Proceedings of the Indian National Science Academy (2026) 92:63–69
https://doi.org/10.1007/s43538-025-00400-7

REVIEW ARTICLE

BMP modulation of osteogenesis: molecular interactions and clinical applications

Akshit Sen[1] · Rayed Qamar[1] · Raghvendra Choubisa[1] · Mit Parikh[1] · Dhairya Shah[1]

Received: 10 July 2024 / Accepted: 10 February 2025 / Published online: 26 February 2025

Abstract
Bone fractures pose a substantial medical burden in the population. Despite advancements in surgical techniques, internal fixation methods, and our comprehension of biologics, fracture healing experiences delays or impairment in as much as 4% of all fractures. Complications arising from impaired fracture healing pose therapeutic challenges for orthopedic surgeons and frequently result in chronic functional and psychological disabilities for patients. Consequently, there is a clinical imperative to enhance mechanical fixation with biologic strategies to expedite the process of osteogenesis. The identification of bone morphogenetic protein (BMP) has been a crucial milestone in comprehending the biology of fracture healing, sparking intensive clinical research as an adjunct to fracture treatment. Numerous in vitro and in vivo studies in animals have shed light on the intricate biologic interactions between BMPs and cellular receptors. These studies have compellingly demonstrated that recombinant human BMP-2 (rhBMP-2) stands out as a safe and effective treatment option for augmenting bone healing. Human clinical trials have yielded valuable insights into the optimal dosage, time course, carriers, and effectiveness of BMP-2 in the healing of tibial defects. The encouraging outcomes from these trials inspire optimism that a new frontier in biologic technology has emerged, offering a promising adjunct for the treatment of skeletal injuries and conditions. These advancements signify a potential paradigm shift in the approach to managing fractures and underscore the potential transformative impact of biologic interventions in the realm of skeletal health.

Keywords Bone morphogenic protiens · Fracture healing · Orthopaedic surgery

Introduction

Bone stands out as one of the rare tissues in the adult human body with the remarkable capacity for spontaneous repair, regeneration, and functional restoration following a fracture. In 2019, there were globally 178 million new fractures (a 33.4% increase since 1990), 455 million prevalent cases of acute or long-term symptoms of a fracture (a 70.1% increase since 1990), and 25.8 million YLDs (a 65.3% increase since 1990) (GBD 2019). StoneKL et al. 2003 found that a 1 standard deviation (SD) decrease in total hip bone mineral density (BMD) was associated with a hazard ratio of 2.22 (95% CI 2.0–2.47) for hip fracture, 1.88 (1.42–2.48) for lower leg fracture, and 2.49 (1.85–3.35) for patella fracture.

✉ Rayed Qamar
rayedqmr@gmail.com

[1] Department of Orthopaedics, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India

Methodology

This study comprehensively reviewed the literature regarding the use of Bone Morphogenetic Proteins (BMPs) in orthopedic surgery, focusing primarily on their role in fracture healing. The methodology produced reliable results through the following systematic approach:

1. **Literature Search Strategy:**
    - o A structured search of the PubMed database was performed using the keywords "BMP" and "bone morphogenetic protein." This search was limited to studies published from 2013 to the present to ensure the relevance and currency of the data.
2. **Inclusion and Exclusion Criteria:**
    - o Included studies were those that specifically involved the application of BMPs in orthopedic settings. This encompassed clinical trials, cohort studies, case reports, and other relevant research articles

documenting the use and outcomes of BMPs in fracture healing.
- Studies not primarily focused on BMPs or lacking adequate detail on BMP application in fractures were systematically excluded from further analysis.

3. **Data Extraction:**
   - Key data from the included studies were meticulously extracted. This included the type of BMP used, methodology employed (in vitro vs. in vivo), sample size, patient demographics, treatment protocols, reported outcomes (including rates of union, complications, and functional recovery), and any comparative results against control groups or traditional treatments.
4. **Analysis of BMP Physiology:**
   - An essential component of the review involved exploring the physiological roles of BMPs, particularly those recognized for their osteogenic potential. Emphasis was placed on understanding how BMPs initiate and enhance the fracture healing process, including the molecular pathways involved and their interactions with mesenchymal stem cells (MSCs).
5. **Evaluation of Animal Trials and Clinical Trials:**
   - The study included analyses of various preclinical animal models that assessed the efficacy of recombinant human BMP-2 (rhBMP-2) and its influence on fracture healing. Results from notable trials in rabbits, rats, and primates were reviewed for understanding the translational potential of BMPs.
   - Additionally, human clinical trial data was examined focusing on efficacy, safety profiles, optimal dosages, and the type of carriers used for BMP delivery. The comparative effectiveness of BMPs versus traditional grafting methods was also reviewed.
6. **Assessment of Complications and Cost-Effectiveness:**
   - Reported complications associated with BMP treatments were analyzed, synthesizing data on the frequency and severity of adverse effects in relation to clinical outcomes.
   - Furthermore, a brief cost-analysis of BMP utilization was performed to evaluate the economic implications of using BMPs in treating various bone fractures compared to conventional methods.
7. **Synthesis of Findings:**
   - All findings from the literature were synthesized to provide a holistic view of the current understanding of BMPs, encapsulating the biochemical mechanisms, clinical efficacy, associated risks, and overall impact on fracture healing practices.

