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(REVIEW ARTICLE)

Exploring regenerative medicine strategies for osteoporosis treatment: Progress, potential, and hurdles

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Abstract

A major worldwide health problem is osteoporosis, particularly in older people. There are restrictions on current therapies, such as anti-resorptive medications. Promising techniques including stem cell treatment, gene therapy, and growth factors are available in regenerative medicine. Preclinical and clinical research indicate promise for mesenchymal stem cells derived from bone marrow, adipose tissue, and umbilical cord blood. Enhancing bone regeneration with gene therapy that targets osteogenic factors such as BMPs is a promising approach. In order to mend bones, growth factors, cytokines, and scaffold materials are essential. Realising the benefits of regenerative medicine in treating osteoporosis requires cooperation and ongoing research, despite obstacles such limited clinical acceptability and regulatory barriers.

Keywords: Osteoporosis; Regenerative Medicine; Stem Cells; Gene Therapy; Growth Factors.

1. Introduction

Insufficient bone strength, which causes skeletal deformities and an elevated risk of fracture, is the hallmark of osteoporosis. It includes both primary and secondary types. Primary osteoporosis is mostly caused by changes in metabolism and typically affects people in their 50s to 70s. Conversely, endocrinopathies, prolonged immobilisation, malabsorption, and other pathological conditions might result in secondary osteoporosis. Age- and gender-specific variations in the disease's manifestations include juvenile osteoporosis, postmenopausal osteoporosis, which affects women aged 51-75, juvenile osteoporosis, osteoporosis in smokers aged 30-50, and involutional osteoporosis, which affects both sexes and is linked to decreased physical activity, hormonal fluctuations, and nutritional disorders. Globally, osteoporosis is a serious health concern, particularly for ageing populations. Approximately 10 million adults over 50 in the US suffer from osteoporosis, and 1.5 million of them break a fragility fracture each year. In the United Kingdom, 1 in 5 men and 1 in 2 women over 50 will suffer an osteoporotic fracture. Fractures of the wrist, spine, and hip are common; within six months, hip fractures have significant death rates (3% for women and 8% for males). Distal forearm fractures have an impact on daily life but a lower death rate than vertebral fractures, which increase morbidity, particularly in older women. A person's risk of getting another fracture increases after they have one. These results highlight the necessity of efficient management and preventative plans to mitigate the effects of osteoporosis. One can classify non-modifiable and possibly modifiable osteoporosis risk factors. Non-modifiable variables include old age, female sex, family predisposition, Caucasian race, history of adult fractures, dementia, poor health, and sensitive constitution; these factors collectively considerably increase the risk of osteoporosis.Vitamin D insufficiency, smoking, alcohol use, inadequate calcium intake, imbalances in phosphorus intake (either too low or excessive), and a high-protein diet are examples of risk factors that may be changed. These unfavourable conditions might hasten the normal ageing process of bone tissue loss. Osteoporosis cannot be prevented or treated without addressing modifiable risk factors through lifestyle modifications and medication. Bisphosphonates, denosumab, and modulators of selective

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oestrogen receptors are examples of anti-resorptive medicines for osteoporosis (SERMs). Alendronate and zoledronate are examples of bisphosphonates that suppress osteoclast activity, lowering bone resorption and raising bone mineral density. By preventing osteoclast production, the RANKL antibody denosumab reduces bone resorption and raises bone mineral density. By suppressing osteoclast activity, Postmenopausal bone loss and osteoporosis are prevented by SERMs like raloxifene. Treatments based on parathyroid hormones, such as abaloparatide and teriparatide, promote the growth of new bone but may also accelerate the resorption of existing bone. Sclerostin inhibitors like romosozumab promote bone growth and effectively lower the risk of fractures, especially spinal fractures. Combining bisphosphonates with potent anti-resorptive or PTH-based treatments could not offer any benefit at all and might even reduce their efficacy. It's important to watch for possible adverse effects such as atypical femur fractures and osteonecrosis of the jaw while using anti-resorptive drugs. The inadequacies of osteoporosis therapy include restricted alternatives for severe cases, high prices, probable adverse effects, difficulties with adherence, and inadequate effectiveness.

