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Functions and clinical applications of bone morphogenetic proteins (BMPs)

Md. Shaifur Rahman[1 Ψ], Sudarshan Chatterjee[2], Hossen M. Jamil[1], Naznin Akhtar[1], Madhuri Haque[2], Sikder M Asaduzzaman[1]

[1]Tissue Banking and Biomaterial Research Unit, Atomic Energy Research Establishment, Dhaka-1349, Bangladesh
[2]Department of Biotechnology and Genetic Engineering, Jahangirnagar University, Dhaka-1342, Bangladesh

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Abstract

Clinically important polypeptides, in particular bone morphogenetic proteins (BMPs) family, are being increasingly studied due to their contribution in embryonic development and physiological functions in human body throughout life. Appropriate concentration of these small molecules namely BMP-2 and -7 are able to induce bone formation on scaffold and ectopic site. BMP carrier is a factor for maintaining local concentration. Preclinical tests and applications in clinical situations such as open fracture of long bones, non-unions and vertebral arthrodesis, lumbar fusion or in various maxillofacial and dental regenerative procedures have already been successful and practically accepted. But not all BMPs are well effective, and only two FDA-approved applications are available now. However, more clinical use of these molecules is under investigation. Researchers are now focusing strongly to improve the methods of production of these multifunctional cytokines in terms of quality and quantity. This review describes a brief informative understanding of BMPs functions, clinical importance, and introduces to the recombinant approach of BMP production.

Keywords: Bone morphogenetic proteins, embryonic development, recombinant BMP, clinical applications.

1. Introduction

Bone morphogenetic proteins (BMPs) are one of the important molecules responsible for bone formation. Their role in different physiological circuits has come up day by day. These extracellular signaling molecules-BMPs are cytokines belonging to the transforming growth factor β (TGF-ß) superfamily (Wang *et al.* **2014**). Urist isolated BMP and first noticed that crude bone extracts induced new bone in an ectopic site. And he referred these molecules as "bone morphogenetic protein" or "osteogenic protein". From crude bone extracts, in 1983, a highly reproducible method was developed for ectopic bone formations which support Urist observations (Sethi **2013**).

Correspondence to: Md. Shaifur Rahman, Tissue Banking and Biomaterial Research Unit, Atomic Energy Research Establishment, Dhaka-1349, Bangladesh. E-mail: mdshaifur@gmail.com

However, in general, through the regulation of target gene transcription, BMP controls cellular processes such as proliferation, differentiation, apoptosis and migration as well. They are also involved in controlling cell type specification, and it is an indispensable factor in hematopoiesis maintenance (Basson **2012**). Furthermore, pathophysiologically, they act as auto or paracrine modifiers of tumor growth and have functional impact in a number of cancer entities (Johnsen and Beuschlein **2010**). A plethora of evidences of profound dysregulation of the BMP signaling in cells from patients with FOP has been identified recently. The exact physiology behind FOP is still unclear, but the ectopic bone is thought to originate from MSCs which lie dormant in soft tissues and differentiate into osteogenic cells. Nevertheless, trauma is the second

most expensive medical burden in the USA, and cut $56 billion each year from health care budget, out of which about 50% is gone for the treatment of broken bones alone. It is noticed that roughly 8 million fractures are supported annually, with 5–10% resulting in delayed or impaired healing and around 1.5 million bone grafting operations are accomplished in the USA. Evidently, BMPs are now broadly being applied clinically (Epstein **2013**). Two recombinant proteins are now commercially available, FDA approved rh-BMP-7 in 2001 and rh-BMP-2 in 2002. They were found to be a potential alternative to bone auto-grafting in a variety of clinical situations, including spinal fusions, internal fixation of fractures, treatment of bone defects, and reconstruction of maxillofacial conditions (Roberts and Rosenbaum **2012**). The large amounts and with specific qualities of BMPs production for clinical use depends on genetic engineering technology. Clinical application requires defined delivery system, such as type I collagen and calcium phosphate ceramics, to ensure controlled release and to boost up BMP activity at the target site only (Hustedt and Blizzard **2014**).

