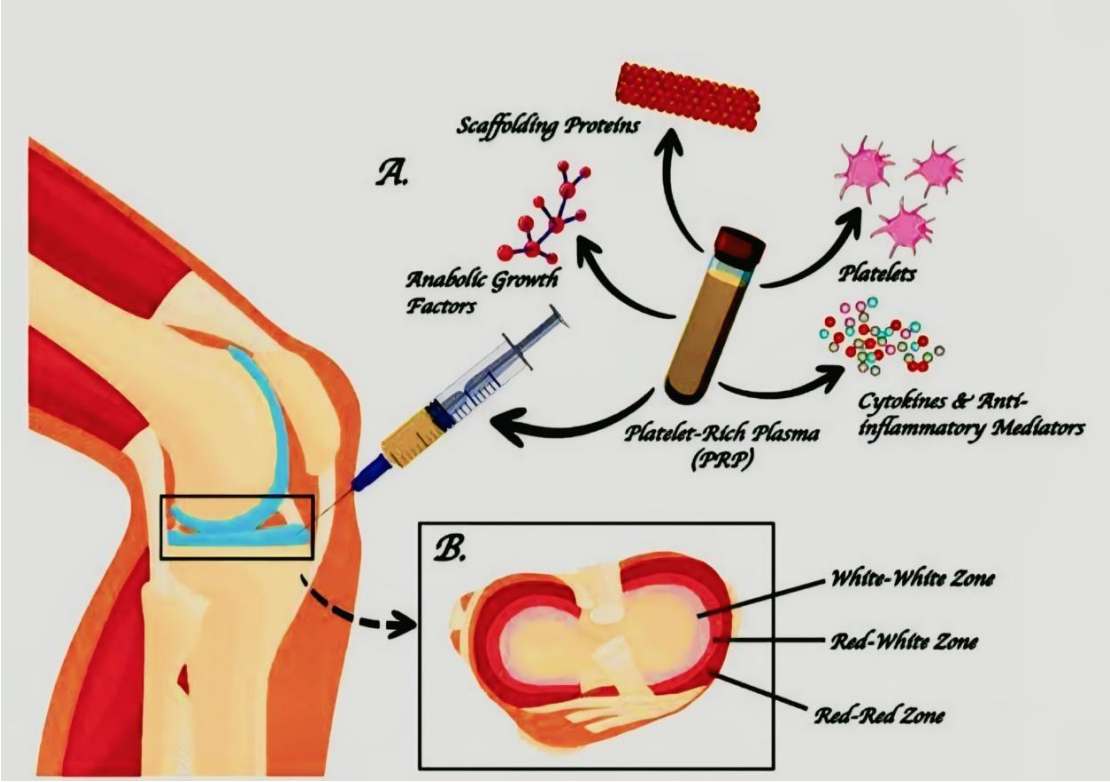
Preclinical studies have demonstrated that MSC-derived exosomes enhance bone regeneration in AVN models by activating key signaling pathways, including PI3K/Akt, Wnt/β- catenin, and HIF-1α/VEGF pathways. Additionally, exosomes can be incorporated into biomaterial scaffolds, hydrogels, or nano-carriers to improve retention, targeted delivery, and sustained biological activity. These properties position exosome-based therapy as a next- generation regenerative strategy for AVN treatment.

E. Platelet-Rich Plasma (PRP) and Combinatorial Approaches

BIOLOGICAL BASIS AND THERAPEUTIC ROLE OF PRP

Platelet-rich plasma (PRP) is an autologous blood-derived product enriched with platelets and growth factors such as platelet-derived growth factor (PDGF), VEGF, TGF-β, and insulin-like growth factor-1 (IGF-1). These bioactive molecules promote angiogenesis, stimulate osteoblast proliferation, and regulate inflammation, making PRP a valuable adjunct therapy for avascular necrosis.

THE ROLE OF PLATLET RICH PLASMA IN THE TREATMENT OF A VASCULAR NECROSIS



CLINICALAPPLICATIONS OF PRP IN AVN

Clinically, PRP has been widely used in combination with core decompression procedures, particularly in early-stage AVN. Studies have reported improved pain relief, enhanced functional outcomes, and delayed disease progression following PRP administration. Its autologous origin provides advantages such as low immunogenicity, minimal ethical concerns, and ease of preparation, increasing its clinical acceptability.