1.1. Regenerative medicine approaches

The goal of regenerative therapy is to rebuild or replace human organs, tissues, and cells in order to create or restore normal function. It includes a range of techniques like tissue engineering, gene therapy, stem cell transplantation, and the application of soluble chemicals. The field seeks to address problems resulting from illness, injury, ageing, and congenital malformations. It expands upon earlier medical innovations including organ transplants, implants, and surgery. It differs from traditional transplantation and substitution therapies and has potential uses for the management of a variety of medical conditions, including chronic disorders. Governments and the healthcare sector are starting to focus a greater emphasis on regenerative therapy, which has the potential to be a game-changing technology that takes the place of essential drugs and prosthetics. In order to reduce burden and rejection concerns, regenerative treatment for osteoporosis employs the patient's own cells to regenerate bone. There are three different kinds of stem cells that are available: induced pluripotent, somatic and embryonic. Derived mesenchymal stem cells from bone marrow have potential for bone repair. Muscle, adipose tissue, vascular cells, and the periosteum are other possible sources. Determining stem cells and improving harvesting techniques are still difficult. Both in vivo and ex vivo techniques are used in tissue engineering for osteoporosis. While ex vivo techniques produce custom bone constructions for transplantation, in vivo techniques promote bone repair locally or across the body. Improved bioreactors, biofabrication methods, and intelligent scaffold materials are examples of recent developments. To address cellular abnormalities in bone regeneration, two techniques are being considered: targeting regeneration inhibitors and altering differentiation pathways. The objective is to use customised tissue engineering techniques to quickly establish stability and recovery following fractures. Because gene therapy promotes bone regeneration, it has potential for treating fractures caused by osteoporosis. Ex vivo treatment alters osteogenic cells prior to implantation, whereas in vivo administration inserts genes directly into afflicted regions. Bone development is aided by cytokines like VEGF and growth factors like BMPs. Several gene products together improve the chance for healing. There is research being done on ways to reduce immunological reactions and improve delivery methods. In general, focused and customised methods to enhance bone regeneration and lower fracture risk in osteoporosis are provided by gene therapy. Because they may address the issues of weak bone and poor healing, biomaterials are essential in the treatment of fractures caused by osteoporosis. Although there are challenges with traditional fixation techniques, attempts are being made to improve fracture reduction with metallic cements and implants. Surface alterations enhance osteointegration, whereas greater surface area in metallic implants promotes better fixation. Calcium phosphate coatings, for example, show potential, although problems still exist. Bioceramics, such as bioactive glasses and calcium phosphate, promote bone regrowth. Potential is provided by gene and cellular treatments, which encourage vascularization and bone formation. Notwithstanding obstacles, developments in biomaterials have the potential to revolutionise the treatment of osteoporosis by offering individualised approaches for better bone regeneration and repair.

2. Stem cell therapy

2.1. Bone marrow-derived mesenchymal stem cells

Mesenchymal stem cells obtained from bone marrow for osteoporosis treatment (BM-MSCs) has shown promise. Numerous investigations have exhibited their efficacy in preclinical settings and elucidated diverse approaches to augment their medicinal possibilities. Research utilising animal models of osteoporosis, such OVX-induced rats and rabbits, has demonstrated that the transplantation of BM-MSCs results in enhancements to bone microarchitecture, strength, and mass. The implantation of BM-MSCs into osteoporotic areas or their direct injection into the bone marrow cavity has been shown to enhance bone apposition, trabecular thickness, and overall bone stiffness. To increase the therapeutic benefits of BM-MSCs, researchers have looked at genetic changes of the cells. For instance, transducing MSCs with genes such as receptor activator of nuclear factor-kB-Fc (RANK-Fc) or human bone morphogenetic protein 2 (hBMP-2) has demonstrated potential in stimulating the production of new bone and suppressing osteoclast activity.

Systemic injection of BM-MSCs has been studied to reach various locations requiring repair, given that osteoporosis is a systemic condition. Research has indicated that the intravenous infusion of Mesenchymal stem cells produced from bone marrow (BM-MSCs) results in enhanced bone density and volume in animals with osteoporosis. Additionally, clinical trials are being conducted to assess the effectiveness and safety of BM-MSC therapy in the treatment of osteoporosis. By evaluating the viability of injecting autologous BM-MSCs intravenously into osteoporosis patients, these trials hope to shed light on the potential therapeutic uses of these cells. Finally, BM-MSCs have great potential as a therapeutic method for treating osteoporosis. They are a strong contender for treating the underlying pathophysiology of osteoporosis due to their capacity to promote bone formation, prevent bone resorption, and serve as a home for bone marrow. Their efficacy and safety in clinical practice will be further validated by ongoing research and clinical studies.