2. BMPs are bone morphogenetic protein

A comprehensive review on BMP and Osteoblastogenesis has been published by Rahman et al. (**2015**). So, in this study we have discussed briefly on BMP as a bone morphogenetic protein. BMP is a growth factor with unique manner. It is only morphogen that has the ability to transform connective tissue cells into osteoprogenitor cell. Other growth factors induce multiplication of cells only but do not transform one into the others. BMP, FGF and Wnt pathways with associated receptors dominate the control of cartilage and bone formation by determining the temporal–spatial expression of stimulatory and inhibitory transcription factors. Glucocorticoids mediate their action on osteoblasts through BMP and RA, which is a possible modulator of BMP expression (Sykaras and Operman **2003**). Cellular adhesive such as laminin, N-CAM, and integrin are known to interact with BMP and localize at the areas of initial mesenchymal condensation (Rahman *et al.* **2015**). Depending on concentration gradient, BMPs also attract various types of cells and thus acting as chemotactic, mitogenic or differentiating agents (Rici *et al.* **2012**). BMPs might affect proliferation of cartilage and bone-forming cells and can induce differentiation of mesenchymal progenitor cells into myriad cell types, including chondroblasts and osteoblasts (Giuliani *et al.* **2013**). It can be assumed that BMPs might influence both the endochondral bone induction pathway and direct bone formation. In ectopic bone formation, after implantation of BMP, the sequence of events recapitulates the process observed during embryonic long bone development.

3. BMPs are body morphogenetic protein also!

BMPs shape structures and regulate processes throughout the body, ranging from embryonic patterning to tissue homeostasis and regeneration. For examples, BMP involves in osteo-induction at different developmental phases, regulation in the primal stages of embryogenesis, formation of left–right asymmetry, neural and skeletal patterning, limb formation, and organogenesis (Zhao **2003**). Certain BMPs are vital for development because Bmp2 and Bmp4 null mutant mice die during embryogenesis and Bmp7 null mutant mice shortly after their birth (Wang *et al.* **2014**). BMPs also significantly contribute in development and regulation of renal and ocular machinery and in hair pigmentation (Slominski *et al.* **2004**). In particular, BMP4, in togetherness with BMP7, regulate early ovarian follicle growth and primordial-to-primary follicle transition (Dole *et al.* **2008**).

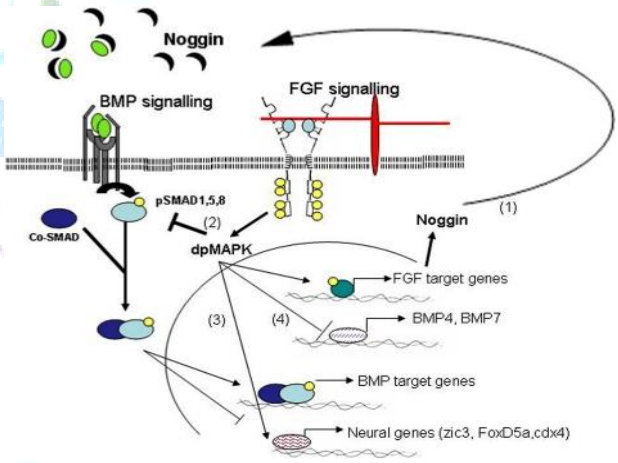

Fig 1. There are many levels where FGF can impact on neural induction. (1) FGF signaling is required for the expression of Noggin, which acts outside the cell to bind and inhibit the activity of BMP ligands. (2) FGF signaling results in the phosphorylation of SMAD1, 5, 8 in a central domain, which inhibits its ability to move to the nucleus or activate the transcription of BMP target genes. (3) FGF signaling can directly activate the transcription of a set of posterior neural genes. (4) FGF can inhibit the expression of genes coding for BMP ligands (Pownall and Isaacs **2010**).