COMBINATORIAL REGENERATIVE STRATEGIES

Combinatorial regenerative approaches have gained considerable attention due to their synergistic therapeutic effects. The combination of PRP with mesenchymal stem cells (MSCs) enhances cell survival, proliferation, and osteogenic differentiation by creating a growth factor-rich microenvironment. Similarly, incorporation of PRP into biodegradable scaffolds improves cell adhesion, vascularization, and bone ingrowth.

ADVANCED MULTIMODAL THERAPIES

Advanced regenerative strategies include scaffold-based delivery systems integrating PRP, stem cells, and bioactive molecules. These multifunctional platforms provide mechanical support while simultaneously promoting osteogenesis and angiogenesis. Such multimodal therapies address the multifactorial pathogenesis of AVN and offer superior regenerative outcomes compared to single-modality treatments.

CHALLENGES AND LIMITATIONS

BIOLOGICALAND CELLULAR CHALLENGES

Despite promising results, several biological challenges limit the clinical translation of regenerative therapies for AVN. Poor cell survival and engraftment in the ischemic and hypoxic environment of necrotic bone significantly reduces the long-term efficacy of stem cell-based treatments. Variability in stem cell source, isolation methods, cell dose, and delivery techniques further contributes to inconsistent clinical outcomes.

SAFETY CONCERNS AND IMMUNOLOGICAL ISSUES

Immune rejection and inflammatory responses remain concerns, particularly with allogeneic stem cell therapies. Additionally, the use of induced pluripotent stem cells (iPSCs) raises safety issues related to tumorigenesis, genetic instability, and uncontrolled differentiation, necessitating rigorous safety evaluation.

REGULATORY, ETHICAL, AND ECONOMIC BARRIERS

Regulatory and ethical challenges pose significant obstacles to clinical adoption. The lack of standardized protocols for cell processing, scaffold fabrication, and quality control makes it difficult to compare studies and establish evidence-based guidelines. Furthermore, high costs associated with stem cell expansion, biomaterial development, and regulatory approval limit accessibility, especially in low-resource settings.

NEED FOR ROBUST CLINICAL EVIDENCE

Most current clinical studies are limited by small sample sizes and short follow-up durations. There is a pressing need for large-scale, randomized controlled trials with long-term outcome assessments to validate the safety, efficacy, and cost-effectiveness of regenerative therapies. Addressing these challenges through interdisciplinary collaboration, technological innovation, and robust regulatory frameworks is essential for translating regenerative strategies into routine clinical practice for avascular necrosis.

CONCLUSION

Avascular necrosis is a debilitating disease caused by multiple factors and involves complex pathological mechanisms. If not diagnosed and managed at an early stage, it can progress to bone collapse and severe joint dysfunction. Early detection, particularly through magnetic resonance imaging (MRI), is essential for identifying the condition before irreversible damage occurs. Timely therapeutic intervention can help slow disease progression and preserve joint function. Recent advances in biologics, regenerative medicine, and minimally invasive treatment strategies offer promising opportunities for improving the future management of avascular necrosis.

REFERENCE

1. Mont MA, Jones LC, Hungerford DS. Nontraumatic osteonecrosis of the femoral head: ten years later. J Bone Joint Surg Am., 2006; 88(5): 1117–1132.
2. Moya-Angeler J, Gianakos AL, Villa JC, Ni A, Lane JM. Current concepts on osteonecrosis of the femoral head. World J Orthop, 2015; 6(8): 590–601.
3. Hernigou P, Beaujean F. Treatment of osteonecrosis with autologous bone marrow grafting. Clin Orthop Relat Res., 2002; 405: 14–23.
4. Hernigou P, Poignard A, Beaujean F, Rouard H. Percutaneous autologous bone-marrow grafting for osteonecrosis of the femoral head. J Bone Joint Surg Am, 2005; 87(7): 1430–1437.

