REVIEW

Current application of dexamethasone-incorporated drug delivery systems for enhancing bone formation

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Abstract

Background Dexamethasone (DEX) is a well-known anti-inflammatory and immunosuppressive drug applied broadly as an osteoinductive agent in bone remodeling. However, the efficacy of DEX is strongly dependent on the dosage and duration of application. Therefore, the optimization of DEX release with the appropriate concentration is crucial for bone tissue engineering.

Area covered This review discusses the incorporation of DEX into drug delivery systems such as nanoparticles, microparticles, and scaffolds, and their effects on bone fracture healing by controlling the long-term release of the drug and preventing systemic side effects. The mechanism of DEX in bone fracture repair and the potential outcomes of DEX-contained approaches for bone regeneration and the osteogenic process are also summarized.

Expert opinion DEX-incorporated drug delivery technologies, such as micro- and nanoparticles and scaffolds, hold great promise for the treatment of bone defects. These systems offer several advantages, including enhanced DEX stability, controlled release with appropriate concentration levels, targeted delivery to the treatment site, inhibition of cytotoxicity, and prevention of systemic side effects of DEX. However, further rigorous research is necessary to optimize DEX-incorporated drug delivery systems and conduct detailed assessments of their in vitro and in vivo osteogenesis and bone formation, as well as determine the optimal application processes.

Keywords Dexamethasone · Bone regeneration · Osteogenesis · Drug delivery systems

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Introduction

Bone defects are a serious disease that affects the quality of life of patients and places a significant burden on the healthcare system and the economy worldwide (Jaiswal et al. 1997; Chen et al. 2017a, b; Cheng et al. 2019; Lin et al. 2020; Liu and Gao 2021). The incidence of hip fractures has risen considerably globally and is expected to double by 2050 due to factors, such as aging, obesity, and lack of physical activity (Amini et al. 2012; Shen et al. 2022). Bone defects can be caused by various factors, including trauma, tumors, infections, osteoporosis, congenital deformities, aging, and other bone-related diseases (Chen et al. 2017a, b; Migliorini et al. 2021; Zhou et al. 2021). Bone regeneration is a complex process that requires the participation of numerous factors to regulate bone formation, as shown in Table 1. While bone defects can sometimes heal naturally under appropriate physiological conditions over a long period, larger defects resulting from injuries may not heal on their own and can cause severe damage (Li et al. 2015). In such cases, surgical

Table 1 Factors affecting bone formation or bone healing

Factors	Function on bone healing	Strategies for bone healing	References
Inflammation	o Attracts immune cells to the injury site, removing debris and necrotic tissue o Releases growth factors and chemokines that stimulate angiogenesis and recruit other cells related to the tissue repair process o The inhibition of the nature of acute inflammation or chronic inflammation can lead to bone healing impairment	o Regulate the M1/M2 ratio to obtain the appropriate macrophage functions in the fracture healing process.	Goodman and Maruyama (2020), Maruyama et al. (2020), Zhu et al. (2021a, b), Chen et al. (2023), Kushioka et al. (2023)
Mesenchymal stem cells (MSC)	o Recruit to the site of injury o Differentiate into the osteogenic cell types: osteoblasts and chondrocytes	o Transplant MSCs into the site of injury to enhance bone regeneration o Enhance MSC migration to the injury o Improve MSC differentiation into bone cells	Lin et al. (2017), Lee et al. (2018), Pan et al. (2021), Banimohamad-Shotorbani et al. (2023)
Growth factors (BMPs, PDGFs, IGFs)	o Bind to the specific receptors on cells related to bone formation, which triggers signaling pathways that improve cell proliferation, differentiation, and migration o Stimulate angiogenesis and support the formation of new blood vessels in the healing bone	o Combine BMPs (BMP-2, BMP-7) in a drug delivery system for improving bone regeneration.	Linkhart et al. (1996), Kloen et al. (2003), Mikami et al. (2010), Spiro et al. (2010)
Extracellular Matrix (ECM) proteins	o Provide the structure support for cell attachment, migration, and the deposition of mineralized bone matrix	o Apply the scaffolds to enhance bone healing	Chen et al. (2018a, b), Donnaloja et al. (2020), Ravoor et al. (2021)
Angiogenesis Factors	o Improve the growth of new blood vessels in the healing bone defects	o Apply or combine the angiogenesis factors in bone healing-related drug delivery system	Cui et al. (2013), Zhang et al. (2023)
Osteoblasts	o Produce collagen, osteocalcin, and other bone matrix proteins for bone healing o Release alkaline phosphatase, which promotes mineralization of the newly formed bone matrix	o Transplant osteoblast cells at the site of injury o Convert other cells into osteoblast cells o Enhance the osteogenic process of osteoblast	Park et al. (2006), Chang et al. (2019)
Mechanical Stability	o Reduce the mobility of the fractured bone ends o Facilitates callus formation and promotes optimal bone remodeling and healing	o External and internal fixation o External support o Bone grafting	Kolasangiani et al. (2020), Battafarano et al. (2021)
Parathyroid hormones (PTH)	o Promote the activity of osteoblasts o Enhance bone formation o Stimulate the release of calcium from the bone matrix	o Local application of PTH to enhance new bone formation, angiogenesis and implant osseointegration	Jiang et al. (2018), Wojda and Donahue (2018), Wojda et al. (2021)

intervention and the use of bone substitutes are necessary to promote bone regeneration. An ideal bone substitute should be osteoconductive, biocompatible, bioresorbable, and capable of proper osteointegration with host tissue. In addition, it should enhance cell migration, proliferation, and differentiation to promote bone formation. (Safari et al. 2021).

Over the past decades, several strategies have been developed to enhance bone defect regeneration. Autografts and allografts are the traditional approaches for repairing bone fractures, but both have their drawbacks (Cypher and Grossman 1996; Yu et al. 2008; Wehrhan et al. 2012). Autografts are hindered by the donor supply, donor site pain, limited availability and quantity, and the risk of hemorrhage. In contrast, allografts carry the risk of rejection reactions and the transmission of infectious diseases. In addition, they have no osteogenesis and weak osteoinductivity (den Boer et al. 2003; Muscolo et al. 2006; Oest et al. 2007; Orciani et al. 2017; Sohn and Oh 2019). To address these limitations, tissue engineering, utilizing material science, bioactive reagents, and stem cell therapy, has emerged as an effective therapy for bone remodeling. Bioactive factors are crucial for supporting bone tissue engineering systems to mimic the native bone microenvironment and processes during bone self-healing (Safari et al. 2021). Bone growth factors are the most promising components for bone restoration because of their interaction with a membrane receptor on a target cell, triggering an intracellular signal transduction system that induces the expression of bone-specific genes in the nucleus and protein production in the cytoplasm (Amini et al. 2012). On the other hand, growth factors have significant drawbacks, including handling difficulties, immunogenicity, high cost, a short half-life, ectopic bone formation and tumorigenesis, which limit their clinical applications (Cho and Juliana 1996; Lo et al. 2011; Lo et al. 2012). Osteoinductive small molecules have shown promising effects on bone regeneration phenotypes and offer an advantageous solution to overcome the limitations of growth factors (Lo et al. 2012; Laurencin et al. 2014; James et al. 2016; Chang et al. 2019; Safari et al. 2021). Unlike growth factors, small molecules are easily manufactured, less expensive, available from bioresources, less prone to denaturation, and are highly stable compounds (Wang et al. 2015; Goonoo and Bhaw-Luximon 2019).

Various small molecules have been used to enhance osteogenesis, including statins, Hedgehog pathway agonists (e.g. purmorphamine), or herbal medicines, such as puerarin, psoralen, and osthole (Mundy et al. 1999; Sugiyama et al. 2000; Wu et al. 2002). Among them, dexamethasone (DEX) is a promising small molecule that can stimulate the expression of osteogenic marker genes and is used widely to promote the differentiation of multipotent mesenchymal stem cells into osteoblasts, chondrocytes, and adipocytes (Koehler et al. 2013; Ghali et al. 2015). However, the systemic administration of DEX requires a high dose and long-term application due to its rapid drug clearance, leading to an increased risk of osteoporosis and nontraumatic osteonecrosis. In addition, the lack of effective drug delivery strategies in clinical settings results in an initial burst of drug release, which can result in high concentrations of DEX to accumulate at local target sites and inhibit osteogenesis and bone remodeling (Birkedal-Hansen et al. 1993). Smart delivery systems that can locally deliver and efficiently control the release of DEX while ensuring safety are needed to prevent the adverse effects of DEX on bone regeneration and osteogenesis (Wang et al. 2010a, b; Qiu et al. 2016). Incorporating DEX into different drug delivery systems, such as nanoparticles, microparticles, hydrogels, and scaffolds, has achieved notable effects on bone fracture healing by controlling the long-term drug release, preventing systemic side effects, and supporting the differentiation of bone cells and bone formation (Gu et al. 2013; Lian et al. 2019). This review focuses on the role of DEX in bone regeneration and discusses DEX-incorporated bone defect remodeling strategies that facilitate osteogenic differentiation and bone healing.