This methodological framework allowed for a robust analysis of the use of BMPs in bone healing, providing insights that are both clinically significant and relevant to ongoing research in orthopedic intervention strategies.

Fracture repair

Bone is a distinctive organ characterized by continuous remodeling and the remarkable ability to regenerate throughout adult life (Cauley 2017). This perpetual capacity for renewal sets bone apart, highlighting its dynamic nature and the ongoing processes that contribute to its structural integrity and function even in adulthood. The fracture of a bone sets off a series of cascading events, involving the activation of the complement cascade and triggering an inflammatory response coupled with vascular injury. This cascade leads to the extravasation of cells and intricate signaling processes (Cheng et al. 2003). Approximately 3 days post-fracture, a repair blastema forms, comprising new blood vessels, macrophages, and collagen (Gautschi et al. 2007). Growth factors selectively bind to collagen, creating a substrate for optimal interaction between TGF-β, β-FGF, PDGF, BMPs, and receptor cells. Osteoprogenitor cells in the periosteum and endosteum of fractured bone attach to granulation tissue, differentiating into chondrocytes and osteoblasts via cell signaling. Cellular transduction and enhanced cellular-growth factor interaction collectively contribute to bone regeneration through osteoblastic and osteoclastic activity, ensuring fracture healing within 6–8 weeks after injury (Gautschi et al. 2007). Degradation products from the extracellular matrix stimulate macrophage differentiation into osteoclasts, providing additional cells for ongoing fracture healing (Hollinger and Wong 1996).

The final bone healing and regeneration pathway depend on the interaction between BMPs/growth factors and various cell lines at the injury site (Schmitt et al. 1999). Adequate quantities of biologically active BMPs and competent cells interact to effectively regenerate bone (Hollinger and Wong 1996).

BMP physiology

Bone morphogenetic proteins (BMPs) belong to the transforming growth factor-beta (TGF-β) superfamily, serving as growth and differentiation factors. During embryogenesis, they provide essential morphogenetic signals for skeletal development and play a crucial role in adult fracture healing by orchestrating a series of cellular events akin to embryonic

bone formation. Identified based on structural similarity, over 30 BMPs have been recognized, with some suggesting roles extending beyond bone-related functions (Reddi 1994; Vukicevic et al. 1995; Vukicevic and Sampath 2008).

The bone-inducing BMPs are categorized into distinct subgroups according to the homology of their amino acid sequences: BMP2/BMP4, BMP5/BMP6/BMP7, BMP9/BMP10, and BMP12/BMP13/BMP14. It's noteworthy that some BMPs don't exhibit proven osteogenic properties (Vukicevic and Sampath 2008).

In a groundbreaking development in 1965, Marshall Urist demonstrated that demineralized bone possesses the capacity to induce new bone formation when implanted at ectopic sites. This phenomenon was aptly described as "bone formation by autoinduction" (Grgurevic et al. 2016; Urist 1965). BMPs exhibit greater efficacy in the presence of abundant pluripotential cells. In cases of bone injuries, skeletal progenitor cells emerge from various tissue compartments, such as the injured periosteum, endosteum, vascular tissue, and surrounding musculature, collectively participating in skeletal healing (Grgurevic et al. 2017). Notably, periosteal bone and the microenvironment outside the bone medullary cavity both lack osteoclasts. Consequently, when a BMP is introduced on a suitable carrier, osteoblast precursor cells are uncoupled and collaborate to form bone (Vukicevic and Sampath 2017). Presently, the effects of BMPs are elucidated following local implantation. Studies indicate that elevated levels of circulating BMP9 appear to be linked with accelerated fracture healing, although the results did not reach statistical significance (Vukicevic et al. 2014).