Genes such as BMP4 and BMP2 are both active within the precursors of the hair shaft. Specifically BMP4 is found in the dermal papilla. BMP4 is part of the signaling network which controls the development of hair (Lee and Tumbar **2012**). In case of eye, BMP6 is necessary for normal retinal iron homeostasis, as $Bmp6^{-/-}$ mice had age-dependent retinal iron accumulation and degeneration. Post mortem eyes from patients with

AMD had been noticed with altered BMP6 levels (Hadziahmetovic *et al.* 2011). Furthermore, in vertebrates, BMPs act as signals for epidermal induction. The inhibition of the BMP signaling pathway in the ectoderm is the hallmark of neural-fate acquisition, and forms the basis of the default model of neural induction (Ozair *et al.* 2013). Neural induction by BMP and FGF signaling has been shown in **Fig 1**. Importantly, studies also indicated that BMP pathway inhibits muscle differentiation, but has the ability to stimulate satellite cell proliferation (Osses and Henríquez 2014), (Ono *et al.* 2011). Accordingly, it has been proposed that BMP signaling is important in stimulating the amplification of committed myoblasts and in preventing precocious differentiation during muscle regeneration. Specific localization of BMP-4 at the border of postsynaptic densities of the NMJ could have a dual effect on muscle fibers; it may represent a sequestering of this BMP ligand to preclude activation of BMP signaling in innervated muscles or may activate local BMP-dependent pathways involved in the disassembly of AChR clusters at the NMJ (Henríquez *et al.* 2011). **Fig 2** represents BMP signaling on the connectivity of the vertebrate neuromuscular synapse. In the adult neuronal tissue, BMPs regulate several features of cell behavior i.e. dendritogenesis, number of neuritis, neurite length. Branch points have been shown to be stimulated or inhibited by different BMPs in diverse neuronal types, including cultured sympathetic, cerebral cortical, hippocampal, postnatal cerebellar and peripheral neurons (Osses and Henríquez 2014). BMP-2 mRNA is expressed in motor neurons after crush injury of the facial nerve in rabbits. Similarly, traumatic injury of the rat spinal cord results in a remarkable up-regulation of BMP-7 and BMP-2 around the injury site during recovery (Henríquez *et al.* 2011).

Kidney is the major site of BMP-7 synthesis during embryogenesis as well as postnatal development (Tanaka *et al.* 2008). BMP-7 expression in adult kidney is limited to distal collecting tubules and podocytes of glomeruli. The expression decreases in acute ischemic renal injury, tubulointerstitial fibrosis, diabetic nephropathy, and remnant kidney model (Li *et al.* 2015). The administration of BMP-7 reverses TGF-β1-induced fibrogenesis and EMT and induces MET in vitro, inhibits the stimulation of inflammatory cytokine expression, weakens inflammatory cell infiltration, and reduces apoptosis of tubular epithelial cells in renal disease models (Dudas *et al.* 2009). Collectively, BMP-7 plays critical roles in repairing processes of the renal tubular damage in kidney diseases. However, the physiological role and precise regulatory mechanism of endogenous BMP-7 activity remain elusive. BMPs in various tissues highlight the therapeutic potential of BMPs throughout the body and can be referred as body morphogenetic proteins.