Dexamethasone in conventional clinical application

Dexamethasone (DEX) is a potent synthetic corticosteroid long established in diverse medical and biological applications. DEX has been used in clinical applications because of its potential to inhibit inflammatory factors, such as cytokines, chemokines, cell adhesion molecules (CAMs), and the acute inflammatory response (Cruz-Topete and Cidlowski 2015). The anti-inflammatory effects of DEX are achieved by affecting two factors: chemotaxis and vasodilation (Ahmed and Hassan 2020). The main anti-inflammatory effects of DEX have been extensively used in the treatment of rheumatoid arthritis, cerebral edema, viral pneumonia, and altitude sickness (Ferrazzini et al. 1987; Verhoef et al. 1999; Nahaczewski et al. 2004; Liu et al. 2008; Duffy et al. 2014). Furthermore, DEX can reduce the adverse effects or enhance the efficacy of cancer therapy (Weber et al. 2007; Hawkins and Grunberg 2009). DEX is used as an immunosuppressive agent (Martins et al. 2012; Li et al. 2017; Giles et al. 2018) and has been reported to inhibit naïve T cell growth and differentiation by decreasing the CD28 costimulatory pathway leading to immunosuppression (Giles et al. 2018). Table 2 lists the clinical trials applying DEX.

The effects of DEX are concentration-dependent and are mediated by genomic and non-genomic mechanisms (Fig. 1). In the genomic mechanism, small lipophilic DEX molecules can diffuse easily to the cell membrane and enter the cytoplasm of the target cells. The molecules then bind to the glucocorticoid receptor in the cellular membrane to

Table 2 The use of dexamethasone in clinical trials

Participants	Dosage	Indication	Results	References
Children (over 16 weeks)	DEX 6.5 mg/m^2	First 5 weeks as part of the chemotherapy for acute lymphoblastic leukemia	DEX affected short-term growth and bone turnover.	Ahmed et al. (2002)
Three men and six women (aged $52 \pm 8{\cdot}4$ years)	DEX 0.1 mg/15 kg body weight	Adrenal insufficiency and treated with glucocorticoid replacements	DEX led to low serum ionized calcium levels without evidence of a compensatory increase in parathyroid hormone levels. Patients with adrenal insufficiency treated with DEX were associated with lower bone turnover.	Suliman et al. (2003)
Forty patients (23 males and 17 females, median age = 53.5 years)	DEX 40 mg/day	Multiple myeloma patients both at diagnosis and during the course of the disease	Combined DEX + thalidomide + zoledronic acid seemed to be highly effective in reducing bone resorption.	Tosi et al. (2006)
Thirty-five participants (23 males and 12 females, median age = 63 years)	DEX 40 mg/day	Refractory or relapsed myeloma	Combination of DEX and thalidomide improved abnormal bone remodeling.	Terpos et al. (2005)

produce a specific complex. This complex then moves to the nucleus and binds to several specific DNA sites, leading to stimulation and suppression of a wide range of gene transcription (Croxtall et al. 2000). On the other hand, a high DEX dose can bind to the glucocorticoid receptor on cell membrane-like T lymphocytes, which attenuates receptor signaling and a T lymphocyte-modulated immune system. (Zhong et al. 2020). Moreover, a larger amount of DEX also interacts with the movement of Ca^{2+} and Na^+ across the cell membrane, causing a rapid decrease in inflammation (Grzanka et al. 2011).

Dexamethasone in osteogenesis and bone formation

Mechanism of DEX in promoting osteogenesis

In recent decades, DEX has been used in the anti-inflammatory and immunosuppressive fields and in a broad application as a potential regulator of mesenchymal stem cells (MSCs) to differentiate into lineages of different types of cells and enhance cellular proliferation (Polimeni et al. 2010; Stefani et al. 2020; Zhang et al. 2021a, b). DEX has been used as a component of standard osteogenic media in vitro to promote the osteogenic differentiation of MSCs (Bruder et al. 1998a, b; Polimeni et al. 2010; Langenbach and Handschel 2013; Gardner et al. 2015; Hanna et al. 2018; Stefani et al. 2020; Zhang et al. 2021a, b). The treatment of MSCs with DEX improves the phenotypic markers of osteoblastic differentiation, including alkaline phosphatase (ALP), Osterix, Runx2, and Osteocalcin (OC), while promoting the production of the protein matrix and mineralization nodules (Chaudhary et al. 2004; Igarashi et al. 2004; Song et al. 2009; Zhang et al. 2021a, b).

The precise mechanism through which DEX enhances the differentiation of MSCs is not completely understood, but it is believed to be related to its modulation of various pathways and factors (Langenbach and Handschel 2013). DEX regulates the differentiation of MSCs into osteogenic cells via the Wnt/β-catenin signaling pathway (Zhou et al. 2008; Langenbach and Handschel 2013; Zhou et al. 2013; Kim et al. 2017). This pathway is a signal cascade that controls numerous cellular functions, including stem cell renewal, proliferation, differentiation, migration, apoptosis, genetic stability during embryonic development, and adult homeostasis (Clevers and Nusse 2012; Pai et al. 2017). In bone formation, the Wnt/β-catenin pathway is essential for maintaining the bone mass by modulating bone formation and resorption through osteoblasts and osteoclasts (Glass and Karsenty 2006). DEX induces mature osteoblasts to produce Wnt proteins, facilitating the release of β-catenin from the degradation complex and leading to cytoplasmic accumulation of β-catenin (Hardy et al. 2018). β-catenin is then translocated into the nucleus, where it binds with the T-cell factor/lymphoid enhancer factor (TCF/LEF-1), enhancing the expression of the target genes. In the cranial development model, Wnt affects β-catenin via two pathways: autocrine and paracrine routes. In the autocrine pathway, the presence of Wnt leads to the increased expression of Dickkopf Wnt signaling pathway inhibitor 2 (DKK2), which promotes osteoblast differentiation and mineralization while remodeling the collagen matrix around osteoblasts by osteoblasts-induced matrix metallopeptidase 14 (MMP-14). In
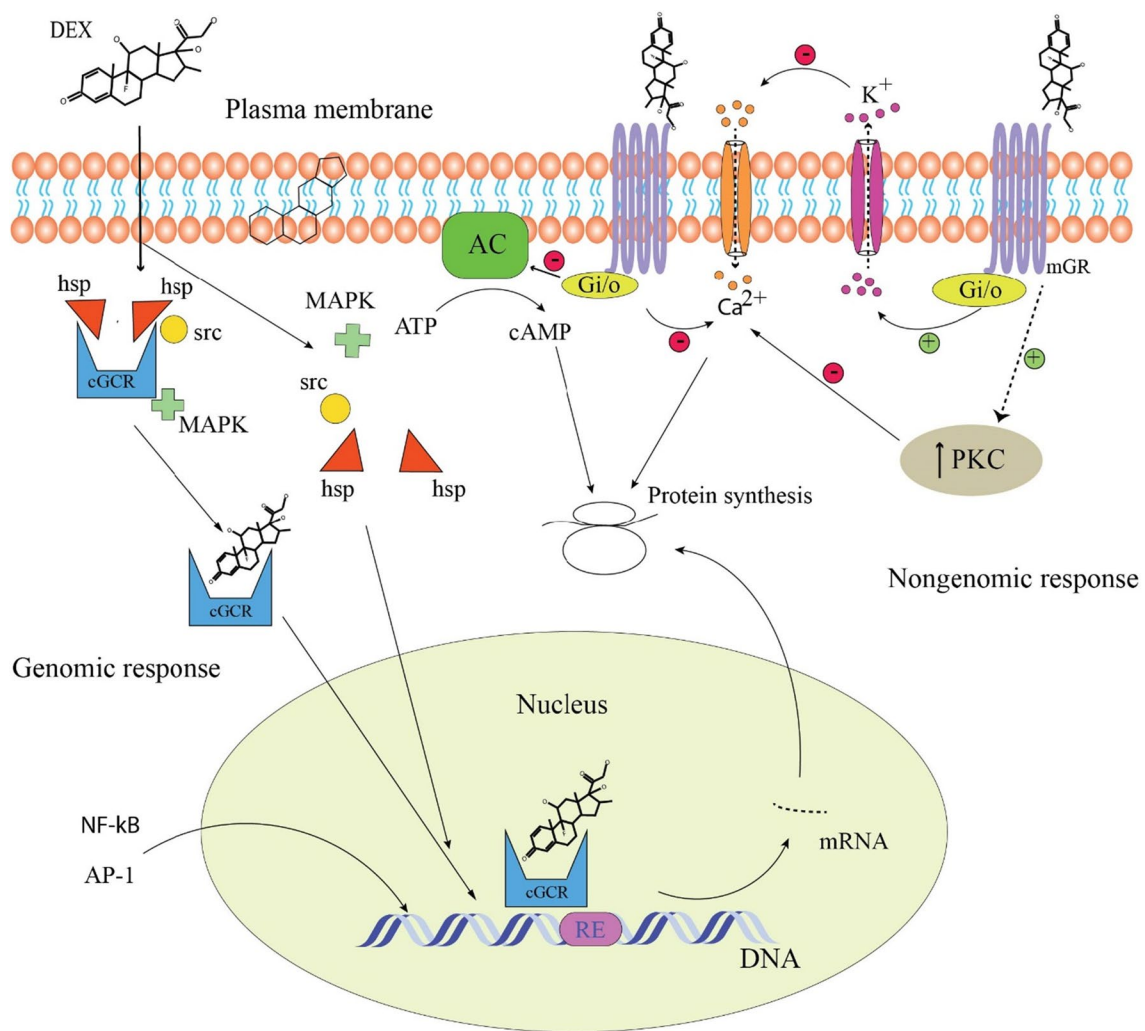
Fig. 1 Schematic illustration of conventional mechanisms of DEX via genomic actions and nongenomic pathways. In the genomic mechanism, DEX crosses the cytoplasmic membrane to bind with the cytosolic glucocorticoid receptor (cGCR), replacing associated proteins such as heat shock protein (hsp), kinase-like mitogen-activated protein kinase (MAPK) and co-chaperones like src. The GC-cGCR complex translocates into the nucleus where it regulates transcriptions. In contrast, nongenomic mechanisms involve membrane-bound or cytoplasmic receptors or nonspecific interaction with the cell membrane. *Gi/o* G protein; *AP-1* activating protein-1; *NF-κB* nuclear factor-κB; *mGR* membrane glucocorticoid receptor; *PKC* protein kinase C; *AC* adenylyl cyclase; *DNA* deoxyribonucleic acid