Role of BMP in fracture repair

Bone fracture healing is a complex and dynamic regenerative process designed to restore the damaged bone to its pre-injury state, including its cellular composition. Stages consists the following – 1. Hematoma Formation 2. Granulation tissue formation 3. Callus Formation and 4. Remodelling (Baardewijk et al. 2013).BMP signalling pathways has been identified in intramembranous as well as endochondral ossification(Einhorn and Gerstenfeld 2015).Granulation stage is characterised by recruitment of mesenchymal stem cells(MSC) and successive chondrogenesis resulting in callus formation(Reddi and Cunningham 1993). BMPs play a crucial role in promoting the differentiation of mesenchymal stem cells (MSCs) into chondroblasts and osteoblasts. Mouse fracture healing studies revealed that BMP2 initiates the repair cascade, with its mRNA expression peaking 24 h after bone injury (Dimitriou et al. 2005). In experiments involving the differentiation of mouse MSCs, BMP2 was found to regulate the expression of several other BMPs, playing a vital role in the successful differentiation of MSCs into osteoblasts (Cho et al. 2002).

During the osteogenic stage of bone repair, BMP3, BMP4, BMP7, and BMP8 are expressed, coinciding with the resorption of calcified cartilage, osteoblastic recruitment, and bone formation. BMP5 and BMP6, on the other hand, are constitutively expressed from days three to 21 during fracture healing in mice, suggesting their active involvement in both intramembranous and endochondral ossification. While BMP8 exhibits high osteogenic potential, BMP2, BMP6, and BMP9 emerge as the most potent inducers of MSC differentiation into osteoblasts. Other BMPs primarily stimulate the maturation of osteoblasts (Edgar et al. 2007).

In the later stages of healing, with adequate angiogenesis, cartilage tissue is replaced by woven bone, undergoing remodeling to enhance the normal function of the healed bone.

Animal trials

In various preclinical studies, a single percutaneous injection of recombinant human BMP-2 (rhBMP-2) in a calcium phosphate paste (alpha bone substitute material [α-BSM]) has demonstrated accelerated healing at osteotomy sites in rabbit ulnar, canine tibial, and primate fibular osteotomy models (Cheng et al. 2003; Finkemeier 2002). Seeherman et al. (Seeherman et al. 2006) conducted a study showing that a single percutaneous administration of 1.5 mg/mL rhBMP-2/calcium phosphate matrix increased the callus area at primate fibular osteotomy sites and accelerated radiographic evidence of healing up to 2 weeks after injury. Notably, a 1-week delay in rhBMP-2 treatment resulted in accelerated healing through direct bone formation. The study observed an increase in the number of Cbfa-1 positive cells at the osteotomy site following rhBMP-2 treatment. Cbfa-1 is a transcription factor that, in collaboration with Osterix (OSX), regulates osteoblast-specific genes crucial for osteoblast differentiation and bone formation. Based on these results, Seeherman et al. (2006a) concluded that an injectable form of rhBMP-2/α-BSM has the potential to be administered up to 2 weeks after fracture injury, thereby accelerating the healing of closed fractures in humans.

Bouxsein et al. (Bouxsein, et al. 2001) conducted a study to investigate the impact of rhBMP-2 on fracture healing in a rabbit ulnar osteotomy model. Seventy-two rabbits underwent mid-ulnar osteotomies and were allocated to three treatment groups: (1) rhBMP-2/absorbable collagen sponge (ACS), (2) absorbable collagen sponge, (3) placebo. The retention of rhBMP-2 at the osteotomy site was assessed using imaging of 125 I-labeled rhBMP-2. The results demonstrated that osteotomy sites treated with rhBMP-2 healed 33% faster than the other two groups. At each analyzed time point (3, 4, 6 weeks), enhanced healing in the rhBMP-2 treated group exhibited a more rapid progression with increased callus formation and advanced callus maturation.

The authors concluded that the presence of larger and more mature callus in the rhBMP-2 treatment group was in line with the observed enhanced biomechanical properties of the ulna treated with rhBMP-2.

In a rat femur fracture model, Lee et al. (Lee et al. 2002) introduced a 2 cm defect filled with rhBMP-2/ACS allograft. The authors reported 75% new bone incorporation into the allograft at 4 weeks and 100% at 8 weeks. Einhorn et al. (Einhorn et al. 2003) employed a femur fracture model in 144 rats to investigate the effects of a single percutaneous injection of rhBMP-2 on fracture healing. The three treatment groups comprised a control group, a buffer vehicle group, and an rhBMP-2/buffer group. Torsional biomechanical testing revealed that the stiffness of the rhBMP-2 treated group was twice that of the two control groups at the 2-, 3-, and 4-week time points. At 4 weeks, the strength of the rhBMP-2 treated fractures was 77% greater than that of the other groups. By 4 weeks, remodeling of the hard callus and recorticalization were observed in the rhBMP-2 treated fracture sites, while cartilage and/or soft tissue were still present in the control fracture sites.