5. Gangji V, Hauzeur JP. Cellular-based therapy for osteonecrosis. Orthop Clin North Am, 2009; 40(2): 213–221.
6. Barry FP, Murphy JM. Mesenchymal stem cells in joint disease and repair. Nat Rev Rheumatol, 2013; 9(10): 584–594.
7. Pittenger MF, Mackay AM, Beck SC, et al. Multilineage potential of adult human mesenchymal stem cells. Science, 1999; 284(5411): 143–147.
8. Lieberman JR, Berry DJ, Mont MA, et al. Osteonecrosis of the hip: management in the 21st century. Instr Course Lect., 2003; 52: 337–355.
9. Assouline-Dayan Y, Chang C, Greenspan A, Shoenfeld Y, Gershwin ME. Pathogenesis and natural history of osteonecrosis. Semin Arthritis Rheum, 2002; 32(2): 94–124.
10. Raghunath J, Salacinski HJ, Sales KM, Butler PE, Seifalian AM. Advancing tissue engineering: stem cell technology. Trends Biotechnol, 2005; 23(10): 460–466.
11. Wang BL, Sun W, Shi ZC, et al. Treatment of osteonecrosis with stem cells. World J Stem Cells, 2014; 6(3): 351–362.
12. Zhao D, Cui D, Wang B, et al. Treatment of early-stage osteonecrosis with autologous bone marrow stem cells. Bone, 2012; 50(1): 325–330.
13. Gupta PK, Das AK, Chullikana A, Majumdar AS. Mesenchymal stem cells for cartilage repair. Stem Cell Res Ther., 2012; 3(4): 25.
14. Steinert AF, Rackwitz L, Gilbert F, Nöth U, Tuan RS. Concise review: The clinical application of mesenchymal stem cells. Stem Cells, 2012; 30(1): 42–52.
15. Zhang J, Liu X, Li H, et al. Exosomes derived from mesenchymal stem cells promote bone regeneration. Biomaterials, 2016; 91: 49–59.
16. Mathieu M, Martin-Jaular L, Lavieu G, Théry C. Specificities of secretion and uptake of exosomes. Nat Cell Biol., 2019; 21(1): 9–17.
17. Li Z, Wang Y, Xiao K, et al. Emerging role of exosomes in bone diseases. Front Bioeng Biotechnol, 2021; 9: 634731.
18. Filardo G, Kon E, Pereira Ruiz MT, et al. Platelet-rich plasma intra-articular injections for cartilage degeneration. Am J Sports Med., 2012; 40(2): 396–407.
19. Sampson S, Gerhardt M, Mandelbaum B. Platelet rich plasma injection grafts for musculoskeletal injuries. Am J Sports Med., 2008; 36(1): 1–9.
20. Marx RE. Platelet-rich plasma: evidence to support its use. J Oral Maxillofac Surg, 2004; 62(4): 489–496.
21. Bose S, Roy M, Bandyopadhyay A. Recent advances in bone tissue engineering scaffolds. Trends Biotechnol, 2012; 30(10): 546–554.

22. O'Brien FJ. Biomaterials and scaffolds for tissue engineering. Mater Today., 2011; 14(3): 88–95.
23. Hutmacher DW. Scaffolds in tissue engineering bone and cartilage. Biomaterials, 2000; 21(24): 2529–2543.
24. Hollister SJ. Porous scaffold design for tissue engineering. Nat Mater, 2005; 4(7): 518– 524.
25. Ma PX. Biomimetic materials for tissue engineering. Adv Drug Deliv Rev., 2008; 60(2): 184–198.
26. Kerachian MA, Séguin C, Harvey EJ. Osteonecrosis of the femoral head: vascular hypotheses. Endothelium, 2009; 16(1): 1–12.
27. Weinstein RS. Glucocorticoid-induced osteonecrosis. Endocrine, 2012; 41(2): 183–190.
28. Cui Q, Wang GJ, Balian G. Steroid-induced osteonecrosis: animal model and cellular mechanisms. J Bone Joint Surg Am., 1997; 79(5): 747–755.
29. Lane JM, Serota AC, Raposo JF. Osteonecrosis of the femoral head: clinical update. Bull Hosp Jt Dis., 2015; 73(1): 35–41.
30. Gangji V, De Maertelaer V, Hauzeur JP. Autologous bone marrow cell implantation in osteonecrosis. Bone., 2011; 49(5): 1005–1010.