the paracrine pathway, Wnt increases Runx2 expression and decreases the expression of chondrogenic transcription factor Sox9 in MSCs, promoting the transformation of MSCs into osteogenic cells (Zhou et al. 2013). DEX enhances this process by inducing a transcriptional mechanism at the FHL2 promoter, which exhibits glucocorticoid receptor elements, resulting in the increased expression of osteoblast transcription agents such as ALP, Runx2, and collagen type I (Col I), as well as the extracellular matrix in vitro (Hamidouche et al. 2008). In the cytoplasm, FHL2 interacts with free β-catenin, enhancing the nuclear translocation of β-catenin and resulting in the transcription of Runx2 and osteogenic differentiation markers.

In addition to enhancing osteogenesis through the Wnt/β-catenin signaling pathway, DEX mediates Runx2 expression via the mitogen-activated protein kinase phosphatase (MKP-1)-phosphorylated Runx2 (Kim et al. 2017). Studies have shown that the combination of DEX and Runx2 has a synergistic effect on osteoblastic differentiation in Runx2-transduced rat primary dermal fibroblasts, enhancing the expression of osteogenic genes, such as ALP, bone sialoprotein (BSP), OC, and mineral markers. The effects of DEX on osteogenic differentiation are associated with the dephosphorylation of Runx2 phosphoserine on serine 125, significantly increasing osteogenesis. DEX upregulates MKP-1, dephosphorylating serine 125 (Phillips et al. 2006).

The role of DEX in promoting osteoinduction has been demonstrated through its interaction with bone morphogenic proteins (BMPs), which are members of the transforming growth factor-beta (TGF-β) family that play a vital role in MSC differentiation into osteogenic cells (Kamiya and Mishina 2011; Sheikh et al. 2015). Mikami et al. reported that DEX synergistically enhances ALP expression through JAK/STAT signaling when combined with BMP-2 in mouse C3H10T1/2 pluripotent stem cells (Mikami et al. 2010). Moreover, the combination of DEX and BMP-2 resulted in more than double the improvement in cell proliferation and bone formation compared to BMP-2 alone in two types of cells: bone marrow-derived stromal cells and muscle tissue-derived stromal cells (Yuasa et al. 2015). BMP-7 is a promising osteoinductive agent that facilitates the proliferation, differentiation, and maturation of MSCs to osteoblasts (Kloen et al. 2003). Figure 2 presents the mechanism of dexamethasone in bone regeneration.

Anti-inflammatory and immunosuppressive effects of DEX in promoting bone repair

Anti-inflammatory activity is one of the crucial processes during bone healing under normal conditions. In the initial phase of inflammation, blood proteins accumulate to form hematoma that recruits abundant participants, including the inflammatory cells and various cytokines that attract the migration of immune cells to the fracture sites. These cells secrete numerous inflammatory agents, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), leading to acute inflammation. This process aids in eliminating pathogens and gradually healing small bone defects. On the other hand, severe inflammation or critical bone defects hinder bone healing, leading to serious conditions (Oryan et al. 2015; Ghiasi et al. 2017; Bahney et al. 2019; Maruyama et al. 2020). DEX is a potential anti-inflammatory agent for treating acute, chronic inflammation, and autoimmune diseases (Phillips et al. 2006; Jiang et al. 2017). The anti-inflammatory effects of DEX occur in the early and late phases of inflammation by preventing initial
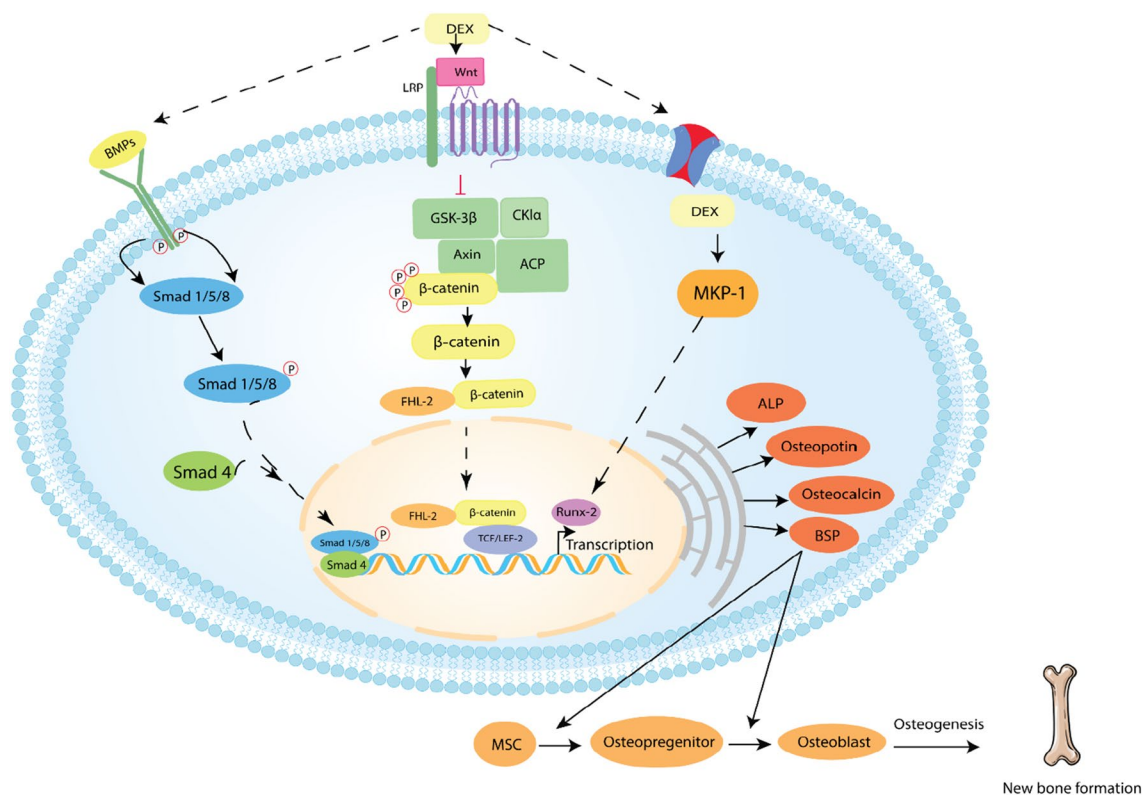
Fig. 2 Mechanism of dexamethasone in bone regeneration. Dexamethasone enhances the expression of FHL-2 by binding β-catenin to the glucocorticoid response element in the FHL-2 promoter, leading to the translocation of β-catenin to the nucleus, where it binds to T-cell factor/lymphoid enhancer factor-1 (TCF/LEF-1) and induces the transcription of Runx-2. Dexamethasone also regulates the expression of Runx-2 through mitogen-activated protein kinase phosphatase (MKP-1)-phosphorylated Runx2. The transcription of Runx-2 supports the expression of osteogenic genes such as alkaline phosphatase (ALP), osteopotin, osteocalcin, bone sialoprotein (BSP), and Osteorix. Additionally, dexamethasone enhances the effect of bone morphogenetic proteins (BMPs), which play a vital role in inducing cell proliferation and differentiation of mesenchymal stem cells (MSCs) into osteoblast cells

vasodilation and leukocyte accumulation at the inflammatory site, changing the cascades associated with vascular permeability, and reducing edema (Tsurufuji et al. 1984; Deutschman et al. 2011; Jiang et al. 2017). DEX also inhibits the migration of inflammatory cells, molecules adhesion, and the expression of pro-inflammatory cytokines in affected areas (Andrade et al. 2018).