BMP in clinical trials

Following FDA approval for specific indications in 2002 and 2004, the safety and efficacy of BMP2 and 7 have undergone extensive investigation in randomized, blinded, and controlled trials (RCT) (Fu et al. 2013; Simmonds et al. 2013).

RhBMP2 received approval for the treatment of open tibial fractures after a large RCT involving 450 patients with different fracture types according to Gustilo-Anderson classification (Govender et al. 2002). Over a 1-year follow-up period, BMP2 at a higher dose (1.5 mg/mL) improved bone healing and reduced the number of secondary interventions compared to patients treated with the standard of care. A major drawback of this study was the lack of blinding for surgeons treating patients receiving rhBMP2. In another RCT, the efficacy of rhBMP7 in tibial non-unions was tested in 124 patients who received autologous bone graft or a device containing rhBMP7 (Friedlaender et al. 2001). The emphasized benefit was mostly related to the absence of morbidity at the autologous bone iliac crest harvesting site and subsequently reduced intra-operative blood loss. However, rhBMP7 was found to be less effective than autograft bone in tibial non-union repair.

FDA and EMA approved rhBMP2 (Infuse) for open tibial fractures and rhBMP7 as a so-called humanitarian device exemption (Osigraft) for tibial non-unions (Giannoudis et al. 2017). Additionally, rhBMP2 and 7 were used off-label in various indications, including scaphoid fractures, distal radius fractures, and cervical and thoracic ALIF (Pecina et al. 2001, 2003; Bilic et al. 2006). A small RCT demonstrated a successful outcome for proximal pole scaphoid non-union by administering rhBMP7 alone or in combination with an autograft (Bilic et al. 2006). Two small-sample studies with a total of 30 patients showed complete restoration of humeral non-unions in all patients when rhBMP7 was used with an autograft (Giannoudis et al. 2009). RhBMP2 was slightly less effective in the same indication, achieving union in eight out of nine patients (Crawford and Seligson 2009). In a retrospective study, rhBMP2 and 7 failed to show an advantage in the treatment of aseptic clavicle non-union. Radical resection of the non-union tissue from the clavicle was a major step in the healing process (Rüden et al. 2016). Many off-label clinical studies were performed during this period, further exploring the potential applications of rhBMP2 and 7 beyond their approved uses(Courvoisier et al. 2014).

RhBMP2 received FDA approval in 2002 for anterior lumbar interbody fusion (ALIF) surgeries, specifically for indications such as one-level degenerative disc disease (Faundez et al. 2016). Following approval, the use of BMP increased, reaching a 25% share in spinal fusion procedures in the US in 2006 (Cahill et al. 2009). It is noteworthy that a high proportion of these surgeries deviated from the originally FDA-approved indications, including posterior and transforaminal lumbar interbody fusion and cervical fusions. In patients treated for spinal fusion with BMP devices, it was observed that application in unstable thoracolumbar fractures resulted in severe bone resorption, loss of reduction, and segmental collapse (Laursen et al. 1999). This effect could be explained by the pronounced impact of a large amount of rhBMP 2 and 7 on osteoclasts at trabecular surfaces, which form the majority of vertebrae. However, retrospective analyses revealed that the initial rhBMP-induced resorption was transient, and subsequent bone formation and repair occurred (Fu et al. 2013). In conclusion, BMP application for spinal fusion should be restricted to approaches with proven safety and efficacy in RCTs, and those in which the vertebral canal remains intact to avoid neurological complications.

Between 2000 and 2003, Jones et al. (Jones et al. 2006) conducted a multicenter randomized controlled trial involving 30 patients to investigate the benefits of rhBMP-2 with allograft compared to autogenous bone graft for reconstructing diaphyseal tibial fractures with cortical defects. Patients included in this study had a residual fracture defect consistent with clinical recommendations for staged reconstruction with bone grafting (i.e. a cortical defect measuring 1–5 cm in length and involving at least 50% of the circumference of the diaphysis) (Watson et al. 1995; Whittle et al. 1995; Templeman et al. 1998). They also had to have had initial treatment with either intramedullary nail or external fixation. All 30 patients were enrolled 6–12 weeks after the initial injury. Patients allocated to the allograft group received 1.5 mg/mL rhBMP-2/ACS as an onlay graft. Clinical