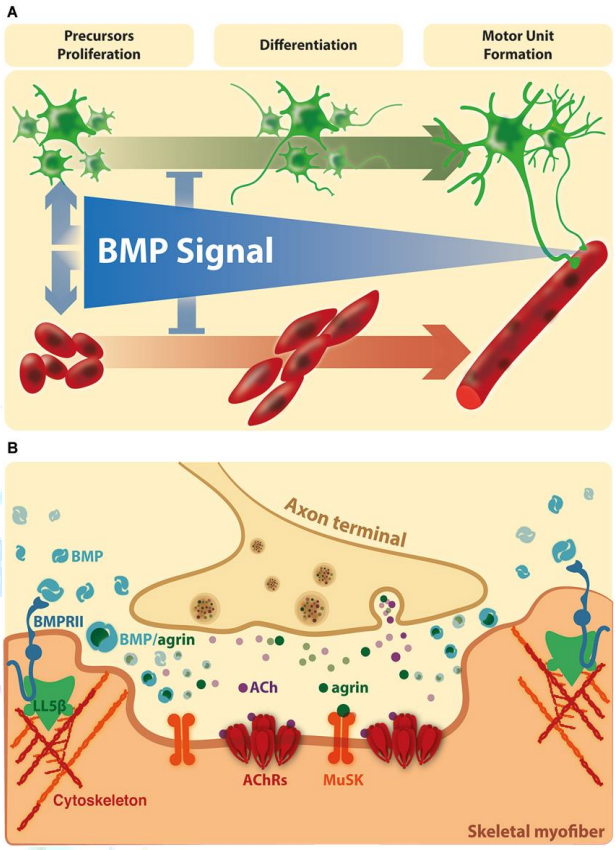

Fig 2. BMP signaling on the connectivity of the vertebrate neuromuscular synapse (Osses and Henríquez 2014). (A) In vertebrates, the evidence suggests that BMPs stimulate the amplification of muscle and motor neurons precursors and repress precocious differentiation. At this stage, the BMP dependent effects are mainly Smad dependent. At later stages, BMP signaling becomes restricted to the site of innervation. (B) Here, activation of BMP pathways could be involved in NMJ formation, maturation and/or maintenance. Agrin and BMPs could modulate the extracellular distribution and availability of each other for receptor binding in synaptic domains. In turn, local BMP-dependent pathways could affect cortical actin rearrangements at extra-synaptic domains.

3. BMPs dictate development

BMPs have been demonstrated to be involved in a variety of key developmental processes such as dorsal–ventral axis specification, epithelial–mesenchymal interactions and apoptosis in adrenal development. Roles in adrenal development are illustrated in following **Fig 3**.

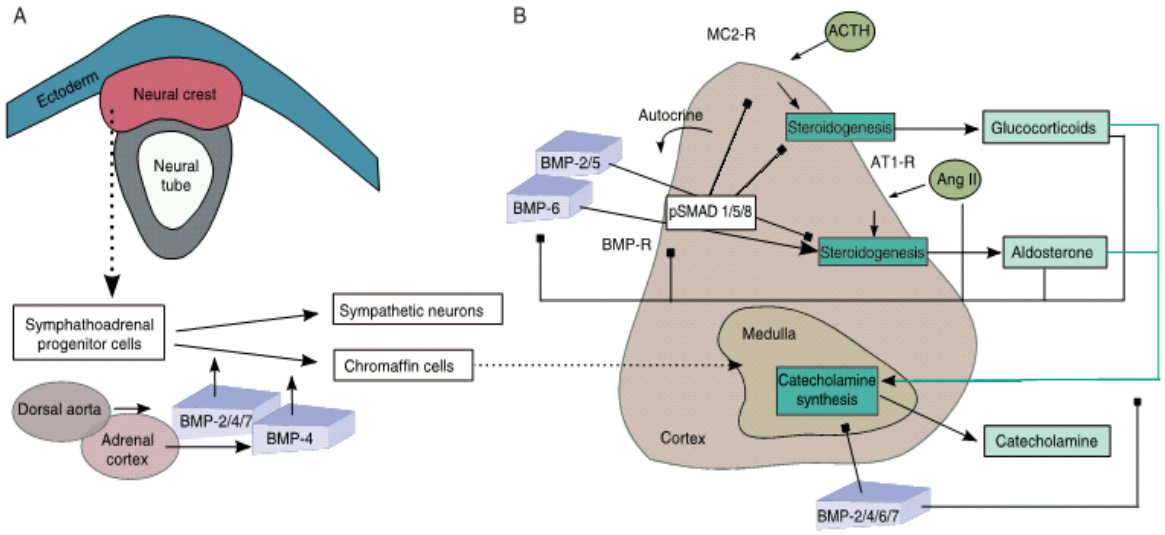

Fig 3. Roles of BMP during adrenal development (Johnsen and Beuschlein **2010**) **and endocrine function during adulthood.** (A) Sympathoadrenal progenitor cells undergo differentiation to adrenomedullary chromaffin cells induced by BMP-2/BMP-4/BMP-7 and secreted by the dorsal aorta and adrenal cortex respectively. (B) Summary of various interrelations of BMPs with adrenocortical steroidogenesis and adrenomedullary catecollamine biosynthesis.

