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CURRENT PERSPECTIVE ON GENE THERAPY AS AN APPROACH FOR OSTEOPOROS IS TREATMENT

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ABSTRACT

Osteoporosis is a worldwide disease characterized by reduction of bone mass and alteration of bone architecture resulting in increased bone fragility and increased fracture risk. Although it is seen in all age groups, gender, and races, it is more common in Caucasians (white race), older people, and women. With an aging population and longer life span, osteoporosis is increasingly becoming a global epidemic. Currently, it has been estimated that more than 200 million people are suffering from osteoporosis. Moreover, osteoporosis results in a decreased quality of life, increased disability-adjusted life span, and big financial burden to health insurance systems of countries that are responsible for the care of such patients. Therefore, increasing awareness in medical field, which, in turn, facilitates increase awareness of the normal populace, will be effective in preventing this epidemic.

KEYWORDS

Osteoporosis, Osteoporosis Management and Gene therapy.

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INTRODUCTION

Osteoporosis is a disease of bones that leads to an increased risk of fracture. It has been denoted a silent disease due to its character of occurring without symptomatic changes in the body. Worldwide estimates show that osteoporosis accounts for over 8.9 million fractures annually which turns out to be an osteoporosis related fracture every 3 seconds[1]. Osteoporosis affects 200 million women worldwide with approximately one-

tenth of women aged 60 affected by osteoporosis[2]. It affects the aged people making them bedridden affecting their quality of life. Worldwide, 1 in 3 women above 50 years age and 1 in 5 men above 50 years age are affected by osteoporotic fracture[3-5]. This shows that osteoporosis is a global healthcare burden.

Pathophysiology of the disease

In osteoporosis, the bone mineral density (BMD) gets reduced, deterioration of bone microarchitechture takes place, and the amount of various transcription factors, growth factors and cytokines etc. in bone are altered. Imbalance between bone resorption and bone formation is the underlying mechanism in all cases of osteoporosis. In normal bone, matrix remodeling of bone is constant. Bone is resorbed by osteoclast cells, after which new bone is deposited by osteoblast cells. The three main mechanisms by which osteoporosis develop are (a) an inadequate peak bone mass (the skeleton develops insufficient mass and strength during growth), (b) excessive bone resorption, and (c) inadequate formation of new bone during remodeling.

These occurs due to various hormonal level defects that lead to cascades of processes which cause increased bone resorption by osteoclasts and/or decreased bone generation by osteoblasts. Lack of estrogen (e.g. as a result of menopause) increases bone resorption, as well as decreasing the deposition of new bone that normally takes place in weight-bearing bones. In addition to estrogen, calcium metabolism plays a significant role in bone turnover, and deficiency of calcium and vitamin D leads to impaired bone deposition; in addition, the parathyroid glands react to low calcium levels by secreting parathyroid hormone (parathormone, PTH), which increases bone resorption to ensure sufficient calcium in the blood.

Main hormones that regulate bone metabolism are as follows: Decrease bone resorption: Calcitonin, estrogen, Increase bone resorption: parathormone (PTH), glucocorticoids, thyroid hormones, high dose vit.D, Increase bone formation: Growth hormone, vit.D metabolites, androgens, insulin, low dose PTH, Decrease bone formation: Glucocorticoids

Various growth factors, cytokines and transcription factors are involved in the pathogenesis of osteoporosis. These include RANK (receptor activator of nuclear factor κβ), RunX2 (Runt related factor X2), VEGF (vascular endothelial growth factor)[6], TNF (tumor necrosis factor), TGF (transforming growth factor), BMPs (bone morphogenetic proteins), OPG (osteoprotegerin), OTX (osterix). Many of these factors have been studied for their potential use in osteoporosis.