2.2. Adipose tissue-derived mesenchymal stem cells

In comparison to bone marrow-derived MSCs (BM-MSCs), Mesenchymal stem cells produced from adipose tissue (ADSCs) have attracted a lot of attention in osteoporosis research because they are easier to isolate, more abundant, and produce more cells per unit. Research has indicated that ADSCs may be able to reduce bone loss associated with osteoporosis. Bone mineral density (BMD) has significantly increased after ADSCs were injected into animal models of osteoporosis, such as OVX mice and rabbits, in comparison to controls. These results imply that ADSCs have the ability to prevent bone deterioration and encourage bone growth. In animal models of osteoporotic bone loss, it has been demonstrated that inhibiting the zinc finger protein 467 (Zfp467) gene in ADSCs promotes their differentiation into osteoblasts and results in the repair of bone volume and trabecular number. In preclinical research, ADSCs have shown encouraging outcomes, showcasing their capacity to enhance bone regeneration, promote osteogenesis, and inhibit adipogenesis of osteoporotic bone marrow-derived MSCs. There are ongoing clinical studies examining the therapeutic potential of ADSCs in the treatment of osteoporosis. For instance, the University Hospital in Basel, Switzerland carried out a Phase II clinical research to assess the effectiveness of ADSCs in treating proximal humeral fractures linked to osteoporosis. But as of yet, no results from this experiment have been made public. In conclusion, ADSCs show potential as a new source of stem cells for the treatment of osteoporosis. They are a strong contender for more study and clinical exploration in the realm of regenerative medicine due to their abundance, simplicity of isolation, and therapeutic potential.

2.3. Umbilical Cord Blood-Derived Stem Cells

The umbilical cord blood-derived stem cells (UCB) have shown great promise in treating osteoporosis because of their unique properties and potent osteogenic differentiation capacity. Research has indicated that the transplantation of UCB stem cells into animal models of osteoporosis can effectively promote bone formation. For instance, within 12 weeks of transplanting human UCB-MSCs into scaffolds into mice, substantial bone growth was seen. When UCB-MSCs or their conditioned media (CM) were injected systemically into osteoporotic mice, the number, thickness, and volume of trabecular bone improved along with the bone mineral density (BMD) levels. This implies that rather than directly engrafting into bone tissue, the therapeutic benefits of UCB-MSCs are mediated by secretory paracrine pathways. Increases in trabecular number, thickness, BMD, and bone volume were seen in osteoporotic animals following the expansion of CD34+ cells isolated from UCB and their systemic injection. This suggests that CD34+ cells produced from UCBs may be able to slow down bone loss and encourage bone regeneration. Because of its many benefits—such as their low immunogenic potential, robust osteogenic differentiation ability, and ease of noninvasive harvesting—UCB-derived stem cells are a popular option for cell-based treatments aimed at treating osteoporosis. In general, studies on stem cells produced from UCBs show potential for improving the treatment of osteoporosis using regenerative medicine techniques. To completely understand their therapeutic processes and maximise their clinical utility, more research is required.

2.4. Human-induced pluripotent stem cell-derived mesenchymal stem cells

Human induced pluripotent stem cells yield mesenchymal stem cells (iPSC-MSCs) present a promising approach to bone regeneration because of their ability to develop unrestrictedly and their resistance to immunological rejection. Nonetheless, there is still worry about the potential for tumorigenicity linked to iPSCs. Since iPSC-MSCs combine the benefits of MSCs and iPSCs, they have being investigated for their potential in bone regeneration. Exosomes produced by MSCs from human-induced pluripotent stem cells, or hiPSC-MSC-Exos, have shown promise as a non-immune response method of bone repair. Studies conducted in vitro have demonstrated that in bone marrow-derived MSCs from osteoporotic rats, hiPSC-MSC-Exos stimulate cell proliferation, alkaline phosphatase activity, and osteoblast-related gene expression. In critical-sized calvarial lesions in ovariectomized rats, in vivo experiments have shown that hiPSC-MSC-Exos greatly enhance bone repair and angiogenesis. The regulation of endogenous stem cell recruitment is achieved by modifications to biological, physical, and chemical variables that impact MSC differentiation. Runx2 and