DEX is also a promising agent that inhibits the immune responses that occur during bone healing processes by directing the development of T helper cells (Th0) towards Th2, causing T-cell apoptosis, prohibiting IL-1 and IL-2 synthesis, and reducing T cell proliferation and antigen presentation (Rook 1999). Along with its osteogenic activity, the anti-inflammatory and immunosuppressive properties of DEX have also been used in bone healing to achieve a synergistic effect (Vacanti et al. 2012; Chauhan et al. 2021).

Optimizing concentration of DEX in bone healing

Dexamethasone has a biphasic effect on bone homeostasis as shown in Fig. 3. Although it has an osteogenic function, high doses and prolonged use can lead to bone diseases such as osteoporosis, bone loss, and osteonecrosis (Canalis and Delany 2002; Zhou et al. 2013; Oryan et al. 2015; Hachemi et al. 2018; Hardy et al. 2018; Bordini et al. 2021). The negative impact of DEX on bone healing has been attributed to various factors such as attenuated osteoblasts proliferation (Shalhoub et al. 1995; Walsh et al. 2001), increased osteoblast apoptosis (Weinstein et al. 1998), reduced expression of osteogenic genes (Chang et al. 1998), inhibition of growth factors (Canalis and Delany 2002; Luppen et al. 2003) and collagen synthesis (Kim et al. 1999), and the transfer of MSCs from osteoblasts to adipocytes (Li et al. 2013). Furthermore, single or interrupted doses of DEX to human mesenchymal stem cells did not achieve the desired effects on bone formation as the continuous application (Zhang et al. 2021a, b). Therefore, optimizing the concentration and
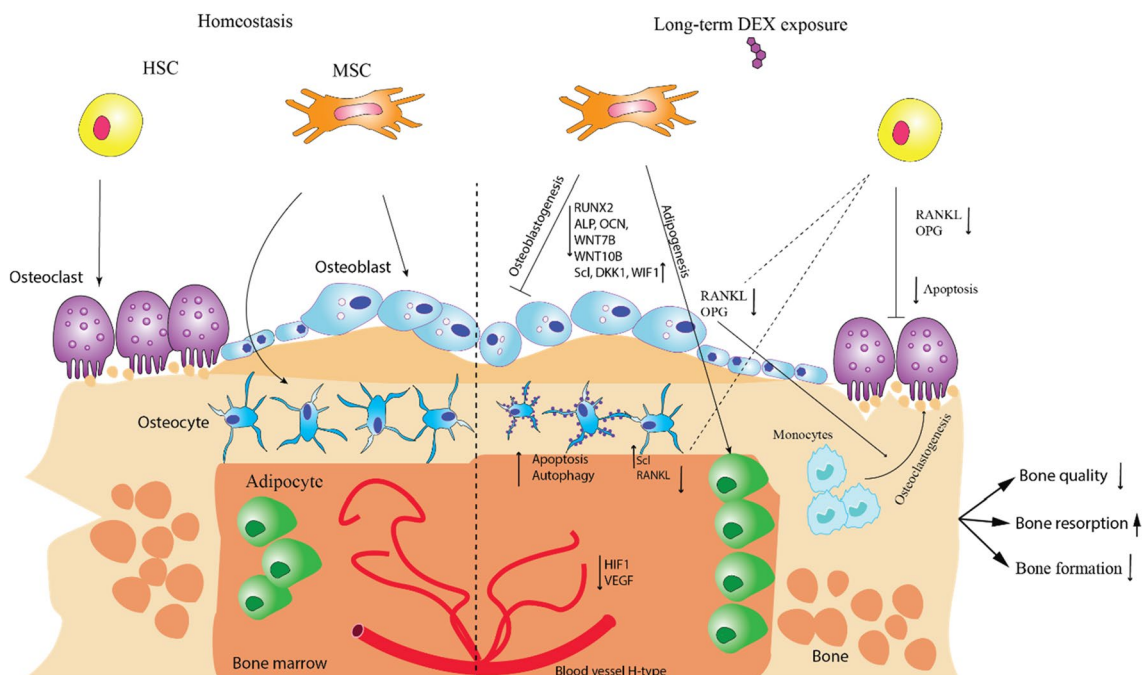
Fig. 3 The effect of long-term exposure to DEX on bone homeostasis. In normal homeostasis, the balance between osteoblastic and osteoclastic activity regulates bone remodeling. Hematopoietic stem cells (HSC) differentiate into osteoblasts through binding to receptor activator of NF-kB ligand (RANKL), while osteoclastogenesis is inhibited by osteoprotegerin (OPG). However, chronic DEX exposure leads to decreased osteoblastogenesis and increased adipogenic differentiation due to reduced expression of RUNX2, alkaline phosphatase (ALP), osteocalcin (OCN), WNT7B, WNT10B, and adipogenic markers such as peroxisome proliferator-activated receptor (PPAR). Additionally, DEX exposure reduces the production of RANKL by osteoblasts and osteocytes, which promotes osteoclastogenesis and increases bone resorption. Long-term DEX exposure also induces apoptosis and autophagy in osteoblasts and osteocytes, while down-regulating hypoxia-inducible factor 1-alpha and vascular endothelial growth factor (VEGF), leading to a reduction in nutrient and oxygen supply. Overall, long-term DEX exposure results in decreased bone formation and quality, with an increase in bone resorption

application time of DEX at local sites is crucial for bone fracture healing. Many studies have suggested that 10 nM is the concentration frequently used to differentiate human marrow stromal cells into osteogenic cells in vitro (Vilamitjana-Amedee et al. 1993; Beresford et al. 1994; Cheng et al. 1994, 1996; Jaiswal et al. 1997; Majors et al. 1997; Bruder et al. 1998a, b). A previous study examined the effect of various DEX concentrations (10 pM to 1 μM) on human osteoblast precursors (Walsh et al. 2001). The report showed that concentrations below 10 nM did not have a significant impact on the ALP levels. At the physiological concentration of 10 nM, DEX improved osteogenic differentiation and maturation. On the other hand, concentrations exceeding 100 nM were observed to inhibit cell growth, despite maintaining the osteogenesis and maturation of target cells.

Several studies have suggested different concentrations of DEX for bone regeneration. Tenenbaum et al. reported that 100 nM of DEX is the appropriate concentration for chick periosteum in vitro, showing the maximal ALP levels (Tenenbaum and Heerschi 1985; Oshina et al. 2007; Alm et al. 2012). Yamanouchi et al. reported that ALP activity increased in a concentration-dependent manner as the DEX concentrations were increased from 10 nM to 1000 nM (Yamanouchi et al. 1997). ALP, procollagen type I carboxy-terminal peptide, and osteocalcin expression were increased significantly at 100 nM of DEX. Furthermore, 100 nM of DEX also increased the expression of Runx2, OC, and Osterix, while inhibiting adipogenic differentiation in bone marrow stromal cells (Tenenbaum and Heerschi 1985; Nuttelman et al. 2006; Ghali et al. 2015). Previous studies have shown that both concentrations enhanced the ALP activity of human bone marrow stromal cells significantly after exposure for 3–4 weeks, reaching a maximum at days 7–14 (Cheng et al. 1996; Walsh et al. 2001; Hong et al. 2009; Seong et al. 2010).

On the other hand, DEX concentrations higher than 1000 nM induced adverse effects on bone healing (Cheng et al. 1996; Jaiswal et al. 1997; Kim et al. 2003; Costa et al. 2015; Li et al. 2018). Based on the above data, the optimal DEX concentration for inducing osteogenic differentiation ranged from 10 nM to 100 nM. The effects of DEX can vary according to the type of cells, animal models, or patients. Hence, further research is necessary to determine the suitable dose for osteogenesis.