Osteoporosis treatment and its management

Osteoporosis risk can be reduced with lifestyle changes and medication; in people with osteoporosis, treatment may involve both. Lifestyle change includes diet and exercise, and preventing falls. Medication includes supplemental calcium, vitamin D, calcitonin, bisphosphonates (zaledronic acid, ibandronate, etc), bone morphogenetic proteins (BMP-2 and-7) and several others[7]. Most of the therapies are long term therapies and require closer monitoring to avoid any adverse effects. Some of the demerits of the current therapeutics of osteoporosis are described in the Figure No.1 below. Effectiveness of oral calcium and vitamin D supplementation has been evaluated extensively. The analyses show that calcium supplementation alone and vitamin D supplementation alone are not effective in preventing fractures in osteoporotic patients as the combination thereof[8,9]. Effect of intravenous calcium infusion has also been evaluated in osteoporotic women for treating osteoporosis, but it was found to be ineffective in altering bone calcium turnover in osteoporotic women. Loss of total body calcium was similar to that in untreated subjects with osteoporosis[10,11].

Glucocorticoid-induced osteoporosis and osteoporosis related to aging are mainly outcome of reduced bone formation due to reduced number of osteoblasts. Moreover, Calcium and vitamin D combination therapy has been found to be non-effective in preventing fractures in elderly (age >70 years)[12,13]. An ideal way to prevent bone loss in such cases would be not only to reduce bone

resorption, but also to promote bone formation. There is therefore an important need to develop therapeutic strategies capable of promoting bone formation in osteoporotic subjects.

Gene therapy as an approach for osteoporosis – current perspective

Gene delivery has been showing promising results for treatment of various diseases[14-16]. In the past decade various gene delivery approaches have been studied for the treatment of osteoporosis. Such gene delivery approaches particularly act either by inducing or one or other growth factors, cytokines, transcription factors, other mediators or their receptors that are implicated in osteoporosis. Advancements made in the treatment of osteoporosis with gene delivery are described below with brief review of various gene delivery systems evaluated for osteoporosis treatment in animals Figure No.1.

Various cytokines, particularly interleukin-1 (IL-1) and tumor necrosis factor (TNF), have been strongly implicated in postmenopausal osteoporosis occurring due to estrogen deficiency. Both of these cytokines are powerful inducers of bone resorption. From this information, it follows that inhibiting the biological activities of IL-1 and TNF should reduce bone loss under conditions of estrogen deficiency[17,18]. Genes encoding for IL-1 receptor antagonist (IL-1Ra) or soluble form of TNF receptors would ameliorate the osteoporotic bone loss by inhibiting osteoclastic activity[19,20].

Intravenous delivery of human osteoprotegerin (hOPG) gene using viral vectors results in systemic circulation of the OPG which in turn inhibits osteoclastic activity. The mechanism involves the binding of OPG to RANKL (receptor activator of nuclear factor κβ ligand) which prevents the binding of latter to RANK. This in turn suppresses its ability to increase bone resorption by osteoclasts[21,22]. LIM mineralization protein (LMP) which induces the bone mineralization and expression of various osteogenic genes, BMP-2, RunX2 (Runt related transcription factor X2), OSX (Osterix) etc., and thereby promotes the osteoblast differentiation. One study has also shown that it induces bone formation more efficiently than even BMP-2[23].

Among all gene delivery approaches, delivery of genes of bone-morphogenetic proteins has been most extensively evaluated Figure No.1. Bone morphogenetic factors (BMPs), mainly BMP-2, BMP-4, BMP-6, BMP-7 and BMP-9, are other osteogenic proteins that have been studied for bone regeneration in fractured bone healing, osteoporosis and osteopenia[24]. Recombinant human bone morphogenetic protein-2 and -7 have been recently granted United States Food and Drug Administration approval for select clinical applications in bone repair[20,24]. These BMPs act primarily as differentiation factors, turning responsive mesenchymal cells into cartilage- and bone-forming cells[25]. While significant progress has been made in the delivery of recombinant osteogenic proteins to promote bone healing, the short half-life and instability of the protein requires the delivery of milligram quantities of factor or multiple dosages[20]. So, delivery of genes encoding for various BMPs have been investigated in various studies Figure No.1. Various transcription factors and growth factors such as VEGF[26], RunX2, TGF etc. have also been found to enhance the effects of various BMPs. Among various BMPs, BMP-9 has been shown to provide most robust and effective osteogenic activity in animal studies Figure No.1.