evaluation of fracture healing included pain assessment with full weight-bearing and fracture-site tenderness. The Short Musculoskeletal Function Assessment (SMFA) was administered before and after treatment, with radiographs used to document union, the presence of bridging callus, and the incorporation of bone graft material. In Jones et al.'s study, 86% of patients in the rhBMP-2/allograft group and 66% in the autograft group experienced healing without further intervention. The rhBMP-2 group showed a 67% lower mean estimated blood loss (117 mL) compared to the autograft group (353 mL) ($p = 0.0073$). Both groups exhibited comparable improvement in SMFA scores. Importantly, no patients in the rhBMP-2/allograft group developed antibodies to BMP-2. This suggests that using rhBMP-2/ACS in combination with cancellous allograft for treating diaphyseal tibial fractures with cortical defects yielded clinical results comparable to autogenous bone grafting. The rhBMP-2/allograft approach offered significant benefits, including reduced intraoperative blood loss and elimination of morbidity associated with autogenous bone graft harvesting.

A new osteogenic device, the osteoinductive autologous bone graft substitute (ABGS), featuring rhBMP6 has been innovated and is presently undergoing clinical trials (Vukicevic et al. 2017). This device consists of a biologically compatible autologous carrier derived from the patient's peripheral blood (autologous blood coagulum, ABC) and incorporates rhBMP6 as the active ingredient. This formulation avoids the use of animal-derived components, minimizes common inflammatory reactions associated with commercial bone devices, and provides a flexible, malleable, and injectable carrier for ease of use.

Complications

Despite extensive clinical testing, significant side effects have been reported for both rhBMP2 and rhBMP7 bone devices, prompting a re-evaluation of their therapeutic use (Fu et al. 2013; Simmonds et al. 2013). Serious complications, including local transient swelling, inflammation, heterotopic ossification, and early osteolysis, were observed following long bone implantation and spinal fusion, particularly in the cervical spine. Pronounced inflammation was noted in patients with distal radius fractures (Ekrol et al. 2008). The average amount of rhBMP incorporated into the collagen carrier varied between 3.5 and 12 mg, depending on the site and size of the fracture gap, whereas the entire human body typically contains only around 2 mg of BMPs. BMPs are not soluble at neutral pH, and only 75 µg of the protein binds to 1 g of bovine collagen, with the rest precipitating and being locally released, posing a potential source for local and systemic side effects. According to previous pharmacokinetic and bioavailability studies with commercial rhBMP devices, it is expected that only 1–2% of locally administered rhBMP will be present in the patient's circulation in the two weeks following implantation. Recent suggestions propose that the impact of potentially systemically released rhBMP2 and 7 might have a positive effect on the skeleton by increasing skeletal bone volume (Dumic-Cule et al. 2014).

Cheng Kuei Wu et al. (Wu et al. 2022) revealed that BMP2 is significantly overexpressed in lung adenocarcinoma patients with lymph node metastasis compared to those without lymph node metastasis. Through an in vivo orthotopic mouse model, they convincingly demonstrated that BMP2 promotes metastasis in lung adenocarcinoma. Depletion of BMP2 or its receptor BMPR2 significantly reduced cell migration and invasiveness. They further identified that BMP2/BMPR2-mediated cell migration involves the activation of the SMAD1/5/8 signaling pathway, independent of the KRAS signaling pathway.

Cost effectiveness

In a cost analysis study evaluating the use of BMP-2 in open tibial fractures, Garrison et al. (Garrison et al. 2007) estimated that the incremental cost per quality-adjusted life-year (QALY) gained exceeded US$50,000, with a 35% probability of it being less than US$50,000. They highlighted the sensitivity of the cost-effectiveness ratio to the price of BMP and the severity of open tibial fractures. According to Ziad Dahabreh et al. (Dahabreh et al. 2007) the mean number of procedures per fracture before applying BMP-7 was 4.16, compared to 1.2 thereafter. The mean hospital stay and cost of treatment per fracture before receiving BMP-7 were 26.84 days and £13,844.68, versus 7.8 days and £7,338.4 thereafter. The overall cost of treating persistent fracture non-unions with BMP-7 was 47.0% less than that of numerous previous unsuccessful treatments ($p = 0.001$). They concluded that treating fracture non-unions is costly, but this cost could be reduced by early BMP-7 administration when a complex or persistent fracture non-union is present or anticipated.