DEX-incorporated drug delivery systems for osteogenesis

As mentioned earlier, the therapeutic efficacy of DEX depends on the dose and application period. Therefore, in drug delivery systems, it is important to maintain the appropriate DEX concentrations and control its release to achieve optimal therapeutic effects. As shown in Fig. 4, DEX-incorporated nanoparticles, microparticles, scaffolds, and hydrogels have attracted significant attention because they
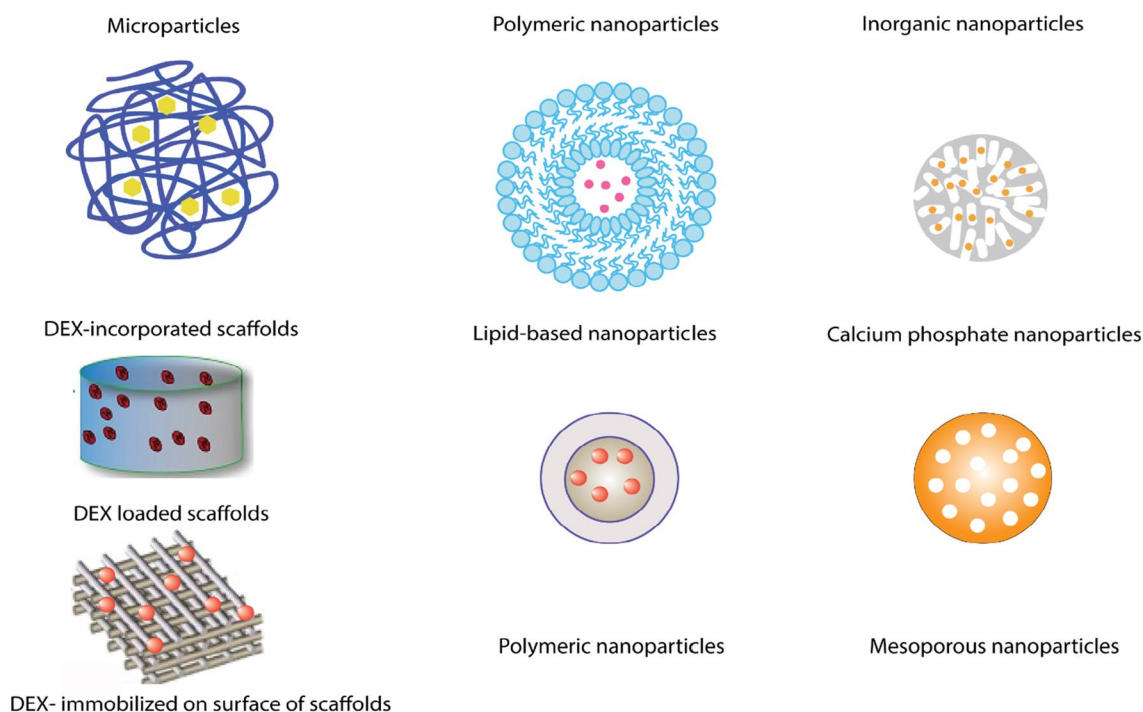
Fig. 4 Dexamethasone-incorporated drug delivery systems to enhance the osteogenesis and bone regeneration

trap DEX and control its release precisely at the bone fracture sites. This can result in enhanced bone formation and reduced DEX-related side effects, as summarized in Table 3.

DEX- loaded microparticles

Microparticles fabricated from natural or synthetic polymers offer many advantages because of their functional and structural properties. They can effectively entrap various cargos, including small drugs, proteins, and nucleic acids, enhancing the medical effects of drugs by improving their bioavailability, stability, and specificity. Drug-loaded microparticles can also protect against degradable agents, such as enzymes, prolong therapeutic effects, and improve the water solubility of poorly soluble drugs (Siepmann and Siepmann 2006; Lengyel et al. 2019). Therefore, the use of microparticles as a drug delivery vehicle for bone fracture healing has attracted interest, particularly for trapping DEX at local defects.

Poly(lactic-co-glycolic acid) (PLGA) is used widely to load DEX (Zolnik and Burgess 2008a, 2008b; Gu et al. 2015; Stefani et al. 2020). Investigations of DEX-loaded PLGA microspheres have shown that this complex can control drug release over 30 days and enhance osteoblastic differentiation markers, including Runx2, ALP, osteopontin (OPN), OC, collagen, BSP, and the extracellular matrix (ECM), in bone marrow-derived mesenchymal stem cells in vitro (Son et al. 2013). Dawes et al. suggested that DEX-loaded PLGA microspheres enhanced osteogenesis in human fetal osteoblasts by improving the ALP activity, particularly at 100 nM DEX, and mineralization, as well as augmenting cell proliferation (Dawes et al. 2012). However, burst release is a problem associated with DEX-PLGA microspheres.

Hickey et al. reported that the initial burst release of DEX-PLGA microspheres was over 30% on the first day, followed by sustained release over one month (Hickey et al. 2002). Many factors can affect the drug release kinetics of DEX-PLGA microspheres, such as the loading concentration of DEX, types of PLGA, molecular weight, and particle size (Yoon et al. 2003; Gu et al. 2015). Zolnik et al. reported that using different molecular weights of PLGA to fabricate DEX-PLGA microspheres resulted in a significant decrease in the initial burst phase with a high molecular weight (28 kDa) compared to low molecular weight (13 kDa), at approximately 20 and 30%, respectively, in vitro and in vivo (Zolnik and Burgess 2008a, 2008b;). Other studies also observed this trend (Bhardwaj et al. 2010). High concentrations of free DEX can affect the cell viability, impairing the osteogenic activity. Thus, well-controlled drug release and initial burst phase are essential for facilitating bone fracture remodeling.

Inorganic components, such as calcium carbonate ($CaCO_3$) and calcium phosphate, can be used to deliver DEX, in addition to polymeric materials (Balaguer et al. 2010; Zarkesh et al. 2017; Chudinova et al. 2021). Calcium carbonate particles are excellent carriers for bone mineralization and DEX delivery because they have favorable properties, such as biocompatibility, osteoconductivity, safety, and low cost (Chen et al. 2017a, b). Chudinova et al. designed a layer-by-layer polymer coating on the surface of DEX-loaded $CaCO_3$ to form microcapsules (Chudinova et al. 2021). This combination facilitated the control drug release seven days after deposition and improved the surface hydrophilicity of the titanium (Ti) implant without toxic effects on fibroblastic cells, which supported cell adhesion, proliferation, and differentiation. The osteoinductive effect of DEX in combination with hydroxyapatite (HA) was used through DEX-loaded hydroxyapatite particles and implanted in rat calvarial defects. After eight weeks of implantation, DEX-loaded HA particles displayed promising bone regeneration and osteointegration without any signs of inflammation, despite 90% of the DEX being released in the first 3 days (Tavakoli-Darestani et al. 2014).

Incorporating DEX microspheres into a polymeric or inorganic materials matrix, such as scaffolds or hydrogels, can decrease the initial burst phase of microspheres, provide a platform to achieve homogenous distribution, prolong drug release, and have synergistic effects on bone remodeling in some cases (Galeska et al. 2005; Son et al. 2011; Heo et al. 2019). The release profile of DEX-containing PLGA microspheres loaded with poly(vinyl alcohol) hydrogel showed an extended release of up to 28 days without an initial burst phase in both in vitro and rat models (Patil et al. 2004). PLGA microspheres loaded with hyaluronic acid prevented the rapid release of DEX in the early days and extended the release profile period for a longer time with an appropriate therapeutic dose for more than 1 month (Heo et al. 2019). However, most fabrication processes for microparticle carriers are complicated, involving several steps that limit the large-scale production of microparticles. Furthermore, substances, such as cross-linking agents and surfactants, which commonly participate in microparticle manufacturing processes, can reduce the material biocompatibility, resulting in a decrease in the therapeutic effect of DEX-loaded microparticles (Hossain et al. 2015; Zhang et al. 2021a, b). Therefore, developing a novel, simple, and highly biocompatible microparticle manufacturing methodology is essential for developing and applying DEX microparticles for bone fracture regeneration.

DEX-encapsulated nanoparticles

DEX-encapsulated polymeric nanoparticles

Polymeric nanoparticles loaded with DEX have attracted considerable attention in bone defect remodeling because

Table 3 Dexamethasone-loaded drug delivery systems in the bone tissue engineering field