BMPs which are secreted locally by the adrenal cortex are able to change the cellular fate of tissue progenitor cells in the adult adrenal medulla. Furthermore, direct functional effects of BMPs have been postulated on adrenomedullary hormone secretion (Wurtman *et al.* **1972**). Glucocorticoids secreted by the adrenal cortex have been found to be transported mainly through a cortico-medullary portal system into the medulla involved in stimulating the synthesis of catecholamine enzymes and thus, retain the phenotype of chromaffin cells (Shepherd and Holzwarth **2001**). Interestingly, BMPs are assumed to influence catecholamine production of adrenomedullary cells indirectly where they interfere with steroid hormone-dependent signaling pathways (Goto *et al.* **2009**). In addition, the modulating effects of BMPs on steroid hormone-dependent mechanisms, they have also been demonstrated to have direct impact on steroidogenesis. BMP-6-induced and SMAD1/SMAD5/SMAD8-mediated augmentation of aldosterone secretion has been revealed through in vitro experiments in NCIh295R adrenocortical tumor cells while the process of augmentation requires a crosstalk with Angiotensin II-dependent pathways (Johnsen and Beuschlein **2010**). However, it is not found that BMP-6 influences potassium-induced aldosterone production.

Experiments that are supporting the results had endogenous BMP-6 inhibited through neutralizing antibodies that reduced Ang II-induced aldosterone secretion but not potassium-induced aldosterone secretion. These experimental outcomes specify the possibility that endogenous BMP-6 produced by adrenocortical cells could play an important autocrine role in modulating the steroidogenic actions of Angiotensin II. Formation of embryonic hematopoietic tissue by BMP-4 specifies the role of BMPs in hematopoiesis. Subcutaneous implantation of BMP-2 has been found to be capable of inducing a hematopoietic microenvironment those maintenances clonogenic lymphoid and myeloid progenitors (Inagaki *et al.* **2006**). Expression of the genes for the BMP type I receptors and their downstream signal transducers has also been found in hematopoietic stem cells. In a study, BMP-9 was also found to act as a hematopoietic hormone (Larsson and Karlsson **2005**).

4. Production of recombinant human BMP (rh-BMP) for clinical application

In recent years, BMP is being used clinically but the isolation of BMP directly from the bone tissue is problematic and is not cost effective. For example, 40 kg of bovine bone powder provides only 40 µg of BMP mixture which is indeed a very low yield (Oryan *et al.* **2014**). Furthermore, isolation of BMP from human bone is ethically dubious and does not ensure that it will be free of contaminants like prions, HCV etc. Alternatively, usage of homologous proteins from pigs or cattle is equally immunologically risky. Inclination is consequently given to formulate recombinant BMP. Rh-BMP-7 and rh-BMP-2 are now produced by recombinant technology; conversely optimum industrial procedure is essential.

For eukaryotic expression system, proper technologies are available for post translational modification to produce clinically active protein. But it is indeed problematic when relatively low quantity of recombinant protein can be attained with relatively high technical input and costs (Wozney *et al.* **1988**). Conversely, prokaryotic expression system requires simple technical manipulation with low costs and it results in high yield. However, bacterial post-translational modification systems are unable to process the precursor protein correctly. For this limitation, the expression of matured domain of BMP-2 (Gln283–Arg396) was limited in bacterial system (Wang *et al.* **1990**). Though proteins were formed, the domain accumulates in an insoluble, biologically inactive form, which is designated as inclusion bodies (Marston **1986**). To overcome the situation, Ruppert's group used a mild detergent to renature the monomeric denatured mature form of BMP into biologically active conformation. By this scheme, 0.2 mg of active protein can be obtained per 1 g of cell which is three orders of size higher than eukaryotic system (Ruppert *et al.* **1996**). In this scenario, the usage of protozoan Lexy vector could be a good preference from all standpoints. In this system, part of the protein is obtained in the form of inclusion bodies, which is then followed by isolation and solubilized under denaturing condition. The denatured monomeric and biologically inactive protein is then renatured with folding and dimerization to produce the soluble protein with biologically active conformation.