other transcription factors are essential for promoting the osteoblast development of MSCs; their activity is influenced by a variety of signalling pathways and small molecules. MicroRNAs, also known as miRNAs, are crucial in controlling MSC development. Some miRNAs govern the Wnt/β-catenin pathway, which stimulates osteogenic differentiation, while others manage the pathways leading to adipogenic differentiation. In general, these pathways provide prospective avenues for therapeutic intervention aimed at treating osteoporosis and promoting bone growth.

2.5. Growth factors, cytokines and scaffold materials in bone regeneration -

Growth factors, cytokines, and scaffold materials perform vital roles in bone regeneration by controlling cellular activity and inducing crucial processes such as swelling, blood vessel development, cell proliferation, and matrix synthesis. Bone morphogenetic proteins (BMPs), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), growth factor that resembles insulin (IGF), and vascular endothelial growth factor (VEGF) are important growth factors in bone regeneration. While other growth factors such as VEGF, FGF, and IGFs show promise in pre-clinical research, recombinant BMPs are employed in clinical settings. At various phases of fracture healing, FGFs are released and activate mitogenic actions, which promote the creation of new bone, especially when paired with BMPs. IGFs have anti-apoptotic properties and work in concert with BMPs to promote osteogenesis. VEGF promotes angiogenesis and works in concert with BMPs to improve bone growth. However, because of its effects on osteoprogenitor differentiation and active bone resorption, PDGF may prevent BMP-induced bone growth while stimulating tissue healing. Although scaffold materials, including platelet-rich plasma (PRP), provide a mix of cytokines and growth factors, their effectiveness in promoting bone regeneration varies. Growth factor release is influenced by biomaterials, and this has a direct impact on the outcomes of bone healing. On the other hand, problems like prosthesis loosening can also be brought on by the overproduction of growth hormones. Developing successful methods for bone tissue design and restoration requires optimising growth factor distribution and comprehending the intricate relationships between growth factors, cytokines, and scaffold materials.

2.6. Gene therapy in osteoporosis treatment

In osteoporosis, a disorder marked by reduced bone density and elevated fracture risk, especially in the elderly, gene therapy demonstrates a lot of promise for improving bone recovery. A discrepancy between bone creation and resorption occurs in osteoporosis, which compromises the body's ability to mend fractures and increases the likelihood of implant fixation failure. Recent studies show that impairments in mesenchymal stem cells (MSCs) worsen bone healing processes by reducing osteoblastic differentiation and proliferation. In order to address these issues, a number of gene therapy techniques have been created that improve bone regeneration by introducing genes that encode osteogenic factors right to the site of damage. Bone morphogenetic proteins (BMPs) are a well-researched class of osteoinductive cytokines that have demonstrated effectiveness in encouraging bone growth in animal models. However, due in part to issues with delivery and inadequate cellular response, therapeutic experiments utilising recombinant BMPs have had inconsistent outcomes. In order to overcome these constraints, gene therapy techniques insert BMP genes using viral vectors or non-viral delivery systems with the goal of achieving sustained and localised protein production at the site of damage. Strategies for in vivo gene transfer entail employing viral vectors or gene-activated matrices to deliver genes directly to the site of injury. Despite the widespread use of adenoviral vectors, worries concerning immunological reactions persist. In contrast, ex vivo methods entail the genetic modification of MSCs with BMP genes prior to transplantation, which enhances osteogenesis via paracrine and autocrine processes. Despite advancements, issues including the requirement for customised cell cultures and immunological reactions to viral vectors still need to be resolved. Studies also look into additional gene products, such as angiogenic factors like vascular endothelial growth factor (VEGF) and transcription factors like LIM mineralization protein-1 (LMP-1). Several genes combined in a therapeutic cocktail may work in concert to improve bone healing. Furthermore, anti-inflammatory drugs such as interleukin-1 receptor antagonist (IL-1Ra) and soluble tumour necrosis factor receptor (sTNFR) have potential in reducing excessive bone resorption. To sum up, gene therapy has the potential to significantly improve bone repair in cases of osteoporosis by stimulating osteogenesis and treating underlying abnormalities in MSCs. To minimise immunological reactions, optimise delivery strategies, and investigate the synergistic benefits of many gene treatments, further study is required. In the end, gene therapy presents a fresh and exciting way to transform osteoporosis treatment and enhance the lives of those who are impacted, especially the elderly.