Types of drug delivery systems	Type of cells in vitro test	Animal model	Results	References
DEX-loaded PLGA microspheres immobilized on the surface of Ti coated with hydroxyapatite by electrostatic interaction	Bone marrow mesenchymal stem cells		Sustained the DEX release over 30 days with 38% initial burst release in the first 2 days No toxicity to the cells, and enhanced the cell proliferation Increased the gene markers expression of osteoblast differentiation: ALP, BSP, OPN, ON, OC, COL I.	Son et al. (2013)
DEX-loaded PLGA microspheres	Simian Virus-immortalized Human Fetal Osteoblast (SV-HFO) cells		Sustained the release profile of DEX for up to 30 days No toxicity to the cells with the concentration of DEX ranging from 10 µg/mL to 250 µg/mL Enhanced the expression of ALP, and matrix mineralization	Dawes et al. (2012)
DEX-loaded hydroxyapatite (HA)		Drug delivery systems applied in rat calvarial defects	Sustained release DEX for 10 days with 90% of DOX release over 3 days More than 80% of bone regeneration in bone defect after 8 weeks of implantation	Tavakoli-Darestani et al. (2014)
DEX-loaded PLGA colloidal gel by electrostatic interparticle interactions		Rat cranial defects	Controlled release of DEX for 60 days Increased new bone formation in bone defects	Wang et al. (2010a, b)
Chitosan coated DEX loaded gelatin nanospheres	MC3T3-E1 cell		Controlled release of DEX over 28 days Up-regulation of Runx2, COL I, OCN, ALP, and mineralization Expressed the anti-inflammatory effects	Qi et al. (2018)
DEX-loaded biodegradable gelatin-based micelles	MC3T3-E1 cell Rat bone marrow mesenchymal stem cells	Rat ulna critical-sized defects	Sustained drug release study for 7 days Enhanced the expression of ALP The increase of bone regeneration in vivo	Santo et al. (2015)
DEX-loaded biphasic calcium phosphate nanoparticles/collagen scaffold combined with HUVEC cells	Human mesenchymal stem cells	Scaffolds were implanted in the subcutaneous dorsal of nude mice	Controlled release of DEX for up to 35 days without an initial burst release Improved the angiogenesis (VEGF), and osteogenesis-related genes (COL I, IBSP, BMP-2)	Chen et al. (2018a, b)

Table 3 (continued)

Types of drug delivery systems	Type of cells in vitro test	Animal model	Results	References
Mesoporous silica nanoparticles containing DEX-loaded poly(L-lactic acid)/poly(ε-caprolactone) nanofibrous scaffold	Rat bone marrow-derived mesenchymal stem cells	Rat calvarial defects	The constant release of DEX for 28 days with 40% of initial burst release on the first day. Increased the expression of ALP, mineralized matrix formation, and OCN. Significant promoted calvarial defect healing	Qiu et al. (2016)
Dual-delivery of DEX and BMP-2 in chitosan-coated mesoporous silica	Rat bone marrow-derived mesenchymal stem cells	Evaluation of ectopic formation in the thigh muscle pouches of mice	The release profile of DEX lasted 80 min. Increased ALP activity, mineralization as well as osteogenic marker gene Runx2, OPN, COL I, OCN in vitro. Significant increased ectopic bone formation in vivo	Gan et al. (2015)
DEX-loaded liposomes immobilized on the surface of polystyrene	Human bone mesenchymal stem cells		Sustained release of DEX for up to 20 days with more than 40% of initial burst release on the first day. No toxicity to the cells. Enhanced the cell proliferation and the expression of ALP, OCN, osterix, Runx2, OPN	Monteiro et al. (2015)
DEX-loaded multilayer poly-L-Lactic acid/Pluronic P123 composite electrospun nanofiber scaffolds	Human adipose tissue-derived mesenchymal stem cells		The combination of multilayer controlled the targeted drug release for 23 days. Enhanced cell attachment and proliferation. Increased the expression of ALP and mineralization	Birhanu et al. (2019)
DEX-loaded electrospun PLGA nanofibers	Human mesenchymal stem cells		Controlled the release profile of DEX for over 2 months. Increased cell proliferation, ALP, BSP, and calcium deposition	Nguyen et al. (2012)
DEX incorporated within electrospun scaffolds of PEOT/PBT	Human mesenchymal stem cells		The entrapment of DEX in scaffolds showed the sustained release of the drug over 28 days. Increased level of ALP, and mineralization matrix	Gaharwar et al. (2014)
DEX loaded on collagen/hydroxyapatite sponges	Bone marrow mesenchymal stem cells		Nontoxic to the cells. Enhanced cell proliferation. Improved the expression of ALP, COL I, and OCN	Kook et al. (2017)

Table 3 (continued)

Types of drug delivery systems	Type of cells in vitro test	Animal model	Results	References
DEX loaded aluminosilicate clay nanotubes to design an injectable multifunctional drug delivery system based on photo-cross-linkable gelatin methacryloyl hydrogel	Mesenchymal stem cells from human exfoliated deciduous teeth		Controlled drug release of DEX over 14 days; Nontoxic to the cells, Increased the expression of ALP, and calcium deposition in vitro; Enhanced total bone volume and new bone formation in vivo	Bordini et al. (2021)
Co-delivery of magnesium ions and pro-drug of DEX (dexamethasone phosphate) in hydrogels	Human mesenchymal stem cells	Rabbit femur defects	Sustained the drug release profile of Mg^{2+} and DEX for 15 days; Increased the osteogenesis in terms of up-regulation of ALP, COL I, Runx2, OCN, and mineralization activity in vitro; Significantly increased the new bone formation in rabbit femur defects	Zhang et al. (2018a, b)

they can enhance drug encapsulation, extend drug release, and improve safety and efficiency (Wang et al. 2012; van Rijt and Habibovik 2017). Various polymeric carriers, such as PLGA, gelatin, chitosan, or dendrimers, can entrap DEX. Colloidal gels prepared with PLGA nanoparticles loaded with DEX and different surfactants were applied to rat cranial bone defects. The results revealed the sustained release of DEX from the nanoparticles for up to 60 days without an initial burst release and facilitated an increase in new bone formation (Wang et al. 2010a, b). Gelatin, a natural polymer, is a polymer carrier for delivering cargo and a potential adhesive site for bone cells as the degradation products of gelatin mostly contain arginine-glycine-aspartic acid (RGD) sequences (Wang et al. 2020a, b). Qi et al. incorporated DEX and gelatin into chitosan-coated DEX-loaded gelatin nanoparticles to modify the surface of the Ti substrate and achieve dual effects (Qi et al. 2018).

This system prolonged the release of DEX for up to 28 days. Moreover, the slow release of DEX had an anti-inflammatory effect and augmented osteogenic differentiation by upregulating Runx2, Col1, OCN, ALP activity, and mineralization of MC3T3-E1 cells in vitro. DEX gelatin nanoparticles were also used as core–shell to form DEX micelles, and the sustained release of DEX lasted for more than seven days in physiological PBS. This system enhanced the expression of ALP activity and calcium deposition at seven and 14 days in vitro and significantly increased new bone formation and bone volume after 2–4 weeks of implantation at rat ulna defects (Santo et al. 2015).

DEX-entrapped inorganic nanoparticles

Inorganic nanoparticles, such as calcium phosphate (CaP) and silica, are used widely in synthesizing nanostructured materials for bone regeneration (Jeong et al. 2019; Eivazzadeh-Keihan et al. 2020).

Calcium phosphate, which is the primary component of human bone, comprises 70% of the calcium phosphate mineral. Calcium and phosphate ions modulate bone cell activation to enhance bone regeneration. Calcium phosphate also provides an excellent platform for cell adhesion and extracellular matrix (ECM) protein absorption (Fujii et al. 2006; Tsapikouni and Missirlis 2008). Chen et al. reported that CaP nanoparticles loaded with DEX prolonged the release of the drug for up to 22 days, with an initial burst phase of $40.5 \pm 3.9\%$ during the first 3 days (Chen et al. 2017a, b).In contrast, the controlled release of DEX from CaP nanoparticle-loaded porous collagen scaffolds (DEX-CaP-Col scaffold) was observed for up to 35 days without an initial burst release (Chen et al. 2018a, b). The study reported significant improvement in human MSCs in terms of cell viability, cell growth, ALP activity, mineralization, and the expression of Runx2, BSP, and BMP-2 in a time

and concentration-dependent manner (Chen et al. 2017a, b, 2018a, b). The in vivo implantation of the DEX-CaP-collagen scaffold revealed osteogenesis and clear cell infiltration, uniform cell distribution, and homogenous deposition of ECM throughout all implants (Chen et al. 2018a, b). Scaffolds were prepared with concave microgrooves to promote rapid angiogenesis and enhance the functionality of the DEX-CaP-collagen scaffold. Implantation of the DEX-CaP-collagen scaffold with microgrooves in rat subcutaneous tissue resulted in the formation of new blood vessels in the implants by week 4. The diameter of some blood vessels reached 220 μm at week 8, particularly in scaffolds containing microgrooves with concave widths of 290 μm and convex ridge widths of 352 ± 23 μm (Chen et al. 2018a, b).