5. Carriers to implant BMP

Collagenous or synthetic matrices have been used as delivery vehicles and their physicochemical properties, together with the microenvironment they create, play an effective role in the inductive outcome (Sykaras and Opperman **2003**). Carriers can be solid xenogenic (HA), solid alloplastic (polyethylene polymers) materials or gels of autogenous, allogenic or alloplastic origin and combinations of the above (Kinoshita and Maeda **2013**). One of the functions of these carriers is to maintain the therapeutic at the site of implantation and thus enhance its local concentration. Reciprocally, BMPs help to stabilize the carrier by accelerating bone growth in its mass. As a result, 0.15µg of rh-BMP-2 with matrix induced bone formation subcutaneously in rats, while a minimum of 75 µg of rh-BMP-2 was required in the absence of matrix (Wang **1993**). It is believed that BMPs do not bind to the carrier, but rather become physically entrapped in its structure which makes certain designs more favorable for bone induction over some others. For collagen sponge carriers, the mass, collagen cross-linking and sterilization methods affect BMP precipitation and subsequent resistance of sponge degradation by collagenase (Geiger *et al.* **2003**). Properties of the best carrier may vary depending on the specific implantation site and the intended therapeutic outcome. Considerations include biodegradability, structural integrity, and absence of immunogenicity, absorption and rate of release of BMP. For example, BMP-2 is retained in a hydrogel carrier for more than 30 days whereas direct injection results in its complete elimination within 3 days (Abbah *et al.* **2013**). Collagen carrier also resulted in increased bone density of the regenerate when compared to polymeric matrix, emphasizing the importance of the structural properties of the carrier.

Recently, a novel approach has been suggested which implicates implanting matrices that actively concentrate native BMPs at the implantation site instead of passively storing and delivering rh-BMPs which are thousand times less potent that the native BMP complex. The matrix also serves as a setting in which bone can be formed and therefore helps to define the region in which new bone can be formed (Sims and Martin **2014**). The type of matrix used may also influence and determine the mechanism of bone formation. BMPs combined with porous particles of hydroxyapatite (a biodegradable gelatin hydrogel) or fibrous collagen membrane leads to intramembranous ossification, whereas fibrous glass membrane or insoluble bone matrix supports indirect bone formation via a cartilaginous intermediate (Amini *et al.* **2012**). It is evident that various doses elicit different responses on specific cell types at different time intervals. The dose of the growth factor determines its chemotactic, proliferative or mitogenic signal and should therefore be well regulated. Increased BMP concentrations result in faster bone growth where cartilage being more rapidly replaced by mineralized osteoid (Sykaras and Opperman **2003**). Recently, investigators endeavored the direct (in vivo) or indirect (using viral vectors) delivery of BMP genomic sequences to the implantation site which demonstrates active BMP expression for 2-6weeks and bone formation with trabeculae and bone marrow (Franceschi *et al.* **2004**).

6. Clinical application of rh-BMP and mechanism of action after administration in body

Although the exact mechanism of action in human is not clearly defined, the commonly accepted mechanism of action as determined by in-vitro and in-vivo animal studies may include the phases described in the table. Here the mechanism of action of rh-BMP-2 is summarized in table 1. Animal studies and laboratory experiments reveal a number of conditions that influence the osteoinductivity of BMP, such as BMP

concentration, carrier properties and influence of local and systemic growth factors and hormones (Groeneveld and Burger **2000**).

Table 1 The mechanism of action of rh-BMP-2

1. Implantation	rh-BMP-2/ACS is implanted.
2. Chemotaxis	Migration of Mesenchymal Stem Cells and other bone forming cells to the site of implantation.
3. Proliferation	rh-BMP-2/ACS provides an environment where stem cells multiply prior to differentiation.
4.Differentiation	rh-BMP-2 binds to specific receptors on the stem cell surface inducing them to differentiate into osteoblasts.
5. Bone formation and angiogenesis	Osteoblasts respond to local mechanical forces to produce new mineralized tissue within the ACS. New blood vessel formation is observed at the same time.
6. Remodeling	Body continues to remodel bone in response to the local environmental and mechanical forces, resulting in normal trabecular bone.