3. Animal model and clinical trials

Clinical trials and animal models are important tools in the development of regenerative medicine techniques for bone repair. Osteogenic stem cells, such as stem cells from adipose tissue (ASCs) and mesenchymal stem cells from bone marrow (MSCs), are two examples of stem cells that are widely employed in research, both in experimental animal research and clinical trials involving humans. The homing characteristics and transplantation efficiency of stem cells are evaluated in preclinical studies using animal models for medicinal purposes. Given their encouraging osteogenic

potential, MSCs and ASCs can be used to treat an assortment of bone ailments, including osteoporosis, osteoarthritis, osteonecrosis, and osteopenia, additionally complicated fractures and bone deformities. Notably, because living BMSCs and ASCs may limit T cell proliferation, preserve immune regulating capabilities, and stimulate osteogenesis, there is increased interest in using them in preclinical research. Bone marrow concentrate and the direct delivery of MSCs and ASCs have both demonstrated effectiveness in encouraging bone repair and regeneration in animal models. Treatments for diseases including osteonecrosis, osteoarthritis, and long-bone pseudoarthrosis have shown effectiveness with these methods. Furthermore, in cases of long-bone pseudoarthrosis, the combination of MSCs with allogenic cancellous bone grafts has accomplished full consolidation of the bone. The use of ASCs and MSCs has shown encouraging results in treating an assortment of bone-related illnesses in human clinical studies. For example, ASCs have been studied in clinical trials for the treatment of osteoarthritis in the knee, while BM-MNCs have been used to treat avascular necrosis of the femoral head and long-bone pseudoarthrosis. Moreover, studies investigating the utilisation of autologous osteoblastic cells infused intravenously in cases of severe osteoporosis and stem cell recruitment in osteoporosis treatment are now underway. In general, clinical trials and animal models are important platforms for assessing the therapeutic potential, safety, and effectiveness of regenerative medicine techniques in bone regeneration. These findings open the door for the creation of cutting-edge therapies that use stem cells' osteogenic potential to treat an assortment of bone diseases, ultimately providing patients with these illnesses with hope for better prognoses and a higher standard of living.

4. Challenges and opportunities

The discrepancy between clinical implementation and experimental performance clearly illustrates the potential and problems associated with employing regenerative medicine. While cutting-edge techniques like gene and cell therapy provide hope for therapies that might save lives, advancement is hampered by subpar research, murky financing schemes, and unlicensed commercial clinics. A notable obstacle is the low clinical acceptance, which is partially caused by irrational expectations and the rise of dishonest clinics that provide understudied therapies for profit. Furthermore, there are hazards to patient safety and a decline in public confidence in science as a result of an evidence crisis brought on by early commercial approval and insufficient regulatory monitoring. There are, nonetheless, chances for growth. Reports such as those issued by the FEAM and EASAC emphasise the necessity of consistent funding for ethical advancement, research infrastructure, and regulatory openness. Important next steps include incorporating regenerative medicine into medical education and encouraging collaborations between academic institutions and business. In order to promote responsible innovation, patient safety, and fair access to effective medications, stakeholders must work together to address these issues and seize possibilities.

5. Conclusion

In conclusion, there are encouraging options for treating the problems caused by diseases like osteoporosis in the field of regenerative medicine. Our knowledge and available treatments are being advanced via stem cell therapy, gene therapy, growth factors, cytokines, scaffold materials, and animal models, among other methods. Notwithstanding, notable obstacles persist, such as restricted clinical adoption, regulatory obstacles, and the expansion of unlicensed clinics. Notwithstanding these obstacles, there are unquestionably good chances for advancement with continued funding for research, ethical advancement, and regulatory openness. To fully use these cutting-edge methods to enhance patient outcomes and quality of life, we may seek to promote collaboration among stakeholders and include regenerative medicine into medical education.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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