In recent years, mesoporous silica nanoparticles (MSNs) have recently become popular for drug delivery therapies because of their biocompatibility, biodegradability, large pore size with a high surface area, stability, and the ability to protect encapsulated cargo from premature release and degradation (Jafari et al. 2019). MSNs have beneficial features in bone regeneration, where their porosity can impact calcium deposits, the spread and infiltration of bone cells, and the transport of nutrients and growth factors (Ravichandran et al. 2013). Previous studies reported the delivery of DEX in MSNs for bone defect remodeling (Andrée et al. 2019; Porgham Daryasari et al. 2019; Ghosh and Webster 2021). Qiu et al. reported the sustained release of DEX for approximately one month with a 40% initial burst release on the first day when DEX was loaded in MSNs combined with poly(L-lactic acid)/poly(ε-caprolactone) (PLLA/PCL) nanofibrous scaffolds (Qiu et al. 2016). Rapid initial release was observed in DEX-loaded MSNs combined with polycaprolactone-gelatin fibers, with 30% release within 24 h, followed by a slow release up to 28 days (El-Fiqi et al. 2015). However, the initial burst phase was prevented when loaded in chitosan-alginate-gelatin composite scaffolds (Zhou et al. 2020). DEX-containing mesoporous nanoparticles significantly enhanced the in vitro cell viability, cell proliferation, ALP activity, calcium deposition, and the expression of osteogenic-related genes. In addition, they increased new bone formation in rat models (El-Fiqi et al. 2015; Andrée et al. 2019; Wang et al. 2020a, b; Lei et al. 2021).

Furthermore, nanoparticles have the advantage of easy internalization and transportation into bone cells, facilitating effective internal bone formation. The internalized DEX-MSNs can be degraded directly in bone cells to release DEX at the target site, resulting in an increased osteoinductive effect and bioavailability of DEX (Gan et al. 2015). Zhou et al. synthesized co-loaded DEX and BMP-2 gene-bearing plasmid DNA in MSNs (DEX-pDNA-MSN). They modified the surface of the nanoparticles with polylysine-modified polyethyleneimine copolymer (PEI-PLL) and RGD (Zhou et al. 2019). This complex effectively bonded to the receptors of bone MSCs and controlled DEX release for up to 21 days without initial burst release. The presence of the BMP-2 gene increased the cellular uptake of DEX-pDNA-MSN into bone MSCs and enhanced the osteogenic differentiation effect of these cells, as evidenced by the upregulation of ALP, mineralization, Runx2, OC, and OPN after 21 days, along with the osteoinductive activity of DEX. Furthermore, bone MSCs transfected with DEX and BMP-2 gene-containing mesoporous nanoparticles coated with RGD and PEI-PLL expressed calcification and new bone formation after three weeks of incubation.

DEX-loaded lipid-based nanoparticles

Lipid-based nanoparticles are an excellent option for transporting DEX, which can be applied to osteogenic differentiation and bone formation owing to their various advantages including biocompatibility, high bioavailability, easy fabrication, self-assembly, encapsulation of abundant therapeutics, enhanced solubility of poorly aqueous soluble drugs, and reduced drug-related adverse effects (Fonseca-Santos et al. 2015; Sercombe et al. 2015). DEX-loaded liposome coated with polyethylene glycol (PEG) has been reported as a biological drug carrier facilitating cell viability, proliferation, protein synthesis, and differentiation of human bone MSCs (Monteiro et al. 2015). DEX-loaded liposomes showed no toxicity to the cells but enhanced differentiation and synthesized osteogenic-related genes, supporting bone formation. Furthermore, an antibacterial effect was observed when liposomes were incorporated with antibacterial agents, such as minocycline and graphene oxide. This liposome has also been used to modify the surface of biomedical devices, supporting bone healing (Xu et al. 2017; Ouyang et al. 2018; Barrera et al. 2021).

Despite the potential benefits of nanoparticles in bone regeneration, several challenges remain: a scarcity of effective preparation techniques, low stability in in vitro and in vivo environments owing to the high surface area when exposed to the physiological environment, and inefficient application processes. These limitations restrict the application of DEX-loaded nanoparticles for treating bone defects (Wang et al. 2012). Therefore, simple fabrication methods incorporated with suitable drug delivery designs should be investigated to achieve the highest effects of DEX nanoparticles.

DEX-incorporated scaffolds for bone regeneration

For several decades, scaffolds have been used extensively as a promising approach to facilitate the development of three-dimensional tissue, particularly in bone tissue engineering, owing to several advantages, such as high mechanical strength, the capacity to deliver a vast range of cargo,

including cells, growth factors, and biomolecules, to local defect sites, the provision of an appropriate platform for cell attachment, growth, and differentiation, and the capability to be integrated with various cell types to promote bone remodeling in vivo (Kim and Kim 2014; Polo-Corrales et al. 2014; Gao et al. 2017; Roseti et al. 2017; Donnaloja et al. 2020; Ravoor et al. 2021). Thus, integrating DEX and scaffolds is a promising drug delivery system for osteogenesis and bone formation.

DEX-loaded scaffolds

Various materials have been used to design scaffolds incorporating DEX for bone tissue engineering purposes. These materials include polymeric materials such as PLGA, PLA, PCL, chitosan, and inorganic materials such as calcium phosphate and hydroxyapatite, which are incorporated using different techniques (Duarte et al. 2009; Goimil et al. 2018; Ghorbani and Zamanian 2020). DEX can be embedded in scaffolds by mixing it directly with the material solutions during manufacture (Ghorbani and Zamanian 2020). Controlled drug release depends on the characteristics, components, and design of the scaffolds.

DEX-loaded scaffolds were reported to improve cell growth, mineralization of extracellular matrix, and osteogenic differentiation in vitro. Goimil et al. reported that the release of DEX in chitosan scaffolds using supercritical fluid technology lasted only approximately 2 h, with approximately 100% DEX released after 90 min (Duarte et al. 2009). However, other studies have shown prolonged drug release, with or without an initial burst release (Vacanti et al. 2012; Goimil et al. 2018; Birhanu et al. 2019).

Gaharwar et al. reported that the entrapment of DEX in bead-like depots of copolymers of poly(ethylene oxide) terephthalate and poly(butylene terephthalate) (PEOT/PBT) in an amphiphilic fibrillar scaffold resulted in the sustained the release of DEX that enhanced the osteoinductive functions and bone regeneration (Gaharwar et al. 2014). The DEX-loaded scaffolds lasted for 28 days with a 20% initial burst phase on the 1st day, enhancing cell adhesion, proliferation, and osteogenic differentiation in a time and concentration-dependent manner.

Despite the several advantages of using synthetic polymers for scaffold fabrication in bone remodeling, there is a significant limitation in the lack of sites available for cell adhesion. This challenge can be addressed by incorporating natural polymers such as collagen, gelatin, chitosan, and alginate, which possess desirable properties such as good biocompatibility, high immunology, a similar structure to extracellular matrix (ECM) with self-degradable moieties, and high chemical versatility for delivering DEX and enhancing osteogenic differentiation (Alaribe et al. 2016; Bhatia 2016; Filippi et al. 2020).

Kook et al. reported that DEX-loaded collagen derived from duck's feet and hydroxyapatite induced the migration, proliferation, and osteogenic differentiation of mesenchymal stem cells (MSCs) after a 14-day culture period (Kook et al. 2017). Similarly, the use of DEX-loaded cellulose acetate (CA), a polysaccharide-based polymer, demonstrated prolonged and sustained release of DEX for up to 180 days, with an initial burst release of 11.6% within 24 h. Furthermore, the scaffolds exhibited enhanced cell proliferation and adhesion (Tsiapla et al. 2018).

Hydrogel materials offer a promising avenue for delivering DEX owing to their structural and compositional similarity to the extracellular matrix (ECM). Their flexibility allows for integration with surrounding tissues and their hydrophilicity, which minimizes potential immune responses. The porous structure of hydrogels allows for easy diffusion of oxygen, nutrients, and other bioactive agents, thereby supporting cell migration, adhesion, differentiation, and behavior (Gao et al. 2013; Basu et al. 2018; Panek et al. 2019). Bordini et al. developed an injectable drug delivery system for bone regeneration by fabricating DEX-loaded aluminosilicate clay nanotubes in a photo-cross-linkable gelatin methacryloyl (GelMA) hydrogel (Bordini et al. 2021). The study showed that incorporating DEX-loaded nanotubes in the hydrogel improved the mechanical properties of the GelMA without compromising the degradation and swelling ratio. Furthermore, the released DEX from hydrogels showed high cytocompatibility with MSCs and enhanced bone formation in rat calvarial defects after six weeks of implantation under inflammatory conditions. Basu et al. reported a similar effect of the combination of DEX and silicate, where a two-step gelation method of DNA backbone and silicate nanodisk formed injectable hydrogels that entrapped DEX and improved osteogenic differentiation in vitro of human MSCs and new bone formation in rat cranial defects (Basu et al. 2018).

However, the intrinsic permeability and limited network interaction of hydrogels with the hydrophobic characteristics of DEX can lead to aggregation, precipitation, or uneven distribution of the drug in hydrogels, resulting in a significant impact on the drug release kinetics, mechanical properties, and stability of hydrogels (Zhang et al. 2018a, b; Chauhan et al. 2021). Various approaches have been applied to overcome these drawbacks, such as prodrugs, hydrolytic linkages, and reversible Diels-Alder conjugation (Wang et al. 2007; Koehler et al. 2013). For example, DEX phosphate, a prodrug, has been loaded in a nanocomposite hydrogel network via phosphate-Mg^{2+} interactions. These interactions were reported to enhance the stability of DEX phosphate in hydrogels until it was exposed to ALP released from MSCs under the effects of Mg^{2+}. The presence of ALP facilitated the hydrolysis of DEX-phosphate, leading to the release of DEX from hydrogels and supporting the osteogenic

differentiation of MSCs (Zhang et al. 2018a, b). Chauhan et al. reported the modification of DEX with 8-arm-PEG hydrazine via hydrazone linkages, which provided a great controlled/sustained release of DEX over 28 days, as well as enhancing the anti-inflammatory and osteogenic effect of murine osteoblast precursor cells (Chauhan et al. 2021).