BMPs, in particular BMP-2, are predominantly suitable for locally restricted applications. These include, inter alia, spinal fusions in connection with degenerative diseases of the vertebral column, the neoformation of cranial bones, maxillofacial surgical interventions and the treatment of the complicated fractures of the bones of the extremities (Barba *et al.* **2013**). Two recombinant proteins are now commercially available, rh-BMP-2(InFUSE system) and rh-BMP-7(OP-1). OP-1 system consists of rh-BMP-7 and bovine collagen, which is reconstituted with saline to form a paste. The addition of carboxymethylcellulose forms putty. The InFUSE system consists of rh-BMP-2 on an absorbable collagen sponge carrier. Recombinant human bone morphogenetic protein-7 for the treatment of tibial non-unions was investigated by Friedlaender *et al.* (**2001**). It was concluded that OP-1 implanted with a type-I collagen carrier is a safe and effective treatment for tibial non-unions. There are multiple clinical examples of resistant tibial nonunions treated with rh-BMP-7 (White *et al.* **2007**). Recombinant human bone morphogenetic protein-2 (rh-BMP-2) for treatment of open tibial fractures was investigated by the BESTT trial and a subgroup analysis. The addition of rh-BMP-2 for the treatment of type-III open fractures can significantly reduce the frequency of bone-grafting procedures and other secondary interventions (Sheikh *et al.* **2015**). Recombinant human bone morphogenetic protein-2 has also been tested in clinical settings in single-level interbody fusion of the lumbar spine. Currently the only clinical use of BMP lies in promoting bone healing. But they are expressed in a wide range of non-skeletal tissues during mammalian development, including germ layer, whiskers, hair, teeth, urogenital system, gut, heart and brain (Groeneveld and Burger **2000**). These suggest that BMPs have a much broader role in overall tissue morphogenesis, and in repair of other tissue systems. Successful use of BMPs has been reported in several animal models of disease. OP-1(BMP-7) enhanced functional recovery after focal cerebral infarction in mature and infant rats when injected intra-peritoneally or into the cisterna magna (Kawamata *et al.* **1998**). OP-1 also reduced the severity of injury after ischaemic acute renal failure in rats by minimizing tubular necrosis and tissue infarction in addition to reducing apoptosis (Vukicevic *et al.* **1998**). These data suggest that OP-1 may represent a potential new treatment with which to enhance functional recovery after stroke, and acute renal ischaemic injury, in man. In dental research, BMPs have been used to stimulate periodontal wound healing in dogs, with good result; again clinical studies are, as yet, lacking. These animal studies still indicate that BMPs have possibilities for clinical use other than bone repair alone (Groeneveld and Burger **2000**).

7. Conclusion

In essence, BMPs are very distinctive type of growth factor that plays a dynamic role in various physiological aspects of human from embryonic development to death. Changes in BMP genes or its receptor genes or in their regulation or in the downstream signaling process may lead to severe developmental disturbance such as fibrodysplasia ossificans progressiva and dentinogenesis imperfecta (Wang *et al.* **2014**). It also plays a prominent role in fractured bone healing and recovery. Recombinant gene technology using prokaryotic system paved an efficient and easier way for large scale production of BMP in highly purified form that reduce the possibilities of immunogenic response to a great extent. In recent years BMP is extensively studied for their relation with cancer such as adrenal tumorigenesis, breast cancer etc. which may lead to an outcome of a

potential therapeutic for cancer treatment (Epstein **2014**). Reconstitution of BMP expression in target tissues can be achieved by gene delivery. This high throughput tool has been described in a growing body of literature in the fields of tissue engineering, orthopaedics, and orthodontics which also show promising outcome that holds hope for a specific and potent therapy with reduced side effects in the future. In Bangladesh, a large number of patients are suffering from same diseases and different accidents like bone fractures, congenital deformities, non-union, and bone loss from traumatic accidents. To rehabilitate these sorts of health problems, people are now depending on bone allografts or autografts which take longer time for recovery. BMPs can play a vital role for quick and more efficient recovery and to save from sufferings.

8. Conflict of interest statement

We declare that we have no conflict of interest.

9. References

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