Conclusion

In vitro and in vivo studies in animals have revealed the intricate biological interactions between BMPs and cellular receptors, demonstrating rhBMP-2 as a safe and effective treatment for enhancing bone healing. Human clinical trials have provided insights into BMP-2 dosage, time course, carriers, and efficacy in fracture healing, particularly in tibial defects. The positive outcomes from these trials suggest the emergence of a new biologic technology that could

serve as a valuable adjunct in treating skeletal injuries and conditions. However, further research and clinical studies are needed to fully understand the molecular mechanisms underlying bone formation and fracture healing.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Akshit Sen, Rayed Qamar, Raghvendra Choubisa, Mit Parikh and Dhairya Shah. The first draft of the manuscript was written by Rayed Qamar and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Declarations

Competing interest The authors have no relevant financial or non-financial interests to disclose.

References

Bilic, R., Simic, P., Jelic, M., Stern-Padovan, R., Dodig, D., van Meerdervoort, H.P., et al.: Osteogenic protein-1 (BMP-7) accelerates healing of scaphoid non-union with proximal pole sclerosis. Int. Orthop. **30**, 128–134 (2006). https://doi.org/10.1007/s00264-005-0045-z

Bouxsein, M.L., et al.: Recombinant human bone morphogenetic protein-2 accelerates healing in rabbit ulnar osteotomy model. J. Bone Joint Surg. Am. **83**, 1219–1230 (2001)

Cahill, K.S., Chi, J.H., Day, A., Claus, E.B.: Prevalence, complications, and hospital charges associated with use of bone-morphogenetic proteins in spinal fusion procedures. JAMA **302**, 58–66 (2009). https://doi.org/10.1001/jama.2009.956

Cauley, J.A.: Osteoporosis: fracture epidemiology update 2016. Curr. Opin. Rheumatol. **29**, 150–156 (2017). https://doi.org/10.1097/BOR.0000000000000365

Cheng, H., Jiang, W., Phillips, F.M., Haydon, R.C., Peng, Y., Zhou, L., et al.: Osteogenic activity of the fourteen types of human bone morphogenetic proteins (BMPs). J. Bone Joint Surg. Am. **85**, 1544–1552 (2003). https://doi.org/10.1016/j.urolonc.2003.12.008

Cho, T.J., Gerstenfeld, L.C., Einhorn, T.A.: Differential temporal expression of members of the transforming growth factor beta superfamily during murine fracture healing. J. Bone Miner. Res. **17**, 513–520 (2002). https://doi.org/10.1359/jbmr.2002.17.3.513

Courvoisier, A., Sailhan, F., Laffenêtre, O., Obert, L.: French Study Group of BMP in Orthopedic Surgery. Bone morphogenetic protein and orthopaedic surgery: can we legitimate its off-label use? Int. Orthop. Orthop. **38**, 2601–2605 (2014). https://doi.org/10.1007/s00264-014-2534-4

Crawford, C.H., III., Seligson, D.: Atrophic nonunion of humeral diaphysis treated with locking plate and recombinant bone morphogenetic protein: nine cases. Am. J. Orthop. (Belle Mead N.J.) **38**, 567–570 (2009)

Dahabreh, Z., Dimitriou, R., Giannoudis, P.V.: Health economics: a cost analysis of treatment of persistent fracture non-unions using bone morphogenetic protein-7. Injury **38**(3), 371–377 (2007). https://doi.org/10.1016/j.injury.2006.08.055

Dimitriou, R., Tsiridis, E., Giannoudis, P.V.: Current concepts of molecular aspects of bone healing. Injury **36**, 1392–1404 (2005). https://doi.org/10.1016/j.injury.2005.07.019

Dumic-Cule, I., Brkljacic, J., Rogic, D., Bordukalo-Niksic, T., Tikvica Luetic, A., Draca, N., et al.: Systemically available bone morphogenetic protein two and seven affect bone metabolism. Int. Orthop. **38**, 1979–1985 (2014). https://doi.org/10.1007/s00264-014-2425-8

Edgar, C.M., Chakravarthy, V., Barnes, G., Kakar, S., Gerstenfeld, L.C., Einhorn, T.A.: Autogenous regulation of a network of bone morphogenetic proteins (BMPs) mediates the osteogenic differentiation in murine marrow stromal cells. Bone **40**, 1389–1398 (2007). https://doi.org/10.1016/j.bone.2007.01.001

Einhorn, T.A., Gerstenfeld, L.C.: Fracture healing: mechanisms and interventions. Nat. Rev. Rheumatol. **11**(1), 45–54 (2015). https://doi.org/10.1038/nrrheum.2014.164

Einhorn, T.A., et al.: A single percutaneous injection of recombinant human bone morphogenetic protein-2 accelerates fracture repair. J. Bone Joint Surg. Am. **85**, 1425–1435 (2003)