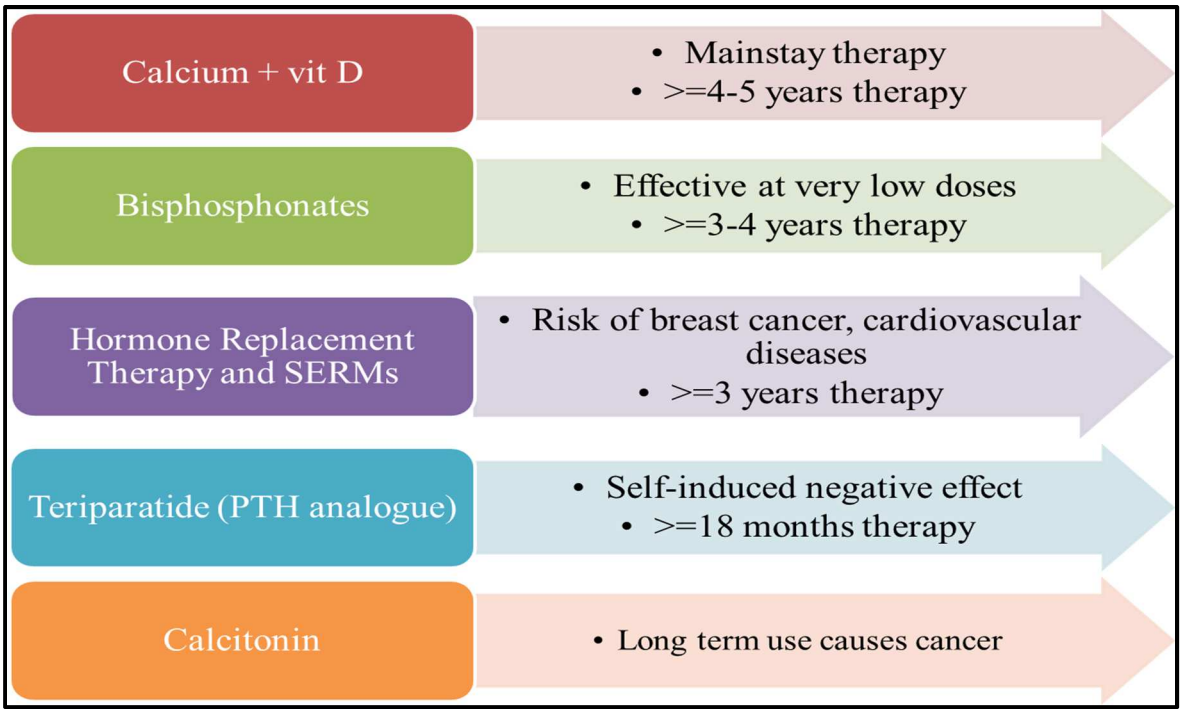

Figure No.1: Current treatment options of osteoporosis and their drawbacks

CONCLUSION

Osteoporosis is a skeletal disorder characterized by compromised bone strength leading to an increased risk of fracture. Osteoporosis is a common and silent disease until it is complicated by fractures that become common. It was estimated that 50% women and 20% of men over the age of 50 years will have an osteoporosis-related fracture in their remaining life. These fractures are responsible for lasting disability, impaired quality of life, and increased mortality, with enormous medical and heavy personnel burden on both the patient's and nation's economy. Therefore, the prevention, detection, and treatment of osteoporosis should be a mandate of primary healthcare providers.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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