Surface modification of scaffolds with DEX

The modification of biomaterial surfaces is a critical factor for successful implantation in bone remodeling because it can inhibit biofilm formation, reduce inflammation, and enhance osseointegration (Bazaka et al. 2012; Zhou et al. 2016; Holban et al. 2021). Previous studies reported that the local release of DEX immobilized on scaffold surfaces could facilitate bone healing (Kim et al. 2012; Barrera et al. 2021). DEX can be conjugated directly with scaffolds or linked via an intermediate substance. Chiang et al. immobilized DEX on the surface of a chitosan film using a nucleophilic addition reaction between the amino groups of chitosan and carbonyl groups of DEX (Chiang et al. 2012). The scaffold-conjugated DEX showed signs of osteogenic differentiation of human adipose-derived mesenchymal stem cells, considerably enhancing ALP activity. β-cyclodextrin is one of the linkers used to conjugate osteoinductive drugs with scaffolds. Incorporating DEX with β-cyclodextrin improves the function of DEX in promoting the expression of osteogenic genes and bone formation (Li et al. 2021). Zhang et al. reported that co-immobilizing DEX incorporated with hydroxypropyl β-cyclodextrin, a derivative of β-cyclodextrin, and stromal cell-derived factor-1 (SDF-1) augments the recruitment of cells and osteoinductivity of the hydroxyapatite scaffold (Zhang et al. 2018a, b). In this study, the presence of hydroxypropyl β-cyclodextrin effectively controlled the release of DEX for up to 40 days. The composite scaffolds showed promising osteogenic differentiation of MSCs in vitro and new bone formation in the dorsal muscles of dogs in vivo.

The immobilization of DEX on the scaffold surfaces can be achieved by coating a DEX-containing drug delivery system using various mechanisms, such as electrostatic or chemical interactions (Son et al. 2011; Monteiro et al. 2014). Liposome-loaded DEX was conjugated to the surface of polycaprolactone nanofibers via maleimide reaction and exhibited sustained release of DEX for up to 21 days without cytotoxicity. Moreover, it effectively enhanced the osteogenic differentiation of bone mesenchymal stem cells in vitro (Monteiro et al. 2014). Kim et al. developed a surface modification method for hydroxyapatite scaffold using DEX-loaded PLGA microspheres via electrostatic interaction facilitated by the positive charge of polyethyleneimine and negative charge of the hydroxyapatite scaffold (Kim et al. 2012). The modified scaffolds revealed the sustained

release of DEX with a therapeutic dose for bone regeneration. However, the stability of drug delivery therapies containing a DEX coating on the scaffold surface needs to be evaluated carefully in vivo and clinically to achieve greater efficiency.

DEX-incorporated implants for improving bone regeneration

Implantable medical devices have become essential in various clinical applications, including dental implants, orthopedics, cardiovascular treatments, neurology, and joint and hip replacements (Cobelli et al. 2011; Zhu et al. 2021a, b). Important factors, such as biocompatibility, surface properties, mechanical characteristics, and chemical properties, must be considered when fabricating implants to ensure successful implantation. The compatibility of implants with the biomechanical properties of bone and surrounding tissues, along with their integrity throughout the required duration, influences the likelihood of successful implantation (Kim et al. 2020). However, deficiencies in any of these factors can lead to implant failure in clinical settings (Bosshardt et al. 2017; Wu et al. 2021). Therefore, the modification of implant surfaces with osteoinductive factors such as DEX can enhance the bone healing process.

One study utilized a layer-by-layer approach, incorporating DEX, gelatin, and chondroitin sulfate (CS) on the surface of a metal device through 3D printing and cross-linking with glutaraldehyde. This approach improved the surface roughness of metallic implants and prolonged the release profile of DEX for up to 4 days (Poudel et al. 2020). The sustained release of DEX showed promising results in preventing the inflammatory cascade following surgery and improving bone fracture healing. Another study achieved similar results by developing a multilayer bioactive coating of DEX and carboxymethyl cellulose (CMC) on the surface of stainless steel implants. The DEX release profile was extended up to four days, promoting increased collagen type I and osteocalcin (osteogenesis markers) levels during 14 and 21 days of culturing with mesenchymal stem cells (Rožanc et al. 2021).

In another approach, the sustained release of DEX over 30 days was achieved by coating silk fibroin-dexamethasone@zeolitic imidazolate framework-8 on titanium implants (Ran et al. 2018). This strategy showed good cytocompatibility with MC3T3-E1 cells and enhanced cell differentiation, calcium deposition, and expression of osteogenic genes, such as Runx2, osteopontin, and osteocalcin in vitro. In addition, integrating nanoscale graphene (RGO) and DEX coating on the surface of titanium implants significantly increased the regenerated bone area. After 8 weeks of transplantation in a rat model, the DEX-RGO-titanium group showed a regenerated bone area of 93.38% compared

to 68.72% in the non-DEX-RGO-titanium group (Jung et al. 2016).

These designs incorporating DEX with other osteogenic factors immobilized on the implant surface exhibit promising effects on the bone healing process. Nevertheless, it is essential to achieve a sustained release profile of DEX with an appropriate concentration for the required duration, ensure the stability of drug delivery systems containing DEX on the implant surface, and evaluate the biocompatibility of materials required through in vivo and clinical trials to achieve better clinical outcomes.

Conclusion

The treatment of critical bone defects with rapid and effective regeneration remains a major challenge in bone remodeling. DEX, a glucocorticoid small molecule, has attracted significant research attention because of its osteoinductive, anti-inflammatory, and immunosuppressive properties. However, long-term systemic administration of DEX can lead to adverse effects, such as cytotoxicity to cells, bone loss, and osteoporosis. Therefore, researchers have designed various novel drug delivery systems to locally deliver and control the release of DEX at bone defects, inhibiting DEX-related side effects, improving bioavailability, and increasing osteogenic functions. In addition to its osteoinductive activity, its anti-inflammatory and immunosuppressive properties prevent biofilm formation at the early post-implantation stages and inhibit the host immune response at the local injury site. The local prolonged release of DEX can enhance Runx2 expression through various signaling pathways, such as the Wnt/β-catenin pathway, MKP-1 phosphorylation, TAK1 phosphorylation, or interaction with BMP-2. In vitro and in vivo experiments have confirmed the potential of DEX in bone regeneration by improving the ALP levels, Col1, Runx2, OC, OPN, BSP, and new bone formation. The local delivery of DEX is dose-dependent, with an optimal dose of 10–100 nM for promoting the osteogenic differentiation of MSCs. On the other hand, concentrations exceeding 1000 nM exhibit cytotoxicity to cells. Therefore, adequate drug delivery therapy, appropriate materials, and design methodology are necessary to maintain the local therapeutic effect of DEX. Several studies reported that combining DEX with nanoparticles, microparticles, or scaffolds enhances osteogenic differentiation in vitro and bone defect remodeling in vivo.

Despite the remarkable advances in developing DEX-incorporated drug delivery therapies for bone regeneration, several theoretical and technical challenges need to be addressed. The detailed mechanisms through which DEX induces bone regeneration remain unclear. Hence, further studies will be needed to elucidate the precise molecular pathways of DEX in bone healing, which will enhance its application in bone tissue engineering. Moreover, the bone-promoting ability of DEX is concentration-dependent and should be evaluated within the optimal ranges based on different cell lines and site defects to support clinical utilization.

The release kinetics of DEX from different drug delivery systems have been evaluated using phosphate buffers as the release medium, which does not fully represent the interaction between materials and the microenvironment of the body. Therefore, additional investigations will be needed to evaluate the drug release kinetics in a simulated body fluid environment in vitro or estimate the release kinetics of DEX in an in vivo environment. The initial burst release is one of the factors that affect cell viability. Therefore, the optimal release profile should be controlled in parallel with the osteogenesis process using novel and smart biomaterials and an ideally designed process. Overall, suitable biomaterials and innovative fabrication methods are needed to release the appropriate concentrations of DEX at bone defects and enhance bone formation.

Declarations

Conflict of interest All authors (T.P. Mai, J.-B. Park, H.D. Nguyen, K.A. Min, and C. Moon) declare that there are no conflicts of interest.

Research involving human and animal participants This article does not contain any studies with human and animal subjects performed by any of the authors.

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