Ekrol, I., Hajducka, C., Court-Brown, C., McQueen, M.M.: A comparison of rhBMP-7 (OP-1) and autogenous graft for metaphyseal defects after osteotomy of the distal radius. Injury **39**(Suppl 2), S73–S82 (2008). https://doi.org/10.1016/S0020-1383(08)70018-4

Faundez, A., Tournier, C., Garcia, M., Aunoble, S., Le Huec, J.C.: Bone morphogenetic protein use in spine surgery-complications and outcomes: a systematic review. Int. Orthop. **40**, 1309–1319 (2016). https://doi.org/10.1007/s00264-016-3149-8

Finkemeier, C.G.: Bone-grafting and bone-graft substitutes. J. Bone Joint Surg. Am. **84**, 454–464 (2002)

Friedlaender, G.E., Perry, C.R., Cole, J.D., Cook, S.D., Cierny, G., Muschler, G.F., et al.: Osteogenic protein-1 (bone morphogenetic protein-7) in the treatment of tibial nonunions. J. Bone Joint Surg. Am. **83**, S151–S158 (2001). https://doi.org/10.2106/00004623-200100002-00010

Fu, R., Selph, S., McDonagh, M., Peterson, K., Tiwari, A., Chou, R., et al.: Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion: a systematic review and meta-analysis. Ann. Intern. Med. **158**, 890–902 (2013). https://doi.org/10.7326/0003-4819-158-12-201306180-00006

Garrison, K.R., et al.: Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review. Health Technol. Assess. **11**(1–150), iii–iv (2007)

Gautschi, O.P., et al.: Bone morphogenetic proteins in clinical applications. ANZ J. Surg. **77**, 626–631 (2007)

GBD 2019 Fracture Collaborators. Global, regional, and national burden of bone fractures in 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019. Lancet Healthy Longev. 2021;2(9):e580-e592. https://doi.org/10.1016/S2666-7568(21)00172-0.

Giannoudis, P.V., Kanakaris, N.K.: BMPs in orthopaedic medicine: promises and challenges. In: Vukicevic, S., Sampath, T.K. (eds.) Bone morphogenetic proteins: systems biology regulators, 1st edn., pp. 187–214. Springer International Publishing AG (2017)

Giannoudis, P.V., Kanakaris, N.K., Dimitriou, R., Gill, I., Kolimarala, V., Montgomery, R.J.: The synergistic effect of autograft and BMP-7 in the treatment of atrophic nonunions. Clin. Orthop. Relat. Res. **467**, 3239–3248 (2009). https://doi.org/10.1007/s11999-009-0846-2

Govender, S., Csimma, C., Genant, H.K., Valentin-Opran, A., Amit, Y., Arbel, R., et al.: Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. J. Bone Joint Surg. Am. **84**, 2123–2134 (2002). https://doi.org/10.2106/00004623-200212000-00001

Grgurevic, L., Christensen, G.L., Schulz, T.J., Vukicevic, S.: Bone morphogenetic proteins in inflammation, glucose homeostasis and

adipose tissue energy metabolism. Cytokine Growth Factor Rev. **27**, 105–118 (2016). https://doi.org/10.1016/j.cytogfr.2015.12.009
Grgurevic, L., Pecina, M., Vukicevic, S., Marshall, R.: Urist and the discovery of bone morphogenetic proteins. Int. Orthop. Orthop. **41**, 1065–1069 (2017). https://doi.org/10.1007/s00264-017-3402-9
Hollinger, J., Wong, M.E.: The integrated processes of hard tissue regeneration with special emphasis on fracture healing. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. **82**, 594–606 (1996)
Jones, A.L., et al.: Recombinant human BMP-2 and allograft compared with autogenous bone graft for reconstruction of diaphyseal tibial fractures with cortical defects. A randomized, controlled trial. J. Bone Joint Surg. Am. **88**, 1431–1441 (2006)
Laursen, M., Høy, K., Hansen, E.S., Gelineck, J., Christensen, F.B., Bünger, C.E.: Recombinant bone morphogenetic protein-7 as an intracorporal bone growth stimulator in unstable thoracolumbar burst fractures in humans: preliminary results. Eur. Spine J. **8**, 485–490 (1999)
Lee, F.Y., et al.: Repair of bone allograft fracture using bone morphogenetic protein-2. Clin. Orthop. Relat. Res. **397**, 119–126 (2002)
Pecina, M., Giltaij, L.R., Vukicevic, S.: Orthopaedic applications of osteogenic protein-1 (BMP-7). Int. Orthop. **25**, 203–208 (2001). https://doi.org/10.1007/s002640100262
Pecina, M., Haspl, M., Jelic, M., Vukicevic, S.: Repair of a resistant tibial non-union with a recombinant bone morphogenetic protein-7 (rhBMP-7). Int. Orthop. **27**, 320–321 (2003). https://doi.org/10.1007/s00264-003-0475-4
Reddi, A.H.: Bone and cartilage differentiation. Curr. Opin. Genet. Dev. **4**, 737–744 (1994)
Reddi, A.H., Cunningham, N.S.: Initiation and promotion of bone differentiation by bone morphogenetic proteins. J. Bone Miner. Res. **8**(Suppl 2), S499–S502 (1993). https://doi.org/10.1002/jbmr.5650081313
Schmitt, J.M., et al.: Bone morphogenetic proteins: an update on basic biology and clinical relevance. J. Orthop. Res. **17**, 269–278 (1999)
Seeherman, H., et al.: rhBMP-2/calcium phosphate matrix accelerates osteotomy-site healing in a nonhuman primate model at multiple treatment times and concentrations. J. Bone Joint Surg. Am. **88**, 144–160 (2006)
Simmonds, M.C., Brown, J.V., Heirs, M.K., Higgins, J.P., Mannion, R.J., Rodgers, M.A., et al.: Safety and effectiveness of recombinant human bone morphogenetic protein-2 for spinal fusion: a meta-analysis of individual-participant data. Ann. Intern. Med. **158**, 877–889 (2013). https://doi.org/10.7326/0003-4819-158-12-201306180-00005
Stone, K.L., Seeley, D.G., Lui, L.Y., Cauley, J.A., Ensrud, K., Browner, W.S., Nevitt, M.C., Cummings, S.R.: Osteoporotic Fractures Research Group. BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. J. Bone Miner. Res. **18**(11), 1947–1954 (2003). https://doi.org/10.1359/jbmr.2003.18.11.1947
Templeman, D.C., et al.: Update on the management of open fractures of the tibial shaft. Clin. Orthop. Relat. Res. **350**, 18–25 (1998)
Urist, M.R.: Bone: formation by autoinduction. Science **150**, 893–899 (1965)
van Baardewijk, L.J., van der Ende, J., Lissenberg-Thunnissen, S., Romijn, L.M., Hawinkels, L.J., Sier, C.F., Schipper, I.B.: Circulating bone morphogenetic protein levels and delayed fracture healing. Int. Orthop. **37**, 523–527 (2013). https://doi.org/10.1007/s00264-012-1750-z
von Rüden, C., Morgenstern, M., Friederichs, J., Augat, P., Hackl, S., Woltmann, A., Bühren, V., Hierholzer, C.: Comparative study suggests that human bone morphogenetic proteins have no influence on the outcome of operative treatment of aseptic clavicle non-unions. Int. Orthop. **40**, 2339–2345 (2016). https://doi.org/10.1007/s00264-016-3262-8
Vukicevic, S., Sampath, T.K. (eds.): Bone morphogenetic proteins: systems biology regulators, 1st edn. Springer International Publishing AG, Switzerland (2017)
Vukicevic, S., Sampath, T.K.: Bone morphogenetic proteins: from local to systemic therapeutics. Birkauser Verlag AG, Basel-Boston-Berlin (2008)
Vukicevic, S., Stavljenic, A., Pecina, M.: Discovery and clinical applications of bone morphogenetic proteins. Eur. J. Clin. Chem. Clin. Biochem. **33**, 661–671 (1995)
Vukicevic, S., Oppermann, H., Verbanac, D., Jankolija, M., Popek, I., Curak, J., et al.: The clinical use of bone morphogenetic proteins (BMPs) revisited: a novel BMP6 biocompatible carrier device OSTEOGROW for bone healing. Int. Orthop. **38**, 635–647 (2014). https://doi.org/10.1007/s00264-013-2201-1
Vukicevic, S., Grgurevic, L., Pecina, M.: Clinical need for bone morphogenetic proteins. Int. Orthop. **41**, 2415–2416 (2017). https://doi.org/10.1007/s00264-017-3550-y
Watson, J.T., et al.: Management strategies for bone loss in tibial shaft fractures. Clin. Orthop. Relat. Res. **315**, 138–152 (1995)
Whittle, A.P., Wester, W., Russell, T.A.: Fatigue failure in small diameter tibial nails. Clin. Orthop. Relat. Res. **315**, 119–128 (1995)
Wu, C.K., Wei, M.T., Wu, H.C., et al.: BMP2 promotes lung adenocarcinoma metastasis through BMP receptor 2-mediated SMAD1/5 activation. Sci. Rep. **12**, 16310 (2022). https://doi.org/10.1038/s41598-022-20788-2